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STATISTICAL ANALYSIS PLAN

A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent 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, anti-drug antibodies
AE:	adverse event
ALT:	alanine aminotransferase
ANA:	anti-nuclear antibody
ANCOVA:	analysis of covariance
AQLQ:	Asthma Quality of Life Questionnaire
AST:	aspartate aminotransferase
ATC:	Anatomic Therapeutic Chemical
ATS:	American Thoracic Society
BD:	bronchodilator
CI:	confidence interval
ECG:	electrocardiogram
eCRF:	electronic case report form
EOS:	eosinophil
EQ-5D-5L:	EuroQoL Working Group Health Status Measure 5 Dimensions, 5 Levels
ER:	emergency room
ERS:	European Respiratory Society
FEF _{25-75%} :	forced expiratory flow from 25% to 75% of the vital capacity
FEV ₁ :	forced expiratory volume in 1 second
FVC:	forced vital capacity
HADS:	Hospital Anxiety and Depression Scale
HbA1c:	hemoglobin A1c
HBcAb:	hepatitis B core antibody
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HCAb:	hepatitis C antibody
HLGT:	high-level group term
HLT:	high-level term
IgA:	immunoglobulin A
IgG:	immunoglobulin G
IgM:	immunoglobulin M
ILC2:	innate lymphoid type 2
ITT:	intent-to-treatment
K-M:	Kaplan Meier
LLOQ:	lower limit of quantification
LLT:	lower-level term
LS:	least squares
MCID:	minimal clinically important difference

MDI:	metered dose inhaler
MedDRA:	Medical Dictionary for Regulatory Activities
MH:	Mantel-Haenszel
MMRM:	mixed effect model with repeated measures
NIMP:	noninvestigational medicinal product
OCS:	oral corticosteroids
OLE:	open-label extension
PCR:	polymerase chain reaction
PD:	pharmacodynamic
PROs:	patient-reported outcomes
PT:	preferred term
SC:	subcutaneously
SD:	standard deviation
SMQ:	Standardised MedDRA Query
SNOT-22:	22-item Sino Nasal Outcome Test
SOC:	system organ class
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
VAS:	visual analogue scale
WBC:	white blood cell
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multinational, multicenter, randomized, double-blind, placebo-controlled study assessing the effect (efficacy and safety) of dupilumab administered subcutaneously (SC) for a maximum of 24 weeks in patients with severe steroid-dependent asthma.

The clinical trial will be divided into the following periods:

- Screening and oral corticosteroids (OCS) Optimization period (from 3 to up to 8 weeks [up to 10 weeks for patients experiencing an asthma exacerbation that requires a change in OCS dose to allow for 2 weeks of stabilization prior to randomization]): to determine a patient's eligibility status and to ensure that patients enter the treatment period on the lowest dose of OCS that will manage their symptoms
- Treatment period (24 weeks): includes a 4-week induction phase, a 16-week OCS reduction phase, and a 4-week maintenance phase
- Post-treatment/Follow up period (12 weeks): to monitor a patient's status after completing/withdrawing from study drug treatment for patients not participating in the long-term extension study.

Patients who meet the entry criteria will be randomized via Interactive Response Technology (IRT) in a 1:1 ratio to receive a 600 mg loading dose followed by 300 mg once every 2 weeks (q2w) of dupilumab or matching placebo, respectively. Randomization will be stratified by optimized OCS dose at Week 0 (≤ 10 mg/day, >10 mg/day) and country.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate the efficacy of dupilumab, compared with placebo, for reducing the use of maintenance OCS in patients with severe steroid-dependent asthma.

1.2.2 Secondary objectives

Secondary objectives of the study include:

- To evaluate the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab in improving patient-reported outcomes (PROs)
- To evaluate dupilumab systemic exposure and the incidence of treatment-emergent anti-drug antibodies (ADA)

1.2.3 Exploratory objectives

The following objectives will be exploratory:

- To evaluate baseline and on-treatment levels of biomarkers in association with treatment response and for their potential to predict treatment responses
- To evaluate patient genetic profiles and their potential to predict treatment responses
- To evaluate the effect of dupilumab on airway markers of inflammation (at select study sites within Canada)

1.3 DETERMINATION OF SAMPLE SIZE

The sample size estimation is based on the comparison between dupilumab doses versus placebo with regard to the primary endpoint, percentage reduction of OCS dose at Week 24 compared with the baseline dose, and a key secondary endpoint, proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24, while maintaining asthma control. For the primary endpoint, assuming a common standard deviation of 50%, with 90 randomized patients per group, the study will have 94% power to detect a treatment difference of 27% (1) at the 2-tailed significance level of $\alpha=0.05$. For the key secondary endpoint, with the same sample size of 90 randomized patients per group, the study will have 81% power to detect a difference, at the 2-tailed significance level of $\alpha=0.05$, in the proportion of patients achieving reduction of 50% or greater in their OCS dose, assuming that the proportions are 33% in the placebo group, compared to 54% in the dupilumab group (2).

Calculations were made using nQuery Advisor 7.0.

Recruitment of patients whose eosinophil level is below 150 cells/ μ L will stop when approximately 46 (25% of the total sample size) of such patients are randomized. Recruitment will continue with patients whose eosinophil (EOS) level is greater than or equal to 150 cells/ μ L until reaching the total sample size of 180. In addition, the number of patients receiving 5 mg OCS at Visit 3 will be limited to approximately 54 patients (approximately 30% of the study population).

1.4 STUDY PLAN

The total duration of the study (per patient) is expected to be up to 44 weeks (or up to 46 weeks in patients who experience an asthma exacerbation during the OCS Optimization phase that requires a change in OCS dose to allow for 2 weeks of stabilization prior to randomization) and consists of:

- Up to 10 weeks for the Screening period/OCS Optimization phase
- 24 weeks for the Treatment period
- 12 weeks for the Post-treatment/Follow-up period (for patients not participating in the open-label extension [LTS12551] study)

Screening and OCS Optimization Period

Patients who meet eligibility criteria at the Screening visit will enter the OCS Optimization Phase. Prednisone or prednisolone will be the only OCS used. At the Screening visit (V1), patients currently using other forms of maintenance OCS will have their corticosteroids switched to either of these corticosteroids at a dose clinically equivalent to their current stable OCS maintenance dose. The definition of stable OCS maintenance dose in EFC13691 is no change of OCS dose within 4 weeks of Screening Visit 1.

The lowest effective or optimized OCS dose will be defined during this phase as the lowest dose a patient can tolerate without experiencing any of the following OCS optimization phase interruption criteria:

- Increase in Asthma Control Questionnaire-5 question version (ACQ-5) of ≥ 0.5 from the last ACQ-5 score recorded in the e-diary
- Severe asthma exacerbation
- Clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment

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

- Use of systemic corticosteroids for ≥ 3 days (at least double the dose currently used) and/or
- Hospitalization or emergency room (ER) visit because of asthma requiring intervention with a systemic corticosteroid treatment (at least double the dose currently used)

In general, the investigator can refer to the ACQ-5 score at Screening Visit 1 to guide the OCS dose adjustments made during the optimization phase of the study; however, the decision to titrate can be based on the investigator's clinical judgment. Once determined, the optimized dose must remain stable for 2 consecutive weeks along with baseline medications without meeting any of the OCS optimization phase interruption criteria in order to be eligible for randomization.

Investigators should adjust the OCS dose according to a pre-specified titration schedule [Table 1](#) based on the OCS optimization phase interruption criteria, and in accordance with their clinical judgment. During the OCS optimization phase, the patient's asthma control will be assessed weekly by reviewing these criteria via scheduled phone calls after Visit 2. If the patient's asthma status remains controlled and none of the above criteria are met, the investigator should down-titrate the patient's OCS dose. The downward titration will continue until a point when at least 1 of the OCS optimization phase interruption criteria is met. If the down-titration is stopped, the investigator should up-titrate the OCS dose by 1 step per [Table 1](#), unless the patient's medical condition requires treatment with a higher dose of OCS.

No change in OCS dose will be made at Visit 1. One week after the Screening visit (Visit 1), patients will return to the clinic for Visit 2. At Visit 2, and weekly throughout the Optimization phase, patient stability will be assessed by the above outlined criteria.

Table 1 - Oral corticosteroid optimization titration schedule

Time course	OCS dose (mg/day)								
Starting dose (Visit 1)	35	30	25	20	15	12.5	10	7.5	5
Dose reduction (Visit 2)	30	25	20	15	12.5	10	7.5	5	2.5
+1 week	25	20	15	12.5	10	7.5	5	2.5	
+1 week	20	15	12.5	10	7.5	5	2.5		
+1 week	15	12.5	10	7.5	5	2.5			
+1 week	12.5	10	7.5	5	2.5				
+1 week	10	7.5	5	2.5					
+1 week	7.5	5	2.5						

OCS=oral corticosteroid

Deterioration is defined as an increase in the ACQ-5 score of ≥ 0.5 from the last ACQ-5 score recorded in the e-diary, the occurrence of a severe asthma exacerbation, or a clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment. In these cases, the patient will return to the prior OCS dose at which none of the OCS optimization phase interruption criteria were met.

If at Visit 2, or weekly thereafter, the subject's asthma status deteriorates as outlined above, their OCS dose should be increased by 1 step (Table 1). In this manner, the Screening/OCS Optimization phase can range from 3 to 8 weeks until an optimized dose of OCS is achieved (Note: If an asthma exacerbation occurs that demands a change in OCS dose, this period can be extended up to 10 weeks to allow for 2 weeks of stabilization prior to randomization.)

In cases where the stable OCS dose for 4 weeks prior to Visit 1 does not conform to a dose found on Table 1, the initial dose reduction should be the most conservative decrease that approximates the Table 1 protocol guidance. As an example, 6 mg could be reduced to 5 mg and then per protocol to 2.5 mg thereafter, or 8 mg to 7.5 mg and then 5 mg, depending upon the individual patient and the investigator's judgment. In the event of any uncertainty, the Investigator will discuss the therapy directly with the Sponsor prior to the first OCS dose reduction.

Those patients who are able to down titrate their OCS dose to 2.5 mg during the OCS Optimization phase without meeting any of the above criteria will be considered screen failures and will not be randomized.

If a patient experiences a severe asthma exacerbation during the OCS Optimization Phase, the exacerbation should be treated with the use of oral or parenteral steroids at least double the dose of current maintenance dose of OCS. Following exacerbation treatment, the patient should be placed on the OCS dose 1 step higher than the dose they were on when the exacerbation occurred in accordance with Table 1.

Once the optimized OCS dose has been identified, the patient will be maintained on their optimized OCS dose, along with their baseline medications, for 2 weeks prior to randomization.

If a patient is unable to maintain their optimized OCS dose and experiences an increase in ACQ-5 of at least 0.5 or a severe exacerbation, the dose of OCS should be increased 1 step or as detailed for treatment of severe exacerbation in protocol unless there is a clinically significant contraindication to an increase in the OCS dose. The patient will be eligible for randomization after the increased OCS dose remains stable for a 2-week period (provided there is sufficient time remaining in the Screening Period [up to 10 weeks]).

Randomized Treatment Period

Induction Phase (4 weeks)

During this phase patients will remain on their optimized dose of OCS along with their baseline asthma medications.

OCS Reduction Phase (16 weeks)

The OCS dose should be down-titrated during this phase following a pre-determined schedule, provided in [Table 2](#) that is based upon the optimized OCS dose identified during the OCS Optimization Period. Dose reductions may occur every 4 weeks which should allow the minimization of any carryover effects from the previous dose and reduce the risk for adrenal insufficiency. The last possible dose reduction can occur at Week 20. No down-titration beyond this time point is permitted.

Table 2 - Oral corticosteroid titration schedule during the Oral Corticosteroid Reduction phase

Time course	OCS dose (mg/day)								
Optimized OCS dose	35	30	25	20	15	12.5	10	7.5	5
First dose reduction	25	20	15	10	10	10	5	5	2.5
+4 week	15	10	10	5	5	5	2.5	2.5	0
+4 week	10	5	5	2.5	2.5	2.5	0	0	
+4 week	5	2.5	2.5	0	0	0			
+4 week	2.5	0	0						

OCS=oral corticosteroid

The reduction in OCS dose should occur per the schedule unless the patient meets defined criteria indicating that it is not acceptable for the patient to reduce the dose. A clinical assessment should be completed prior to each dose reduction. Primary reasons for not following the scheduled dose reduction include:

- Mean morning PEF <70% of baseline stability limit
- Forced expiratory volume in 1 second (FEV₁) 20% reduction from baseline stability limit
- Rescue medication (metered dose inhaler) use requiring 4 or more puffs/day above the mean baseline value for any 2 consecutive days in the prior week, or 12 puffs or more on any 1 day in the prior week

- Change in ACQ-5 score $\geq +0.5$ from the prior month OCS dose assessment
- Clinically significant asthma exacerbation
- Clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment

The Investigator should decide, depending on the reason for not reducing the OCS dose per schedule, whether to maintain or increase his/her current OCS dose by 1 step.

Maintenance Phase (4 weeks)

Patients will be maintained for the last 4 weeks of the Randomized Treatment period on the same OCS dose established at Week 20. However, when any of the above criteria for not reducing OCS dose is met, the Investigator should decide whether to maintain or increase the current OCS dose accordingly.

Oral Corticosteroid Dose after an Asthma Exacerbation

If a severe asthma exacerbation occurs during the Reduction or Maintenance Phases of the Randomized Treatment period, the exacerbation should be treated with the use of oral or parenteral steroids at a dose at least equivalent to double the dose of current maintenance dose of OCS. Following resolution, the subject should be placed on the OCS dose 1 step higher than that which he/she was on when the exacerbation occurred for at least 4 weeks and continue with dose reductions (only during the Reduction phase) as per the predefined schedule at the following visit. If a patient experiences 2 exacerbations, no further OCS dose reductions will be allowed.

Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. Study investigators should continue OCS dose adjustment after treatment discontinuation, as guided by their medical judgment, including up-titration and down-titration in accordance with [Table 2](#) (Titration schedule for oral corticosteroids during the OCS Reduction Phase of the Randomized Period).

Post-treatment/Follow-up Period

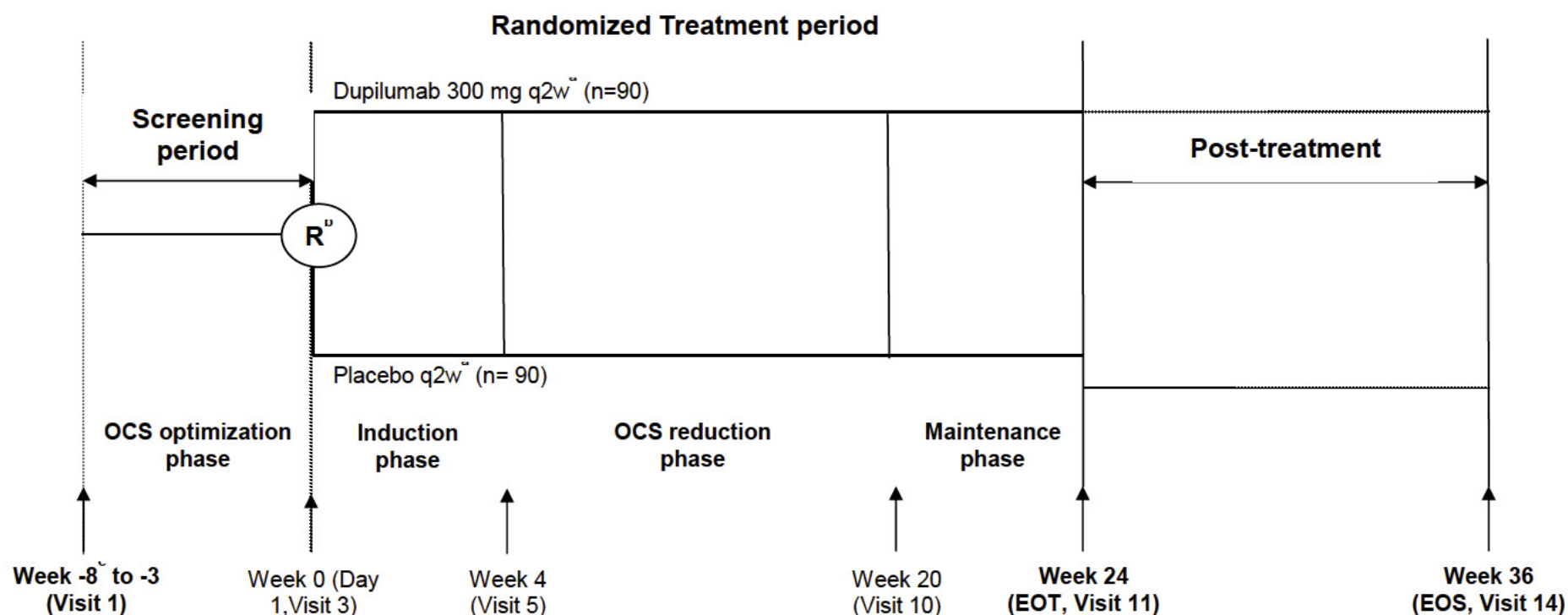
After completing the treatment period, patients who do not rollover into a long-term study will be evaluated for 12 weeks in the post-treatment period. During this follow-up period, patients will continue treatment with their stable dose of controller medication (includes all medications used to control asthma symptoms, with the exception of the investigational medicinal product [IMP]) that can be modified based on their level of asthma control, as determined by the Investigator.

During the post-treatment period, patients will continue to collect e-diary information that can be used to determine asthma control.

Eligible patients completing the treatment period may have the opportunity to roll over into a long-term study with dupilumab. Patients subsequently enrolled in this long-term study will not participate in the Post-treatment period of this trial.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits. In addition, patients who discontinue early from treatment or patients who choose not to roll over into a long-term study may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall assessment of antibody titers and clinical presentation.

1.4.1 Graphical study design



^a 600 mg (or matching placebo) loading dose on Day 1.

^b Randomization and first IMP administration occurs at this visit.

^c The Screening period can be increased to 10 weeks for patients experiencing an asthma exacerbation that requires a change in OCS to allow for 2 weeks of stabilization prior to randomization.

EOS=end of study; EOT=end of treatment; OCS=oral corticosteroid; q2w=every 2 weeks; R=Randomization visit

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).

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 3 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	20-Jul-2016	Based on the clinical relevance and statistical power considerations of the secondary endpoints	The endpoint 'Proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24 while maintaining asthma control' was moved from the 5th place to the 3rd place in the multiplicity control procedure defined in Section 2.4.4.3.
2	25-Jan-2017	Increase the power of detecting a significant difference in the key secondary endpoint of patients achieving a 50% reduction in oral corticosteroid (OCS) dosing	<p>Sample size was increased from 150 to 180. Specifically,</p> <p><u>The following text:</u></p> <p>The sample size estimation is based on the comparison between dupilumab doses versus placebo with regard to the primary endpoint: percentage reduction of OCS dose at Week 24 compared with the baseline dose, while maintaining asthma control. Assuming a common standard deviation of 50%, with 75 randomized patients per group, the study will have 90% power to detect a treatment difference of 27% at the 2-tailed significance level of $\alpha=0.05$.</p> <p><u>Was replaced with:</u></p> <p>The sample size estimation is based on the comparison between dupilumab doses versus placebo with regard to the primary endpoint and the key secondary endpoint: percentage reduction of OCS dose at Week 24 compared with the baseline dose and proportion of patients achieving a reduction</p>

Amendment Number	Date Approved	Rationale	Description of statistical changes
			<p>of 50% or greater in their OCS dose compared with baseline at Week 24, while maintaining asthma control. For the primary endpoint, Assuming a common standard deviation of 50%, with 7590 randomized patients per group, the study will have 9094% power to detect a treatment difference of 27% at the 2-tailed significance level of $\alpha=0.05$. For the key secondary endpoint, with the same sample size of 90 randomized patients per group, the study will have 81% power to detect a difference in the proportion of patients achieving 50% or greater in their OCS dose of 33% in the placebo group, compared to 54% in the dupilumab group, at the 2-tailed significance level of $\alpha=0.05$.</p> <p><u>The following text:</u></p> <p>Recruitment of patients whose eosinophil level is below 150 cells/μL will stop when approximately 38 (25% of the total sample size) of such patients are randomized. Recruitment will continue with patients whose eosinophil (EOS) level is greater than or equal to 150 cells/μL until reaching the total sample size of 150. In addition, the number of patients receiving 5 mg OCS at Visit 3 will be limited to approximately 46 patients (approximately 30% of the study population).</p> <p><u>Was replaced with:</u></p> <p>Recruitment of patients whose eosinophil level is below 150 cells/μL will stop when approximately 3846 (25% of the total sample size) of such patients are randomized. Recruitment will continue with patients whose eosinophil (EOS) level is greater than or equal to 150 cells/μL until reaching the total sample size of 450180. In addition, the number of patients receiving 5 mg OCS at Visit 3 will be limited to approximately 4654 patients (approximately 30% of the study population).</p>

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This section summarize 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 not based on any unblinded study data.

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 4 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	This version	The medical significance of the endpoint	The endpoint 'The proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24 while maintaining asthma control' becomes a key secondary efficacy endpoint.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value of the efficacy parameters is defined as the last available value up to randomization date but prior to the first dose of IMP unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of the 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 date if the patient is not exposed to IMP.

All baseline safety, efficacy, and pharmacodynamic (PD) parameters (apart from those listed below) are presented along with the summary statistics in the safety and efficacy sections (Sections 2.4.5, 2.4.4 and 2.4.6.2).

Demographic characteristics

Demographic variables are:

- Gender (Male, Female),
- Race (Caucasian/white, Black, 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 years),
- Ethnicity (Hispanic, non-Hispanic),
- Region (East Europe: Hungary, Poland, Romania, Russia, and Ukraine; Latin America: Argentina, Brazil, Chile, Colombia, and Mexico; Western Countries: Belgium, Canada, Israel, Italy, Netherlands, Spain, and USA),
- Weight in kg (quantitative and qualitative variable : <50, ≥50-<100 and ≥100 kg),
- BMI in kg/m² (quantitative and qualitative variable: <25, ≥25 - <30, and ≥30 kg/m²).

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 and includes:

- Any comorbidity history (if occurred, if ongoing condition)
- Atopic dermatitis history (if occurred, if ongoing condition)
- Allergic conjunctivitis history (if occurred, if ongoing condition)
- Allergic rhinitis history (if occurred, if ongoing condition)
- Allergic conjunctivitis and rhinitis history (if occurred, if ongoing condition)
- Chronic rhinosinusitis history (if occurred, if ongoing condition)
- Nasal polyposis history (if occurred, if ongoing condition)
- Eosinophilic esophagitis history (if occurred, if ongoing condition)
- Food allergy history (if occurred, if ongoing condition)
- Hives history (if occurred, if 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 ≥ 0.35 IU/mL at baseline.

Disease characteristics at baseline

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

- Age of asthma onset (quantitative variable and qualitative variable: <18, 18-40, >40 years)
- Time since first diagnosis of asthma (years)
- Time since last severe asthma exacerbation (months)
- Number of severe asthma exacerbations experienced within 1 year before Visit 1 (quantitative variable and qualitative variable: 0, 1, 2, 3, ≥ 4)
- Number of severe asthma exacerbations experienced requiring hospitalization or urgent medical care within 1 year before Visit 1 (quantitative variable and qualitative variable: 0, 1, 2, 3, ≥ 4)
- With ongoing atopic medical condition (qualitative variable: yes)
- Smoking history (Never, Former), time since cessation of smoking (months) and smoking quantity in pack-years for former smokers
- Baseline blood eosinophil level (quantitative variable and qualitative variable: <0.15, ≥ 0.15 - <0.3, ≥ 0.3 Giga/L)
- Daily OCS dose at Visit 1 (quantitative variable and qualitative variable: 5mg/day, >5- ≤ 10 mg/day, >10- ≤ 15 mg/day, >15- ≤ 25 mg/day, >25 mg/day)
- Optimized daily OCS dose at baseline (quantitative variable and qualitative variable: 5mg/day, >5- ≤ 10 mg/day, >10- ≤ 15 mg/day, >15- ≤ 25 mg/day, >25 mg/day)

- Number of puffs of salbutamol/albuterol and levosalbutamol/levabuterol per day
- Spirometry data including pre-bronchodilator (BD) FEV₁ (L), percent predicted FEV₁, post-bronchodilator FEV₁ (L), FEV₁ reversibility (L), and percent FEV₁ reversibility (%).
- AM and PM PEF (L/min)
- AM and PM symptom scores
- Number of nocturnal awakenings/day
- ACQ-5 score (quantitative variable and qualitative variable: ≤ 2 , >2)
- Asthma Control Questionnaire 7-question version (ACQ-7) score
- Asthma Quality Of Life Questionnaire (AQLQ) global score
- With hypersensitivity to aspirin or other NSAID (qualitative variable: yes, ongoing condition)

Any technical details related to computation, dates, and imputation 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 oral corticosteroids and asthma controller medications are to be reported in the case report form pages.

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

- Prior medications are those the patient used prior to first IMP intake. 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 (2 weeks after last administration of IMP plus 12 weeks of residual treatment epoch) or till rollover to the LTS12551 study. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the posttreatment epoch (as defined in the observation period in [Section 2.1.4](#)).

- Posttreatment medications are those the patient took in the period running from the last administration of IMP + 99 days up to the end of the study.

Oral corticosteroids

To be enrolled in the study, a patient should be on well-documented, regular prescribed treatment of maintenance systemic corticosteroids in the 6 months prior to Visit 1 and using a stable OCS (ie, no change of OCS dose) dose for 4 weeks prior to Visit 1. At Visit 1, patients currently using other forms of maintenance OCS will have their corticosteroids switched to

prednisone/prednisolone at a dose clinically equivalent to their current stable OCS maintenance dose. During the course of the study, including the post-treatment period, patients will receive variable doses of OCS.

Inhaled corticosteroid with a second or third controller

Prior to and during the Screening period, patients must be on a stable dose of high dose ICS (>500 µg total daily dose of fluticasone propionate or equivalent) in combination with a second controller medication (LABA, LTRA, theophylline, etc) for at least 3 months with a stable dose of ICS for ≥1 month prior to Visit 1. In addition, patients requiring a third controller for their asthma are considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1.

During the Randomized Treatment period and Post-treatment period (for those patients not enrolling in the LTS12551), patients will continue taking their controller medication(s).

The recognized controllers in this study will include the following 5 classes: ICS, LABA, LAMA, anti-leukotrienes and methylxanthine. For examples of commonly used asthma controller therapies, refer to [Appendix A](#) for a list of controller medications approved for this study.

Reliever Medication

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol metered dose inhaler (MDI) as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method. Nebulizer doses recorded in mg can be converted to puff unit using the following conversion factors:

- Salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs;
- Levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs.

Any technical details related to computation, dates, imputation for missing dates are described in [Section 2.5](#).

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint for this study is the percentage reduction of OCS dose at Week 24 compared with the baseline dose, while maintaining asthma control. The percent reduction in OCS dose will be calculated as: (optimized OCS dose at baseline – final OCS dose at Week 24)/optimized OCS dose at baseline × 100. A patient will be considered as having maintained asthma control between Week 20 and Week 24 if he/she does not have a clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment during this period. For those patients who experience an exacerbation, the final OCS dose will be considered to be 1 step higher than the dose they were receiving at the time of the exacerbation. Both the optimized dose at baseline and the final OCS dose at Week 24 will be recorded on the electronic

case report form (eCRF). Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the Investigator will continue to prescribe OCS at the dose specified for OCS titration. The off-treatment OCS dose at Week 24 will be used in the primary analysis.

2.1.3.1.1 Oral corticosteroid dose adjustments

The dose adjustment of OCS through the OCS Reduction phase of the study will be based on the following:

- Asthma symptom data collected through the eDiary (ACQ-5 score)
- Clinically significant asthma exacerbation(s)
- Mean morning PEF <70% of baseline stability limit as assessed in the week prior to the clinical visit
- FEV₁ 20% reduction from baseline stability limit
- Rescue medication use requiring 4 or more puffs/day above the mean baseline value for any 2 consecutive days in the prior week, or ≥12 puffs on any 1 day in the week prior to the clinical visit
- Clinically significant event, based on Investigator judgment that requires treatment by OCS dose adjustment

The patient will complete the ACQ-5 on a weekly basis and record the score in the eDiary (starting with Visit 1 onwards). The Investigator will review the eDiary data on a weekly basis during the OCS Optimization phase and monthly during the Randomized Treatment period. Daily OCS dose will be recorded using the eDiary.

2.1.3.2 Additional efficacy endpoint(s)

2.1.3.2.1 Secondary efficacy endpoints related to adjustments in oral corticosteroid dosing

2.1.3.2.1.1 Key secondary endpoints

- The key secondary endpoints of this study are:
- The proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24 while maintaining asthma control, and
- The proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24 while maintaining asthma control.

2.1.3.2.1.2 Other secondary efficacy endpoints

- Absolute reduction of OCS dose at Week 24 compared with the baseline dose while maintaining asthma control

- Proportion of patients achieving their maximum possible reduction of OCS dose per protocol at Week 24 while maintaining asthma control
- Proportion of patients no longer requiring OCS at Week 24 while maintaining asthma control

2.1.3.2.2 *Other efficacy measures*

The following additional disease-specific efficacy endpoints will be evaluated:

- Annualized rate of severe asthma exacerbation events during the treatment period
- Time to first severe asthma exacerbation event
- Change from baseline in pre-bronchodilator FEV₁ at Weeks 2, 4, 8, 12, 16, 20, and 24
- Percent change from baseline in pre-bronchodilator FEV₁ at Weeks 2, 4, 8, 12, 16, 20, and 24
- Change from baseline in other lung function measurements (percent predicted FEV₁, morning/evening PEF, forced vital capacity [FVC], forced expiratory flow from 25% to 75% of the vital capacity [FEF_{25-75%}]), at Weeks 2, 4, 8, 12, 16, 20, and 24
- Percent and absolute change from baseline in post-bronchodilator FEV₁ at Weeks 12 and 24
- Change from baseline in ACQ-5 score at Weeks 2, 4, 8, 12, 16, 20, and 24
- Annualized rate of severe asthma exacerbations requiring hospitalization or ER visit during the treatment period
- Time to first severe asthma exacerbation requiring hospitalization or ER visit
- Change from baseline at Weeks 12 and 24 in:
 - AQLQ
 - 22-item Sino Nasal Outcome Test (SNOT-22) in patients with bilateral nasal polyposis/chronic rhinosinusitis
 - Hospital Anxiety and Depression Scale (HADS)
 - EQ-5D-5L
- Change from baseline at Weeks 2, 4, 8, 12, 16, 20, and 24 in:
 - Morning/evening asthma symptom score and nocturnal awakenings (eDiary)
 - Use of rescue medication
 - Health Care Resource Utilization
- Change from baseline in airway hyperresponsiveness at Week 24 (for select study sites in Canada)

2.1.3.2.2.1 Disease-specific efficacy measures

2.1.3.2.2.1.1 Severe asthma exacerbation events

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

- Use of systemic corticosteroids for ≥ 3 days (at least double the dose currently used); and/or
- Hospitalization because of asthma symptoms or emergency room visit because of asthma requiring intervention with additional systemic corticosteroid treatment

Two events will be considered as different if the interval between their start dates is equal or greater than 28 days.

The period of time for which severe asthma exacerbation information will be included in the endpoint analysis will be from randomization until Visit 11 at Week 24.

For safety reasons, alerts will be programmed into the eDiary that will notify both the patient and the site to monitor the clinical situation closely in case the patient's asthma worsens. However, an alert in itself will not be classified as a clinically significant asthma exacerbation.

The reasons (eg, infections including viral and bacterial, allergen exposure, exercise, or others) of the severe asthma exacerbation events will be collected on the eCRF.

2.1.3.2.2.1.2 Time to first severe asthma exacerbation event

If a patient has an event during the 24-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 asthma exacerbation event is defined as (onset date of the first severe asthma exacerbation event – randomization date +1). If a patient has no severe asthma exacerbation event during the study up to Visit 11 at Week 24, then the patient will be considered as free of event till the date of Visit 11 or the last contact date, whichever happens earlier.

2.1.3.2.2.1.3 Spirometry

The following parameters will be measured using spirometry: FEV₁ (pre- and post-bronchodilator), percent predicted FEV₁, FVC, and FEF_{25-75%}.

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 (3). For pre-bronchodilator measured parameters, including FEV₁, PEF, FVC, and FEF_{25-75%}, spirometry will be performed after 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 and withholding the last dose of LAMA for at least 24 hours.

For post-bronchodilator FEV₁, the measure should follow the steps described for reversibility validation.

At all visits, spirometry should be performed in the morning if possible, but if the test can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements.

Pulmonary function tests will be measured in the sitting position; however, if necessary to undertake the testing with the subject standing or in another position, this should be noted on the spirometry report. For any subject, the position should be consistent throughout the study.

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 patient fails to provide repeatable and/or acceptable maneuvers, an explanation should be documented.

The largest FEV₁ and largest FVC should be recorded after the data are examined from all of the acceptable curves, even if they do not come from the same curve. The 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 performance).

Reversibility/post-bronchodilator FEV₁

A reversibility test will be administered (if not done and documented within 12 months of Visit 1) following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Subjects will receive 2 to up to 4 puffs of albuterol/salbutamol. Alternatively, and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. If the subject does not meet the reversibility at Visit 1, 2 additional assessments can be performed at any time (ie, unscheduled visits) prior to randomization (Visit 3). FEV₁ reversibility is calculated as post-BD FEV₁ - pre-BD FEV₁. Percent FEV₁ reversibility is calculated as (post-BD FEV₁ - pre-BD FEV₁) / pre-BD FEV₁ * 100.

2.1.3.2.2.1.4 Electronic diary/peak expiratory flow meter

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
- Record daily prednisone/prednisolone usage

- Indicate the number of puffs/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
- Record the use of daily controller medications
- Record the number of nocturnal awakenings due to asthma symptoms
- Record oral steroids use for asthma exacerbation event

At Screening (Visit 1), patients will be issued an eDiary/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:

- Morning PEF performed within 15 minutes after arising (between 5:30 AM and 10 AM) prior to taking any albuterol or levalbuterol
- Evening 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/salbutamol or levalbuterol/levosalbutamol for at least 6 hours prior to measuring their PEF
- Three PEF efforts will be performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation

Baseline morning PEF will be the mean AM measurement recorded for the 7 days prior to the randomization, and baseline evening PEF will be the mean PM measurement recorded for the 7 days prior to the randomization. Period stability limit is defined as the respective mean morning or evening PEF obtained over the last 7 days prior to Day1. There should be at least 4 days' measurement for setting up the stability limit, 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.

2.1.3.2.2.1.5 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. During the OCS Optimization period, the ACQ-5 will be completed weekly in the patient's eDiary. During the treatment period, the ACQ-7 will be performed at clinic visits and the ACQ-5 will be completed on a weekly basis for those weeks that the patient does not have a scheduled clinic visit.

Asthma Control Questionnaire-5 question version

The ACQ-5 is a 5-item questionnaire, which has been developed as a measure of subjects' asthma control that can be quickly and easily completed in clinical practice (4). The questions are designed to be self-completed by the subject. The 5 questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, shortness of breath, and wheezing). The response options for all these questions consist of a 0 (no

impairment/limitation) to 6 (total impairment/ limitation) scale ([Appendix B](#)). The ACQ-5 score is a mean of the values recorded for the individual questions. 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.

Throughout the study subjects should complete the ACQ-5 on a weekly basis using their eDiary. The results from the ACQ-5 will be used as a part of the assessment to determine subject eligibility for OCS dose adjustment. If the ACQ-5 is completed through the eDiary while the subject is at a scheduled in-clinic visit, it is recommended that the ACQ-5 be administered at the same time during the visit.

Based on the eDiary device design, each question needs to be completed otherwise a patient cannot proceed to submit his/her response to the entire ACQ-5 questionnaire. Therefore, no partial missing data is expected.

Asthma Control Questionnaire-7 question version

The ACQ-7 consists of 7 questions. The first 5 questions 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 use, % and % predicted use). 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; [Appendix C](#)).

Clinic staff scores the FEV₁% predicted on a 7-point scale.

A global score is calculated: the questions are equally weighted and the ACQ-7 score is the mean of the 7 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control.

The answer to the first 5 questions will be used to calculate an ACQ-5 score for the analysis of the ACQ-5 endpoint.

2.1.3.2.2 Patient Reported Outcomes (Health-related Quality of Life/health economic variables/other endpoints)

Patients should complete PROs before undergoing spirometry testing.

For all the questionnaires, similar to the ACQ-5, each question of any questionnaire needs to be completed otherwise a patient cannot proceed to submit his/her response to the entire questionnaire on the ed diary device. Therefore, no partial missing data is expected.

2.1.3.2.2.1 Asthma Quality of Life Questionnaire

The AQLQ was designed as a self-administered PRO to measure the functional impairments that are most troublesome to patients as a result of their asthma (see [Appendix D](#)). The instrument is comprised of 32 items, each rated on a 7-point Likert scale (from 1 to 7). The AQLQ 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)

A global score is calculated as the mean of all the 32 items ranging from 1 to 7 and a score by domain is the mean of items in each domain. Higher scores indicate better quality of life.

2.1.3.2.2.2 SNOT-22

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on health related quality of life (see [Appendix E](#)). 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)
- Emotional (0-15)

The range of the global score is 0-110. Lower scores indicate less impact. The recall period of the assessment is within the past 2 weeks.

2.1.3.2.2.3 Hospital Anxiety and Depression Scale

The HADS is a general scale used to detect states of anxiety and depression and has been validated in patients with asthma (see [Appendix F](#)). The instrument is comprised of 14 items: 7 items each related to anxiety and depression. Each item on the questionnaire is scored from 0-3; with a score for either anxiety or depression ranging between 0 and 21.

2.1.3.2.2.4 EQ-5D-5L

The 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). The 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 visual analogue scale (VAS; see [Appendix G](#)). 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. The EQ 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.

2.1.3.2.2.5 Asthma symptom score

Patients will record overall symptom scores in an eDiary twice a day prior to measuring their PEF. Symptoms experienced during the night will be recorded upon arising (AM symptom score). The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Baseline symptom scores will be the mean AM and mean PM scores recorded for the 7 days prior to randomization. Scores can range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms. There is no global score, just an AM score and a PM score.

2.1.3.2.2.3 Airway hyperresponsiveness (optional; only for patients enrolled in select sites in Canada)

Airway hyperresponsiveness will be assessed through a bronchial provocation test using methacholine (to be done only if the patient's FEV_1 is $\geq 70\%$ predicted normal). A 20% decrease in the FEV_1 will be considered as a positive test and the PC_{20} of agonist to cause this decrease is calculated by interpolation from the dose-response curve.

2.1.4 Safety endpoints

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

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 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 the patient enters the extension 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 the patient enters the extension study.

The treatment-emergent adverse event (TEAE) 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 lost to follow-up or the resolution/stabilization of all serious adverse events and adverse events with prespecified monitoring).

The on-study observation period is defined as the time from start of treatment until the end of the study.

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 epoch.
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment epoch.

All adverse events (including serious adverse events and adverse events with prespecified monitoring) 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 MedDRA currently in effect at Sanofi at the time of database lock.

Adverse events for each patient will be monitored and documented from the time the subject gives informed consent at Visit 1 until the End-of-Study visit (Visit 14) or till the rollover to the extension study, except for:

- Serious AEs
- Adverse events that are ongoing at database lock

For ongoing AEs at database lock, observations may continue beyond the last planned visit per protocol, and additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected. Any SAE brought to the attention of the Investigator at any time after the end of the study and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

Adverse events of special interests include the following terms:

- Anaphylactic or systemic allergic reactions, that are related to IMP and that require treatment (refer to [Appendix H](#) for the definition of anaphylaxis).

- Severe injection site reactions that last longer than 24 hours.
- Any infection meeting at least 1 of the following criteria:
 - Any serious infection (SAE)
 - Requires parenteral (intravenous, intramuscular, subcutaneous) antimicrobial therapy
 - Requires oral antimicrobial therapy for longer than 2 weeks
 - Is a parasitic infection
 - Is an opportunistic infection ([Appendix I](#))

Note: Antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.

- Significant elevation of alanine aminotransferase (ALT)
 - $ALT > 5 \times$ upper limit of normal (ULN) in patients with baseline $ALT \leq 2 \times$ ULN; or
 - $ALT > 8 \times$ ULN if baseline $ALT > 2 \times$ ULN
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/noninvestigational medicinal product (NIMP)
 - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria.
 - In the event of pregnancy in a female participant, IMP should be discontinued.
 - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP
 - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
 - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice of the intended dose within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

Of note, asymptomatic overdose has to be reported as a standard AE.

AESIs and other selected AE groupings will be searched based on the criteria in [Table 5](#).

Table 5 - Criteria for adverse events of special interest and other selected AE groupings

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (<i>Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1</i>): includes anaphylactic reaction narrow SMQ (20000021) terms; for selection based on occurrence of multiple events, the events must have occurred within 24 hours of each other
Hypersensitivity (medically reviewed)	SMQ hypersensitivity (20000214) narrow search and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥ 24 hours or ongoing
Severe or serious infection	Primary SOC = 'Infections and infestations' and with severe or serious status
Parasitic infection	Infection Type 'Parasitic' checked on eCRF Infection Defined as AESI Complementary Form
Opportunistic infection	Infection Type 'Opportunistic' checked on eCRF Infection Defined as AESI Complementary Form
Drug-related hepatic disorder	Drug-related hepatic disorders-Comprehensive search narrow SMQ (20000006)
Pregnancy	Primary SOC = 'Pregnancy, puerperium and perinatal conditions' or PT in (Aborted pregnancy, False negative pregnancy test, Pregnancy test positive, Pregnancy test urine positive, Ectopic pregnancy termination)
Symptomatic overdose with IMP	Is the event a Symptomatic Overdose with IMP? is answered Yes on AE eCRF.
Symptomatic overdose with NIMP	Is the event a Symptomatic Overdose with NIMP? 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)

AE Grouping	Criteria
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'

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 post-study: 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, serum immunoglobulins, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at Visits 1 (Week -8 to -3), 3 (Week 0), 5 (Week 4), 7 (Week 8), 8 (Week 12), 9 (Week 16), 10 (Week 20), 11 (Week 24), 14 (Week 36), and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
 - **Red blood cells and platelets and coagulation:** hemoglobin, hematocrit, platelet count, total red blood cell count
 - **White blood cells:** total white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
 - **Metabolism:** glucose, hemoglobin A1c (HbA1c), total cholesterol, total protein, albumin, creatine phosphokinase
 - **Electrolytes:** sodium, potassium, chloride, bicarbonate
 - **Renal function:** creatinine, blood urea nitrogen, uric acid
 - **Liver function:** ALT, aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin)

- **Pregnancy test:** A serum pregnancy test (β -human chorionic gonadotrophin) will be performed at Screening (Visit 1, Week -8 to -3) in women of childbearing potential
- **Hepatitis screen** (at Visits 1 [Week -8 to -3] and 10 [Week 20]): hepatitis B surface antigen (HBsAg), hepatitis B Surface antibody (HBsAb), Immunoglobulin M (IgM) and Immunoglobulin G (IgG)/total-hepatitis B core antibody (HBcAb), hepatitis C antibody (HCAb). Patients who are IgG/total-HBcAb positive and HBsAg negative at Visit 1 must undergo HBV DNA testing prior to randomization to determine eligibility. In case of results showing HCVAb positive, HCV RNA testing must be negative prior to randomization.
- **HIV screening** (at Visits 1 [Week -8 to -3] and 10 [Week 20]): anti-HIV-1 and HIV-2 antibodies
- **Anti-nuclear antibody (ANA)** (at Visits 1 [Week -8 to -3] and 10 [Week 20]). Note: anti-double-stranded DNA antibody will be tested if ANA is positive ($\geq 1:160$ titer).

Serum immunoglobulins

- Quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and Immunoglobulin A (IgA) at Visits 1 (Week -8 to -3), 3 (Week 0), 8 (Week 12), 11 (Week 24), and 14 (Week 36).

Urine samples will be collected as follows:

- **Urine dipstick analysis** (at Visits 1 [Week -8 to -3], 3 [Week 0], 8 [Week 12], 11 [Week 24], and 14 [Week 36]): 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 3 (Week 0) prior to randomization and Visits 5 (Week 4), 7 (Week 8), 8 (Week 12), 9 (Week 16), 10 (Week 20), 11 (Week 24), and 14 (Week 36) prior to investigational product administration

Technical formulas are described in [Section 2.5.1](#).

2.1.4.4 Vital signs variables

Vital signs including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight will be measured at every visit. Height (cm) will be measured at the Screening visit (Visit 1) only.

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 Visits 1 (Week -8 to -3), 3 (Week 0), 8 (Week 12), 11 (Week 24), and 14 (Week 36). At the post-randomization visits in which an ECG is scheduled, the ECG will be performed prior to investigational product administration.

All measurements will be made from a single lead: lead II, lead I (if lead II is not possible), or lead V5 (if leads II and I are not possible). 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.

The ECGs will be manually read at a central lab.

2.1.4.6 Physical examination

Physical examinations will be performed at Visits 1 (Week -8 to -3) and 11 (Week 24). They will include 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.

2.1.5 Pharmacokinetic variables

Blood samples of serum functional dupilumab will be collected at Visit 3 (Week 0) as sample before the first dose, at Visits 5 (Week 4), 7 (Week 8), 8 (Week 12), 11 (Week 24) as trough samples prior to IMP dosing at each visit, and at Visit 14 (Week 36) during the follow up period.

2.1.6 Anti-drug antibody variables

Determination of anti-drug antibody (ADA) status will be performed at Visits 3 (Week 0), 8 (Week 12), 11 (Week 24), and 14 (Week 36). The ADA status can be negative or a titer value if it is positive. Samples that are positive in the ADA assay will be further characterized for the presence of anti-dupilumab neutralizing antibodies. Patients who discontinue early from treatment or patients who choose not to participate in the LTS12551 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.

ADA incidence will be classified as the following:

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 in the assay at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.

Treatment-emergent anti-drug antibodies is defined as:

- An ADA-positive response in the assay post first dose, when baseline results are negative or missing.

Treatment-boosted anti-drug antibodies 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.

Treatment-emergent (TE) ADA responses are further classified as transient, persistent or indeterminate

- Persistent response is defined as a treatment-emergent response with 2 or more consecutive ADA-positive sampling time points separated by more than a 12-week period (84 days), with no ADA negative samples in between.
- Indeterminate response is defined as a treatment-emergent response with only the last collected sample positive in the ADA assay.
- Transient response is defined as a treatment-emergent response that is not considered persistent OR indeterminate.

Titer values (titer value category)

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

2.1.7 Pharmacodynamics/genomics endpoints

PD endpoints include:

- **Whole blood biomarkers:** Blood eosinophil count will be measured as part of the standard clinical lab test at Visits 1 (Week -8 to -3), 3 (Week 0), 5 (Week 4), 7 (Week 8), 8 (Week 12), 9 (Week 16), 10 (Week 20), 11 (Week 24), 14 (Week 36)
- **Plasma biomarkers:** Eotaxin-3 measured at Visits 3 (Week 0), 5 (Week 4), 8 (Week 12), 10 (Week 20), 11 (Week 24)
- **Serum biomarkers:** Antigen-specific IgE, Total IgE, TARC, and periostin at Visits 3 (Week 0), 5 (Week 4), 8 (Week 12), 10 (Week 20), 11 (Week 24)
- **Fractional exhaled nitric oxide:** will be measured at every visit
- **ILC2 and CD34 cells and cytokines in sputum and blood** (optional; only for patients enrolled in select sites in Canada): Innate lymphoid type 2 (ILC2) cells and CD34+ cells will be measured in the blood and induced sputum. Cytokines will be assayed in the sputum and blood. At Visits 3 (Week 0) and 11 (Week 24), both sputum and blood will be collected. At Visit 14, only a sputum sample will be collected (for patients who have not entered into the long-term study).

Pharmacogenetic testing is optional and voluntary. For those patients who sign the optional pharmacogenetic informed consent form, blood samples for exploratory genetic analysis of DNA or RNA will be collected at Visit 3 (Week 0). The DNA or RNA samples may be used to determine a possible relationship between genes and response to treatment with dupilumab, possible adverse reactions to dupilumab, and to study the genetics of asthma. The DNA may be subjected to a genome-wide association study by whole genome array (common single nucleotide polymorphisms) analysis and/or to whole exome sequencing or whole genome analysis in order to thoroughly explore genetic associations with disease progression or treatment response. The RNA may be subjected to discrete panels of polymerase chain reaction (PCR) analyses, microarray analyses, or RNA sequencing analyses.

2.1.8 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 each visit.

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 patient who 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 using a 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 study treatment period as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Patients who withdraw from study prior to Week 24

- Patients who withdraw from study prior to Week 24 by main reason for study discontinuation
- Patients who continued into LTS12551 study
- 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, the analysis populations for safety, pharmacokinetics/pharmacodynamics, and ADA will be summarized in a table by number of patients in the safety population as the denominator.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, or c) a patient is randomized twice.

OR

2. A patient is dispensed an 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 IRT database. 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:

<i>Randomization and drug allocation irregularities</i>
<i>Kit dispensation without IRT transaction</i>
<i>Erroneous kit dispensation</i>
<i>Kit not available</i>
<i>Randomization by error</i>
<i>Patient randomized twice</i>
<i>Stratification error</i>
<i>Patient switched to another site</i>
<i>Therapy administration without IRT transaction</i>
<i>Erroneous therapy administration</i>
<i>Therapy not available</i>

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy 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.

Per the OCS titration [Table 2](#) for the treatment period, patients starting with 35mg/day at baseline cannot achieve complete (100%) reduction at Week 24. Therefore, for the analysis of the secondary endpoint, proportion of patients no longer requiring OCS at Week 24 while maintaining asthma control, the analysis population will be all the patients in the ITT population whose optimized OCS dose at baseline is less than or equal to 30mg/day.

2.3.1.1 Intent-to-treat population

The intent-to-treat (ITT) population is the randomized population analyzed according to the treatment group allocated by randomization regardless of whether the treatment kit is used or not.

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 actually received. The safety analyses will be conducted 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 receiving both dupilumab and placebo during the trial, the treatment group allocation for as-treated analysis will be the dupilumab group.
- PD biomarkers will be analyzed in the safety population.

2.3.3 Pharmacokinetics population

The PK population will consist of all patients in the safety population with at least 1 evaluable functional dupilumab concentration result. Patients will be analyzed according to the treatment they actually received.

2.3.4 Anti-drug antibody population

The 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.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Parameters described in [Section 2.1.1](#) will be summarized by treatment group and overall treatment groups using descriptive statistics.

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 ITT 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 ITT population for any treatment group.

Medical history will be summarized by SOC and PT by treatment group and overall treatment groups. They will be first sorted by SOC using the internationally agreed order and then by the decreasing frequency of PT within each SOC in the overall treatment groups. Comorbidity medical history will be summarized separately.

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

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 Anatomical Therapeutic Chemical (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.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the dupilumab group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medications will be summarized for the treatment epoch and treatment emergent period separately.

Inhaled corticosteroid in combination with other controllers will be summarized separately.

Oral corticosteroids

Compliance to OCS

Compliance to the prescribed OCS dose will be calculated from Visit 3 (Week 0) until Visit 11 (Week 24) for patients who stay in the study until that time, or until the later between end of treatment and the last scheduled visit that occurred where the OCS dose adjustment is still recorded for patients who withdraw from the study before Visit 11. For each day, a patient is considered as compliant to the prescribed OCS if the patient takes the dose as prescribed. Days with missing OCS dose use record will be considered as non-compliant. Days when the diary record of prescribed OCS dose was later corrected by the investigator (which will result in an inconsistency between the answer to the compliance question in diary and compliance derived from comparing the actual dose to the prescribed dose) will be excluded from the compliance calculation.

Percentage of OCS compliance for a patient will be defined as the number of days that the patient was compliant divided by the total number of days during the period defined above.

Above-prescribed OCS dosing percentage for a patient will be defined as the number of days that the patient took a higher OCS dose than prescribed divided by the total number of days during the period defined above.

Under-prescribed OCS dosing percentage for a patient will be defined as the number of days that the patient took a lower dose than prescribed divided by the total number of days during the period defined above.

Missing actual OCS dose data percentage for a patient will be defined as the number of days that the patient has a missing actual dose record in diary divided by the total number of days during the period defined above.

OCS compliance, above-prescribed and under-prescribed dosing, and missing actual OCS dose data 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 0, (0, 20%], and >20% above-prescribed OCS dose as well of patients with 0, (0, 20%], and >20% under-prescribed OCS dose will be summarized separately.

Inhaled corticosteroid with a second or third controller

Prior asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standardized medication name based on the overall incidence across treatment groups.

Concomitant asthma controller medications at randomization will be summarized by treatment group sorted by decreasing frequency of standardized medication name based on the incidence in the dupilumab group.

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 6](#). After conversion, the total daily dose for inhaled corticosteroid will be calculated.

Table 6 - 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	100
BECLOMETASONE DIPROPIONATE (CFC)	1000
BECLOMETASONE DIPROPIONATE (HFA)	400
BUDESONIDE (DPI)	800
CICLESONIDE (HFA)	320
MOMETASONE FUROATE	440
TRIAMCINOLONE ACETONIDE	2000

Inhaled corticosteroid	Equivalent dose (mcg) to 500 mcg Fluticasone propionate (DPI or HFA)
------------------------	--

HFA=hydrofluoroalkane, DPI= Dry Powder Inhaler

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.

Compliance to controller medications

Compliance to the controller medication(s) with ICS component and overall compliance to all prescribed controller medications will be calculated for each patient during treatment epoch defined under [Section 2.1.4](#). For each day, a patient is considered as compliant to the prescribed controller medication with ICS component if the actual dose of each controller medication with ICS component is same as or greater than the prescribed dose. Similarly, a patient is considered as compliant to all controller medication if the actual dose of each controller medication is 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 to the prescribed controller medication(s) with ICS component divided by the number of days of the patient in the treatment epoch. **Overall controller medication(s) compliance** is defined as the number of days when the patient is compliant to all prescribed controller medication divided by the number of days of the patient stays in the treatment epoch. Patients are considered non-compliance for the days of missing controller medication intake data.

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 day, 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 ≤6 weeks
- >6 and ≤8 weeks

- >8 and \leq 12 weeks
- >12 and \leq 16 weeks
- >16 and \leq 20 weeks
- >20 and \leq 24 weeks
- >24 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 to the investigational medicinal product

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 (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 Main statistical model and adjustment of covariates

The primary estimand is the intent-to-treat estimand, the treatment difference between dupilumab and control in the mean percentage reduction of OCS dose at Week 24 while maintaining asthma control of all patients in the ITT population no matter whether the patients discontinue treatment before Week 24 or not. To estimate the estimand, data of patients who permanently discontinue treatment will be incorporated in the primary analysis, and missing data due to patients dropping out from study will be handled by approaches specified in the missing data handling section below.

The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model. The model will include the percentage reduction of OCS dose at Week 24 as the response variable, and the treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (<0.15 Giga/L, ≥ 0.15 Giga/L) as covariates. The treatment difference will be tested at the 2-sided significance level of $\alpha=0.05$. Descriptive statistics for the primary efficacy endpoint will be provided, including the number of patients, means, standard errors, and least squares (LS) means by the treatment groups, as well as the difference in LS means and the corresponding 95% confidence interval (CI). Provided below is sample SAS code for running the model:

```
proc glm data= ocsdata;
  class eosbgp2n cntygr1 trt01pn;
  model ocspcw24 = ocsbl eosbgp2n cntygr1 trt01pn;
  lsmeans trt01pn / stderr pdiff cl;
  estimate 'Diff Dupilumab vs Placebo' trt01pn -1 1;
  ods output LSMeans=lsmeans Estimates=lsmeandiff
             LSMeanDiffCL=lsmeandiffcl;
run;
```

If there are any missing data in the primary efficacy endpoint, the number of subjects, means, and standard errors by treatment group will be calculated from patients with observed data, while the LS means, difference in LS means and the corresponding CI will be calculated based on each particular missing data handling approach as described below.

A review of the residuals will be done to determine whether the normality assumption is met. If the normality assumption is not met, a rank ANCOVA model will be used to corroborate the result of the significance test. Details will be given below.

2.4.4.1.2 Missing data handling

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the Study investigators should continue OCS dose

adjustment after treatment discontinuation, as guided by their medical judgment, including up-titration and down-titration in accordance with Table 2. The off-treatment OCS dose will be used in the primary analysis. During the study, only monotone missing pattern is expected. The number of patients with missing data will be summarized for each treatment group by reason of treatment discontinuation and the last time without missing data. The percent reduction for these patients will be summarized using descriptive statistics by treatment group and visit.

For statistical inference based on the main model, the following approaches will be used to handle the missing data:

Primary approach – pattern mixture model by multiple imputation

This approach will impute missing percent reduction of OCS dose at Visits 5 (Week 4), 7 (Week 8), 8 (Week 12), 9 (Week 16), 10 (Week 20) and 11 (Week 24), using multiple regression models. Imputation will be conducted sequentially by visit, since the imputation for each visit will incorporate information at prior visits. Specifically, the model for each visit will focus on the percent reduction of OCS dose at the visit as the response variable and include the following predictors: the covariates incorporated in the primary statistical model, including baseline eosinophil level subgroup, region (pooled countries), the treatment group, optimized OCS dose at baseline, and the percent reduction of OCS dose from baseline at all the prior visits. Of note, since per protocol a new dose, and therefore the corresponding percent reduction from baseline, if not missing should be one of three possible values corresponding to decreasing, maintaining, or increasing from the previous dose based on the titration Table 2, the imputed value for each missing percent reduction will be the one among the three possible values that is closest to the initially imputed predicted percent reduction from the imputation model. Forty imputations will be performed. For each imputation, the complete percent reduction of OCS dose at Week 24 will be analyzed using the main statistical model described above. LS means by the treatment groups and difference in the LS means will be obtained. Rubin's rule will be used to combine results from all the imputations into a single inference for each of the parameters. P-value and CI will be obtained for the treatment difference. The details of obtaining the observed OCS doses for each visit are described in the data handling convention section.

This approach will be implemented using procs MI and MIANALYZE with the following steps.

1. For the first visit among Visits 5, 7, 8, 9, 10 and 11 that has missing data on prescribed daily maintenance OCS dose, generate 40 imputed dataset, where the missing percent reduction of OCS dose at the visit is imputed from the model described above. Sample SAS code is provided below:

```
proc mi data=ocsdata nimpute=40 seed=&seed out=data_imp;  
  class eosbgp2n cntygr1 trt01pn;  
  var eosbgp2n cntygr1 trt01pn ocsbl &ocspc_prior  
    &ocspc_curr;  
  monotone reg(&ocspc_curr);  
run;
```

where `&ocspc_curr` is the percent reduction of OCS dose at the current visit/time, and `&ocspc_prior` includes the percent reduction of OCS at all the prior visits considered in the imputation. If the current visit is Visit 5 (Week 4), no prior percent reduction will be included. For each missing percent reduction data, the three possible values can be identified from titration Table 2 based on the dose at baseline and the dose immediately before the current visit. The imputed percent reduction will be the one closest to the predicted from the model. Of note dose increase beyond baseline level is possible and will follow the first row of the titration table. For each of the subsequent visits until Visit 11 (Week 24), similar imputation model will be built with the following sample SAS code:

```
proc mi data=data_imp nimpute=1 seed=&seed out=data_imp;
  by _imputation_;
  class eosbgp2n cntygr1 trt01pn;
  var eosbgp2n cntygr1 trt01pn ocsbl &ocspc_prior
  &ocspc_curr;
  monotone reg(&ocspc_curr);
run;
```

One seed will be used to generate random seeds for the MI at each visit.

2. Each of the 40 imputed datasets will be analyzed using the main statistical model. Sample code:

```
proc glm data= data_imp;
  by _imputation_;
  class eosbgp2n cntygr1 trt01pn;
  model ocspcw24 = ocsbl eosbgp2n cntygr1 trt01pn;
  lsmeans trt01pn / stderr;
  estimate 'Diff Dupilumab vs Placebo' trt01pn -1 1;
  ods output LSMeans=implsmeans Estimates=implsmeandiff;
run;
```

3. Applying Rubin's rule to combine analysis results (point estimates and variance) from 40 imputations using proc MIANALYZE for the LS means and difference in LS means between dupilumab and placebo. Sample code:

```
proc sort data=implsMeans; by trt01pn _imputation_;run;

proc mianalyze data= implsmeans;
  by trt01pn;
  modeleffects lsmean;
  stderr stderr;
  ods output ParameterEstimates=lsmeans;
run;

proc mianalyze data=implsmeandiff;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=lsmeandiff;
run;
```


Sensitivity analysis

Pattern mixture model by control-based multiple imputation

The same MI method as the primary approach will be used except that only data of patients in the control group will be used to fit the MI models and the treatment variable will not be incorporated as one of the covariates in the MI models. In Step 1 above, at each visit, missing data of patients in both dupilumab and control groups will be imputed using the models fitted with control patients. This approach assumes that at each visit the missing OCS percent reduction in both treatment groups has the same distribution as those observed in the control group conditional on the covariates in the MI models.

Worse of the last two observations carry forward

For the missing OCS dose at Week 24, the worse (higher) dose between the doses at the last two scheduled visits with available maintenance OCS doses during the treatment period will be used to impute the OCS dose at Week 24 to calculate the primary efficacy endpoint. If a patient drops out of study before Visit 5, the baseline dose (0% reduction) will be used. The main statistical model will be applied to the complete dataset after the imputation.

Tipping point analysis

Tipping point analysis will be conducted to evaluate the robustness of the primary analysis result. This will be conducted by sequentially increasing the imputed percent OCS reduction at Week 24 in the control group and decreasing the imputed values in the treatment group from the primary missing data handling approach. Specifically, for patients in the dupilumab group missing the endpoint, one sequentially subtracts 10% from each imputed value. For patients in the placebo group missing the endpoint, one sequentially adds 10% to each imputed value, until all the patients in all imputations reach their maximum possible percent reduction of OCS dose per protocol. The mean increase in the percent reduction of OCS dose from the original imputed values will be calculated to reflect the actual amount of shift in the placebo group. For each combination of increase in the placebo group and decrease in the dupilumab group, the new dataset will be analyzed and results will be combined using the same methods in Steps 2 and 3 of the primary missing data handling approach. The LS mean difference in percent reduction of OCS dose between the two treatment groups and the corresponding p-values will be reported.

2.4.4.1.3 Other supportive analysis

Rank ANCOVA

If the normality assumption is not met, rank ANCOVA with the extended Mantel-Haenszel (MH) statistics will be used for nonparametric comparisons between treatment groups. The same covariates in the main ANCOVA model, namely, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (<0.15 Giga/L, ≥ 0.15 Giga/L) will be adjusted for in this method. P-value will be obtained from the MH mean score statistic that is asymptotically chi-square distributed with 1 degree of freedom under the *null* hypothesis that there

is no location shift in the distribution of the rank percent reduction in OCS between dupilumab and placebo groups. Specifically, the approach will be implemented with the following steps.

1. Compute standardized ranks of the percent reduction in OCS at Week 24 and the baseline optimized OCS dose in each combination of region and baseline eosinophil level subgroup. Standardized ranks are used to adjust for the fact that the number of patients differs among the subgroups. Sample SAS code:

```
proc rank data=ocsdata nplus1 ties=mean out=rankdata
  (rename=(base=base_rank ocspcw24=ocspcw24_rank));
  by cntygr1 eosbgp2n;
  var ocsbl ocspcw24;
run;
```

The NPLUS1 option of the RANK procedure requests fractional ranks using the denominator as the subgroup specific sample size plus 1. The TIES=MEAN option requests that tied values receive the mean of the corresponding ranks (midranks).

2. Fit separate multiple regression models for the subgroups. In each model, the standardized ranks of the percent reduction in OCS at Week 24 and the baseline optimized OCS dose are used as the dependent and independent variables, respectively. Residuals from the regression models for each patient are obtained. Sample SAS code:

```
proc glm data=rankdata;
  by cntygr1 eosbgp2n;
  model ocspcw24_rank=base_rank;
  output out=residual r=resid;
run;
```

3. The extended Mantel-Haenszel mean score statistic is used to compare the mean values of the residuals between dupilumab and placebo in all subgroups of patients. Sample SAS code:

```
proc freq data=residual;
  tables cntygr1*eosbgp2n*trt01pn*resid/noprint cmh2;
run;
```

If there are any missing data in the primary efficacy endpoint, the statistical test will be performed based on imputed datasets generated from the primary missing data handling approach. The approach proposed in (6) will be used for combining the MH statistics from each imputation to obtain the p -value of testing treatment difference. Specifically, the combined test statistic is

$$D = \frac{\bar{C} - (m+1)/(m-1) \times R}{1+R},$$

where \bar{C} is the average of MH statistics from all imputations, m is the number of imputations, and R is $(1 + m^{-1})$ times the sample variance of the square root of the MH statistics from all

imputations. The reference distribution is an F distribution with 1 and $(m-1)(1+R^{-1})^2$ as numerator and denominator degrees of freedom.

On treatment analysis

This analysis will only be performed when there are any patients who permanently discontinue treatment and still stay in the study for the remaining visits. The main statistical model will be used. Data collected after treatment discontinuation will be excluded from analysis. Then the primary missing data handling approach, PMM by MI, will be applied to impute missing data and estimate the LS means by the treatment groups and difference in the LS means.

2.4.4.1.4 Subgroup analysis

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be conducted for the primary efficacy endpoint with respect to

- Baseline optimized OCS dose strata ($\leq 10\text{mg/day}$, $>10\text{mg/day}$),
- Age group (<40 , ≥ 40 years),
- Gender (Male, Female),
- Region (East Europe: Hungary, Poland, Romania, Russia, and Ukraine; Latin America: Argentina, Brazil, Colombia, Chile, and Mexico; Western Countries: Belgium, Canada, Israel, Italy, Netherlands, Spain, and USA),
- Race (Caucasian/White, the others),
- Baseline pre-BD FEV₁ ($\leq 1.75\text{L}$, $> 1.75\text{L}$),
- baseline predicted FEV1 % ($<60\%$, $\geq 60\%$),
- ACQ-5 (≤ 2 , >2),
- Weight (< 70 , $\geq 70 - < 90$, ≥ 90 kg),
- BMI (<25 , $\geq 25 - <30$, ≥ 30 kg/m²),
- Smoking history (Former, Never),
- Ongoing atopic medical history (Yes, No),
- Age of onset of asthma (<18 , $18-40$, >40 years),
- Number of severe asthma exacerbation within 1 year before Visit 1 (≤ 1 , >1)
- Baseline eosinophil level subgrouping 1 (<0.15 Giga/L or ≥ 0.15 Giga/L)
- Baseline eosinophil level subgrouping 2 (<0.3 Giga/L or ≥ 0.3 Giga/L)

An ANCOVA model incorporating subgroup-by-treatment interaction will be built for each subgroup factor. The model will include all the covariates in the main statistical model plus the subgroup variable (if not one of the covariates adjusted in the main model) and the subgroup-by-treatment interaction. A p-value for the test of interaction will be provided. If the subgroup factor

has more than two levels, then an F-test will be performed to evaluate the overall significance of all interaction tests.

Forest plots of treatment difference between dupilumab and placebo in percent reduction of OCS dose at Week 24 and corresponding CIs for subgroups will be provided.

If there are any missing data in the primary efficacy endpoint, subgroup analysis will be performed based on imputed datasets generated from the primary missing data handling approach. Rubin's rule will be used to combine estimated interaction effect from all the imputations.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Analysis of the key secondary efficacy endpoints

The proportion of patients achieving a reduction of 50% or greater in their OCS dose at Week 24 compared with baseline and the proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24 will be analyzed using a logistic regression model. The model will use the binary status of whether or not a patient achieved the corresponding OCS reduction criterion as the response variable, and treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (<0.15 Giga/L or ≥0.15 Giga/L) as covariates. The number and proportion of patients achieving the OCS dose reduction criterion of the efficacy endpoint will be summarized by treatment group. The adjusted probabilities of achieving the reduction in the two treatment groups and the estimated odds ratio between dupilumab and placebo groups, its 95% CI and associated p-value will be provided.

```
proc genmod data=ocsdata descending;  
  class trt01pn eosbgp2n cntygr1;  
  model resp = basedose eosbgp2n cntygr1 trt01pn  
    / dist=bin link=logit type3;  
  estimate 'Odds ratio Dupilumab vs Placebo' trt01pn -1 1 /exp;  
run;
```

2.4.4.2.1.1 Missing data handling

If there are any missing data in the percent reduction in OCS at Week 24, the following missing data handling approaches will be used.

Primary approach – pattern mixture model by multiple imputation

The imputed datasets from the primary missing data handling approach for the primary efficacy endpoint will be used, and the binary response status of each patient with missing endpoint will be determined from the imputed percent reduction at Week 24. The logistic regression model described above will be applied to analyze each imputation dataset, and Rubin's rule will be applied to combine results. Of note, Rubin's rule will be applied on log odds ratio (the regression coefficient of the treatment variable) whose posterior distribution given data can be better

approximated by normal distribution. The estimated odds ratio and 95% CI of the odds ratio will be obtained by taking anti-log transformation on the corresponding statistics for the log odds ratio.

Sensitivity analysis

Pattern mixture model by control-based multiple imputation

The imputed datasets using the pattern mixture model by control-based multiple imputation for the primary efficacy endpoint will be used, and the binary response status of each patient with missing endpoint will be determined from the imputed percent reduction at Week 24. The analysis method is the same as the primary missing data handling approach for the key secondary endpoints.

Patients dropped out from study considered as non-responders

The patients who drop out from study will be considered as non-responders. The main logistic regression model will be applied to the complete dataset.

2.4.4.2.1.2 Other supportive analysis

On treatment analysis

This analysis will only be performed when there are any patients who permanently discontinue treatment and still stay in the study for the remaining visits. The imputed data from the on-treatment analysis for the primary efficacy endpoint will be used. The analysis method is the same as the primary missing data handling approach for the key secondary endpoints.

2.4.4.2.2 *Analysis of the absolute reduction of OCS dose*

The absolute reduction of OCS dose at Week 24 will be analyzed using an ANCOVA model in the same manner as for the primary endpoint. The same covariates will be incorporated. If there are any missing data in the endpoint, the imputed datasets generated from the primary missing data handling approach for the primary efficacy endpoint will be used, and the second and third step of the primary missing data handling approach will be applied to analyze data of absolute reduction of OCS dose and combine results from each imputation.

2.4.4.2.3 *Analysis of proportion of subjects achieving a certain reduction of OCS dose*

The proportion of patients achieving a certain reduction of OCS dose will be analyzed in the same manner as the key secondary endpoints. The model will use the binary status of whether or not a patient achieves the prespecified OCS dose reduction criterion as the response variable, and the treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (<0.15 Giga/L or ≥ 0.15 Giga/L) as covariates. The estimated odds ratio between dupilumab and placebo groups, its 95% CI and associated p-value will be provided. Of note, patients in the efficacy population with a baseline optimized OCS dose at 35mg/day will be excluded from the analysis of the proportion of patients achieving a reduction of OCS dose to

0 mg/day at Week 24, because per protocol, 0mg/day is not achievable for these patients. If there is any missing data at Week 24, the primary missing data handling approach for the key secondary endpoints will be applied.

2.4.4.3 Multiplicity issues

The primary endpoint will be tested at a 2-sided 5% significance level. If the primary endpoint meets the significance level, the following secondary endpoints will be tested at a 2-sided 5% significance level in the hierarchical order defined below:

- Proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24 while maintaining asthma control;
- Proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24 while maintaining asthma control;
- Proportion of patients achieving their maximum possible reduction of OCS dose per protocol at Week 24 while maintaining asthma control;
- Proportion of patients no longer requiring OCS at Week 24 while maintaining asthma control.

No multiple testing adjustment will be performed for the other efficacy endpoints.

2.4.4.4 Additional efficacy analyses

2.4.4.4.1 Analysis of annualized event rate

The annualized event rates during the 24-week Treatment Period, including the rate of severe asthma exacerbation and rate of exacerbations requiring hospitalization or ER visit will be analyzed using negative binomial regression models. The model corresponding to each type of event will include the total number of the events occurring during the 24 weeks as the response variable, and the treatment groups, baseline optimized OCS dose strata, regions (pooled countries), number of the events within 1 year prior to the study, and baseline eosinophil level subgroups (<0.15 Giga/L, ≥0.15 Giga/L) as covariates. Log-transformed treatment duration will be the offset variable. Annual rates on the two treatment arms, the ratio of the rates, 95% confidence intervals for the ratio and a p-value for testing treatment difference in the event rate will be provided. Sample SAS code:

```
proc glimmix data=event;
  class ocsblg2n eosbgp2n trt01pn cntygr1;
  model numevents= ocsblg2n eosbgp2n cntygr1 asmanum trt01pn
    /offset=logdur dist=negbin link=log solution;
  estimate 'rate ratio Dupilumab vs Placebo' trt01pn -1 1/alpha=0.05
exp;
  lsmeans trt01pn/alpha=0.05 cl ilink cov;
run;
```


For patients who permanently discontinue the treatment but stay in the study, the events which occurred up to Visit 11 (Week 24) will be included. For all patients stay in the study till Visit 11, the treatment duration is from randomization to Visit 11. For patients who withdraw from study prior to Visit 11, events that occurred up to the last contact date will be analyzed, and the last contact date will be used to calculate the offset variable.

Analysis of the asthma exacerbations requiring hospitalization or ED visits will only be performed if sufficient numbers of patients have multiple exacerbations requiring hospitalization or ED visit for the model to converge satisfactorily.

2.4.4.4.2 Analysis of time to event variables

Time to event parameters, including time to first severe asthma exacerbation and time to first exacerbation requiring hospitalization or ED visit will be analyzed using a Cox regression model with the time to event as the response variable, and the treatment groups, baseline optimized OCS dose strata, regions (pooled countries), number of the events within 1 year prior to the study, and baseline eosinophil level subgroups (<0.15 Giga/L, ≥ 0.15 Giga/L) as covariates. Hazard ratio between treatment and placebo will be estimated with 95% CI. The Kaplan-Meier (K-M) method will be used to estimate the probability of patients with at least one event up to Weeks 12 and 24 specific to each treatment group. Sample SAS code for the Cox regression:

```
proc phreg data=ttevent;  
    class ocsblg2n eosbgp2n trt01pn cntygr1 /param=glm;  
    model aval*CNSR(1) = ocsblg2n eosbgp2n cntygr1 asmanum trt01pn;  
    contrast 'Hazard ratio Dupilumab vs Placebo'  
        trt01pn -1 1/estimate=exp;  
run;
```

The calculation of time has been specified in [Section 2.1.3.2.2.1.2](#). For patients who discontinue the study prior to Week 24, events that occurred up to the last contact date will be considered. If there is no event observed, the last contact date will be used to calculate a free of event duration.

2.4.4.4.3 Analysis of change/ percentage change from baseline for other continuous variables

The change and/or percentage change from baseline for other continuous variables, including pre-BD FEV₁, post-BD FEV₁, FEV₁ reversibility, percent predicted FEV₁, PEF, FVC, FEF_{25-75%}, ACQ-5, asthma symptom scores, nocturnal awakenings, number of puffs/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief, AQLQ, EQ-5D-5L, and HADS, will be analyzed using a mixed effect model with repeated measures (MMRM) approach. For a continuous variable, the corresponding MMRM model will include the change/percent change from baseline as response variables, and factors (fixed effects) for the treatment groups, baseline optimized OCS dose strata, regions (pooled countries), baseline eosinophil level subgroups (<0.15 Giga/L, ≥ 0.15 Giga/L,) visits, treatment-by-visit interaction, the corresponding baseline value of the endpoint, and baseline-by-visit interaction. Additionally, age, gender, and height at baseline will be included as covariates in the models for spirometry variables but not for

other variables. 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. For each endpoint, all visits up to Visit 11 where there is a scheduled measurement will be included in analysis. For ACQ-5, only those questionnaires assigned to each visit will be included. For the daily measurements, the periodical average specified in [Section 2.5.2](#) will be performed.

For each endpoint, descriptive statistics including number of patients, mean, standard error and LS mean for each treatment group will be obtained for the visits specified in [Section 2.1.3.2.2](#). Difference in LS mean, its 95% CI and a nominal p-value with Kenward-Roger adjustment will be provided for comparison between dupilumab and placebo groups. For patients who dropout from study prior to Visit 11 (Week 24), missing data will not be imputed. Provided below is sample SAS code for analyzing change from baseline in pre-BD FEV₁ and estimating treatment difference at Week 24.

```
proc mixed data=adsd.adre method=reml;
  where paramcd='FEV1' and avisitn ge 4 and avisitn le 11 and
    anl01fl='Y' and dtype ne 'LOCF' and ittfl='Y';
  class subjid sex ocsblg2n eosbgp2n trt01pn avisitn cntygr1;
  model chg = trt01pn sex age height ocsblg2n eosbgp2n cntygr1
    avisitn trt01p*avisitn base base*avisitn/ddfm=kr residual;
  repeated avisitn/type=un subject=subjid;
  lsmeans trt01pn*avisitn /cl;
  estimate 'Diff Dupilumab vs Placebo at Week 24'
    trt01pn -1 1 trt01pn*avisitn 0 0 0 0 0 0 0 -1
    0 0 0 0 0 0 0 1/ cl;

run;
```

For the ACQ-5 score, a supportive analysis of the proportion of patients reaching MCID will be performed using logistic regression models at each of the time points analyzed for the endpoint. At each time point, the patients with change from baseline in ACQ-5 ≤ -0.5 at the time point will be considered as responders, while the patients with change from baseline in ACQ-5 > -0.5 or with missing value at the time point will be considered as non-responders. The model will include treatment groups, baseline optimized OCS dose strata, regions (pooled countries), baseline eosinophil level subgroups (<0.15 Giga/L or ≥ 0.15 Giga/L), and baseline ACQ-5 score as covariates. The estimated odds ratio between dupilumab and placebo groups, its 95% CI and associated p-value will be provided.

Change from baseline in airway hyperresponsiveness at Week 24 will be summarized with descriptive statistics including number of patients, mean, and standard error by treatment groups. If the number of subjects with available data is small, then a listing of the endpoint data instead of the summary statistics will be provided.

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 last available value prior to 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 (PCSA version dated May 2014 [[Appendix J](#)]).
- 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.
- 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 postbaseline (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 a safety analysis visit window defined in [Section 2.5.4](#).

2.4.5.1 Analyses of adverse events

Generalities

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.

For tables presented by SOC and PT, SOC's will be sorted by the internationally agreed SOC order and PTs within SOC's will be sorted by decreasing incidence in the dupilumab arm.

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 SOC, 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 to IMP 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
- Listing of all treatment-emergent adverse events

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
- Listing of all treatment-emergent serious adverse events

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 the number (%) of patients sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC

Analysis of all treatment-emergent adverse event(s) of special interests 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 events,
 - Number (%) of patients with any of the specific TEAE
 - Number (%) of patients with any of the specific serious AE (regardless of treatment emergent status)

- Number (%) of patients with any of the specific treatment emergent serious AE
- Number (%) of patients with any of the specific AE leading to death
- Number (%) of patients with any of the specific TEAE leading to permanent study drug discontinuation
- Number (%) of patients with any of the specific TEAE by maximum intensity, corrective treatment, and final outcome
- Number of the specific TEAE adjusted by exposure duration
- All of the specific TEAE, by PT, showing the number (%) of patients, sorted by decreasing incidence of PT
- K-M estimates of cumulative incidence of the specific TEAE at Weeks 12 and 24 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 pretreatment serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment serious 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

The above pretreatment AEs will be presented as listings if there are only a few of them.

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, post-study) 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
- Deaths in nonrandomized patients or in randomized but not treated patients will be summarized separately.

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 post baseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For each continuous laboratory variables listed in [Section 2.1.4.3](#), mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) 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 J](#)) 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.

Drug-induced liver injury

If there is imbalance in the incidence of liver-related adverse events across the treatment groups, the following 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 ($>3 \times \text{ULN}$) and total bilirubin elevation ($>2 \times \text{ULN}$) (time to first observation of ALT $> 3 \times \text{ULN}$ or total bilirubin $> 2 \times \text{ULN}$, 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, creatine phosphokinase, serum creatinine, 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 the 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 the 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 analysis

2.4.6.1.1 Analyses of serum concentrations of dupilumab

Serum concentrations of dupilumab will be summarized in the PK population using arithmetic and geometric means, SD, standard error of the mean, coefficient of variation, minimum, median and maximum by visit. If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. For dupilumab-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 not treated by dupilumab, concentration values 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 negative in ADA assay at all time points analyzed
- Number (%) of patients positive in ADA assay at any time points analyzed
- Number (%) of patients with pre-existing immunoreactivity
- Number (%) of patients with treatment-emergent ADA response
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent ADA response
- Number (%) of patient with transient treatment-emergent ADA response
- Number (%) of patients with persistent treatment-emergent ADA response

- Number (%) of patients with indeterminate treatment-emergent ADA response
- Number (%) of patients with treatment-boosted ADA response
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-boosted ADA response , and patients with persistent, indeterminate and transient ADA response
- 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 response
- Number (%) of patients with ADA status (negative or positive in the ADA assay) at ADA time points analyzed
- Number (%) of patients with neutralizing antibody status (negative or positive in the neutralizing antibody assay) for the ADA positive patients at ADA time points analyzed
- The summary statistics (median, Q1, Q3, minimum and maximum) of ADA titers at ADA time points analyzed
- Listing of ADA peak titer levels and neutralizing antibody status at time points analyzed for patients positive in the ADA assay
- Number(%) of patients with neutralizing antibody status

Kinetics of treatment-emergent ADA positive response

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

Plot of percentage of patients with treatment-emergent ADA positive response at time points analyzed will be provided by each treatment group.

Impact of ADA on PK, clinical efficacy, and clinical safety

Associations between the PK, efficacy and safety endpoints and the following ADA categories will be explored:

- Treatment-emergent +treatment-boosted ADA response
- Pre-existing immunoreactivity + negative at all time points
- Treatment-emergent ADA response
- Persistent treatment-emergent ADA response
- Transient treatment-emergent ADA response
- Indeterminate treatment-emergent ADA response
- Treatment-boosted ADA response
- Pre-existing immunoreactivity
- Negative at all time points

- Neutralizing antibody positive
- Neutralizing antibody negative

Impact of ADA on PK

Associations between the ADA categories and serum concentration of dupilumab may be explored for the dupilumab dosed group. Plot of serum concentration of functional dupilumab by visit will be provided by the ADA categories for the dupilumab dosed group.

Impact of ADA on clinical efficacy

Associations between the ADA categories and the primary efficacy endpoint may be explored for the dupilumab dosed group by generating descriptive statistics of the endpoint (numbers of patients, means, and standard errors) by the ADA categories.

Impact of ADA on clinical safety

Associations between the ADA categories and safety may be explored by providing the number (n) and percentage (%) of patients with the following events by the ADA categories:

- Injection site reaction HLT
- Hypersensitivity reactions (medically reviewed)
- Anaphylactic reactions
- Overall incidence of severe TEAEs
- Overall incidence of serious TEAEs
- Overall incidence of TEAEs leading to permanent treatment discontinuation
- Additionally, the above events occurred on or after the first identified ADA-positive response after the first dose will be summarized for patients with treatment-emergent ADA.

2.4.6.2 Pharmacodynamic/genomic analyses

PD biomarkers will be analyzed in the safety population. Baseline values will be the last value collected prior to the first IMP.

For all parameters including antigen-specific IgEs with ≥ 0.35 kUA/L incidence of greater than 25% at baseline, levels at each visit, absolute changes from baseline and percent changes from baseline will be summarized in descriptive statistics (mean, SD, median, Q1, Q3, min, max) and plotted (mean \pm standard error of the mean) by treatment group and time point. For summarizing and plotting antigen-specific IgEs, only those individuals with a baseline value ≥ 0.35 kUA/L will be included in the calculation of descriptive statistics.

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 ≥ 0.35 kUA/L antigen-specific IgE, with ≥ 0.35 kUA/L for only one antigen, and with ≥ 0.35 kUA/L 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.

Additionally, descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) of biomarkers at baseline will be summarized for the ITT population. For randomized but not treated patients, baseline value will be the last value collected prior to the randomization.

For the PD endpoints collected only for subjects enrolled in selected sites in Canada, if the number of subjects with available data is small, then listings of the levels of the endpoints instead of the summary statistics will be provided.

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

2.4.7 Analyses of quality of life/health economics variables

Change from baseline in ACQ-5, AQLQ, EQ-5D-5L, SNOT-22, and HADS are analyzed as efficacy endpoints as described in [Section 2.4.4.4.3](#).

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:

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

Age of asthma onset is calculated as:

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

- Time since first diagnosis of asthma (years) is calculated as:
 - $(\text{Year of randomization} - \text{Year of first diagnosis of asthma}) + (\text{month of randomization} - \text{month of first diagnosis of asthma})/12$
- Time since cessation of smoking is calculated as:
- $(\text{Year of randomization} - \text{Year of cessation}) \times 12 + (\text{month of randomization} - \text{month of cessation})$
- Time since last asthma exacerbation (months) is calculated as:

$$(\text{Year of randomization} - \text{Year of last asthma exacerbation}) \times 12 + (\text{month of randomization} - \text{month of last asthma exacerbation})$$

BMI is calculated as:

$$\text{Weight in kg} / (\text{height}^2 \text{ in meters})$$

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

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

Renal function formulas

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

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

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

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

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

$$\text{GFR (mL/min/1.73 m}^2\text{)} = k \times \text{height (cm)} / \text{sCr (mg/dL)],}$$

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 efficacy variables

OCS dose handling conventions

The percentage reduction of OCS dose at the visits will be calculated as (optimized OCS dose at baseline – OCS dose at the visit)/optimized OCS dose at baseline $\times 100\%$. A negative percent reduction value is possible if at any visit the prescribed dose is higher than the baseline.

Calculation of salbutamol/albuterol or levosalbutamol/levalbuterol puffs/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 puffs per day is the sum of number of puffs recorded in one diary day

including the evening diary and the following day's morning diary. If one of the values is missing for a diary day, then the data for the diary day is considered missing.

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 time point 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 puffs/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
Week 2	Diary day 2-15	Diary day 1-14	Diary day 1-14
Week 4	Diary day 16-29	Diary day 15-28	Diary day 15-28
Week 6	Diary day 30-43	Diary day 29-42	Diary day 29-42
Week 8	Diary day 44-57	Diary day 43-56	Diary day 43-56
Week 12	Diary day 58-85	Diary day 57-84	Diary day 57-84
Week 16	Diary day 86-113	Diary day 85-112	Diary day 85-112
Week 20	Diary day 114-141	Diary day 113-140	Diary day 113-140
Week 24	Diary day 142-169	Diary day 141-168	Diary day 141-168
Week 28	Diary day 170-197	Diary day 169-196	Diary day 169-196
Week 32	Diary day 198-225	Diary day 197-224	Diary day 197-224
Week 36	Diary day 226-253	Diary day 225-252	Diary day 225-252

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 1 includes the evening diary on day 1 and the morning diary on day 2.

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) \times (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 intake 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 as a prior and a 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 intake 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 $> \text{ULN}$ if $\text{ULN} \geq 0.5$ GIGA/L. When ULN is missing, the value 0.5 should be used.

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

2.5.4 Windows for time points

For the safety assessments, 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 3, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 3 time window.

Table 8 – Time window for safety endpoints

Visit	Target Day	Time windows for				
		Vital signs	Clinical lab testing, Urine pregnancy test	Serum pregnancy test	ECG, Urinalysis, Serum immunoglobulins	Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibody
Visit 1 (Week -8 to -3)	-56 to -21			1-		1-
Visit 3 (Week 0)	1	1-	1-		1-	
Visit 4 (Week 2)	15	1+-21				
Visit 5 (Week 4)	29	22-35	1+-42			
Visit 6 (Week 6)	43	36-49				
Visit 7 (Week 8)	57	50-70	43-70			
Visit 8 (Week 12)	85	71-98	71-98		1+-126	
Visit 9 (Week 16)	113	99-126	99-126			
Visit 10 (Week 20)	141	127-154	127-154			1+
Visit 11 (Week 24)	169	155-182	155-210		127-210	
Visit 12 (Week 28)	197	183-210				
Visit 13 (Week 32)	225	211-238				
Visit 14 (Week 36)	253	>238	>210		>210	

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

For the OCS dose used for efficacy assessment, the baseline dose and the final dose at Week 24/Visit 11 are recorded in the corresponding CRF pages. OCS doses at Visits 5, 7, 8, 9, and 10 during the treatment period will be obtained from the prescribed dose recorded in diary based on the date of OCS adjustments recorded in the 'Oral Corticosteroid Dose Adjustment - Treatment Phase' eCRF pages associated with each visit. If it is recorded that there was no dose adjustment for a visit, the dose of the previous visit will be considered maintained for the current visit and thus carried forward. For patients permanently discontinue treatment before Week 24/Visit 11, any dose adjustment recorded at the Early Treatment Discontinuation visit will be assigned to the regular visit after the last on treatment visit. In case there were more than one adjustments associated with one visit, the last dose will be used for the visit.

For the other efficacy assessments, 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. [Table 9](#) assigns all scheduled measurements of efficacy endpoints for visits to the appropriate visit window. The ACQ-5 questionnaires planned for the weeks between visits will not be assigned to the visits. 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.

Table 9 – Time window for efficacy variables

Visit	Target Day	Time windows for		
		Spirometry, ACQ-5, ACQ-7	Post-bronchodilator FEV ₁ , AQLQ(S), EQ-5D-5L, HADS, SNOT-22	Airway hyperresponsiveness (selected study sites within Canada)
Visit 3 (Week 0)	1	-14-1-	1-	1-
Visit 4 (Week 2)	15	1+-21		
Visit 5 (Week 4)	29	22-35		
Visit 6 (Week 6)	43	36-49		
Visit 7 (Week 8)	57	50-70		
Visit 8 (Week 12)	85	71-98	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	1+
Visit 12 (Week 28)	197	183-210		
Visit 13 (Week 32)	225	211-238		
Visit 14 (Week 36)	253	>238	>210	

1-: up to min(1st dose date/time, end of randomization date); 1+: after min(1st dose date/time, end of randomization date).

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 3, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 3 time window.

Table 10 – Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target day	Time windows for					
		Blood eosinophil	Exhaled NO	Systemic drug concentration	Anti-drug antibodies	Eotaxin-3, total IgE, TARC Antigen-specific IgE, periostin	Sputum ILC2 and CD34 cells and sputum and blood cytokines
Visit 3 (Week 0)	1	<-1-	-14-1-	<-1-	1-	1-	1-
Visit 4 (Week 2)	15		1+-21				
Visit 5 (Week 4)	29	1+-42	22-35	1+-42		1+-56	
Visit 6 (Week 6)	43		36-49				
Visit 7 (Week 8)	57	43-70	50-70	43-70			
Visit 8 (Week 12)	85	71-98	71-98	71-126	1+-126	57-112	
Visit 9 (Week 16)	113	99-126	99-126				
Visit 10 (Week 20)	141	127-154	127-154			113-154	
Visit 11 (Week 24)	169	155-210	155-182	127-210	127-210	>154	1+-210
Visit 12 (Week 28)	197		183-210				
Visit 13 (Week 32)	225		211-238				
Visit 14 (Week 36)	253	>210	>238	>210	>210		>210

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

For not treated but randomized patients: 1-: up to randomization date; 1+: after randomization date

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the by-visit summaries, and will be used for 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 analyses:

- East Europe: Hungary, Poland, Romania, Russia, and Ukraine;
- Latin America: Argentina, Brazil, Chile, Colombia, and Mexico;
- Western Countries: Belgium, Canada, Israel, Italy, Netherlands, Spain, and USA

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

There is no interim analysis planned for this study. The primary analysis is planned when the last patient completes Week 24 visit or discontinues from the study before week 24.

4 DATABASE LOCK

The database is planned to be locked at approximately 30 days after last patient completes Week 24 visit or discontinues from the study before week 24. Additional data between the database lock and the 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

1. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med*. 2009;360:985-93.
2. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189-97.
3. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coateset A, et al. Standardization of spirometry. Series “ATS/ERS TASK FORCE: Standardization of Lung Function Testing” Edited by Brusasco V, Crapo R, and Viegi G. *Eur Respir J*. 2005;26:319-38.
4. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99:553-8.
5. EUroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
6. Li, KH, Meng, XL, Raghunathan, TE, Rubin, DB. Significance levels from repeated p-values with multiply-imputed data. *Statistica Sinica* 1991;1:65-92.