

AMENDED CLINICAL TRIAL PROTOCOL 02

Incorporating Protocol Amendment 05

COMPOUND: dupilumab / SAR231893

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

STUDY NUMBER: PDY14192

VERSION DATE / STATUS: 23-Nov-2016 / Approved

STUDY NAME: EXPEDITION

CLINICAL STUDY DIRECTORS: [REDACTED], [REDACTED] and [REDACTED]
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CLINICAL TRIAL SUMMARY

COMPOUND: dupilumab	STUDY No: PDY14192 STUDY NAME: EXPEDITION
TITLE	An exploratory, randomized, double-blind, placebo-controlled study of the effects of dupilumab on airway inflammation of adults with persistent asthma
INVESTIGATOR/TRIAL LOCATION	North America and Europe
PHASE OF DEVELOPMENT	2a
STUDY OBJECTIVE(S)	<p>Main Objective</p> <ul style="list-style-type: none"> To evaluate the effect of dupilumab, compared to placebo, on airway inflammation in patients with persistent asthma. <p>Additional Objective</p> <ul style="list-style-type: none"> To assess safety, tolerability and immunogenicity of dupilumab compared to placebo. <p>Exploratory Objectives</p> <ul style="list-style-type: none"> To explore the effects of dupilumab, compared to placebo, in patients with persistent asthma on: <ul style="list-style-type: none"> Pulmonary function and asthma control, T-helper cell 2 (Th2)-associated biomarkers in peripheral blood To explore the pharmacokinetic-pharmacodynamic relationship of the inflammatory biomarkers. To evaluate the relationship between the baseline characteristics of patients (eg, demographics, clinical status, clinical lab values, biomarkers, and genetic profiles) and treatment responses.
STUDY DESIGN	<ul style="list-style-type: none"> Phase 2a, multicenter, exploratory, randomized, double-blind, placebo-controlled, parallel group study of repeated doses of dupilumab administered subcutaneously (SC) in patients with persistent asthma. During the study, patients will undergo 2 bronchoscopy procedures for the collection of bronchial biopsy, brushing and lavage samples before treatment and at the end of the treatment period. Dupilumab is used as add-on therapy to inhaled corticosteroid (ICS) in combination with long-acting beta-agonists (LABA). The clinical trial consists of three parts: <ul style="list-style-type: none"> Screening 5 weeks (and potentially additional up to 7 days for confirmation of eligibility or scheduling of bronchoscopy) Randomized Treatment Period (12 weeks) Post-Treatment Period (12 weeks) for patients not participating in the open label extension study Eligible patients, who complete the treatment period, including the end-of-treatment assessments, will be offered the opportunity to participate in an open label extension (OLE) study with dupilumab.

<p>STUDY POPULATION</p> <p>Main selection criteria</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Male and female adults with a physician diagnosis of asthma for ≥ 12 months (Global Initiative for Asthma, GINA, 2015 Guidelines). • Existing treatment with medium to high dose ICS (≥ 250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a LABA for at least 3 months with a stable dose ≥ 1 month prior to Visit 1. <ul style="list-style-type: none"> - Existing treatment with a third asthma controller (eg, long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA]) for at least 3 months with a stable dose ≥ 1 month prior to Visit 1 is allowed. • Pre-bronchodilator forced expiratory volume in 1 second (FEV₁) 55 to 85% of predicted normal at Visit 1. • Signed informed consent. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Patients < 18 years or > 65 years old. • Fractional exhaled nitric oxide (FeNO) < 26 ppb at Visit 1. • Chronic obstructive pulmonary disease or other lung diseases (eg, idiopathic pulmonary fibrosis, eosinophilic granulomatosis with polyangiitis [Churg-Strauss Syndrome], etc) which may impair lung function. • A patient who experiences an asthma exacerbation that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to Visit 1. • Evidence of lung disease(s) other than asthma, either clinical evidence or imaging (chest X-ray, computed tomography [CT], magnetic resonance imaging [MRI]) within 12 months of Visit 1 or at the screening visit, as per local standard of care. • A patient who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to Visit 1. • Previous smoker (smoking history > 10 pack-years) or current smoker (within 6 months prior to Visit 1). • Comorbid disease that might interfere with the evaluation of IMP or conduct of study procedures (eg, bronchoscopy). • Anti-immunoglobulin E (IgE) therapy (omalizumab) or any other biologic therapy within 130 days of Visit 1. • Exposure to another investigative study medication within a time period prior to Visit 1 that is less than 5 half-lives of the study medication. • Treatment with systemic (oral or injectable) corticosteroids within 28 days of Visit 1.
<p>Total expected number of patients</p>	<p>Approximately 42 patients to be randomized (21 per group) with at least 21 patients receiving treatment with high dose ICS and no more than 8 patients with blood eosinophils < 150 cells/μL.</p>

STUDY TREATMENT(s)	
Investigational medicinal product(s) Formulation	Dupilumab (SAR231893/REGN668) or matching placebo (randomization 1:1) <ul style="list-style-type: none"> Dupilumab: 150 mg/mL in pre-filled syringe to deliver 300 mg in 2 mL. Placebo: Pre-filled syringe to deliver 2 mL.
Route(s) of administration	Subcutaneous (SC)
Dose regimen	Highest dose to be used in Phase 3: 300 mg SC every 2 weeks (q2w) Patients are treated for 12 weeks, receiving a loading dose of 600 mg on Day 1 followed by five 300 mg q2w SC administrations of dupilumab or matching volumes of placebo.
Noninvestigational medicinal product(s) (if applicable) Formulation	Inhaled corticosteroid in combination with other controllers <ul style="list-style-type: none"> Patient to continue stable medication with formulation as per label Reliever Medication: albuterol/salbutamol or levalbuterol/levosalbutamol <ul style="list-style-type: none"> Formulation as per label Prednisone or Prednisolone <ul style="list-style-type: none"> Tablets or Capsules
Route(s) of administration	Oral inhalation, nebulizer: ICS, ICS combination, albuterol/salbutamol; For other background controllers: according to label Prednisone or Prednisolone: oral
Dose regimen	Inhaled corticosteroid in combination with other controllers <u>Screening Period</u> Prior to and during the Screening Period, patients must be on a stable dose of medium to high dose ICS in combination with LABA. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1 (patients requiring oral steroids as controller medication or biologics are excluded). <u>Randomized Treatment Period</u> During this period, patients will continue taking their controller medication(s). <u>Post-treatment Period</u> Upon completing the Randomized Treatment Period, patients will continue treatment with the controller medication regimen and dose used during the randomized period, which could be adjusted based on the medical judgment of the Investigator of the patients' asthma control status. 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.

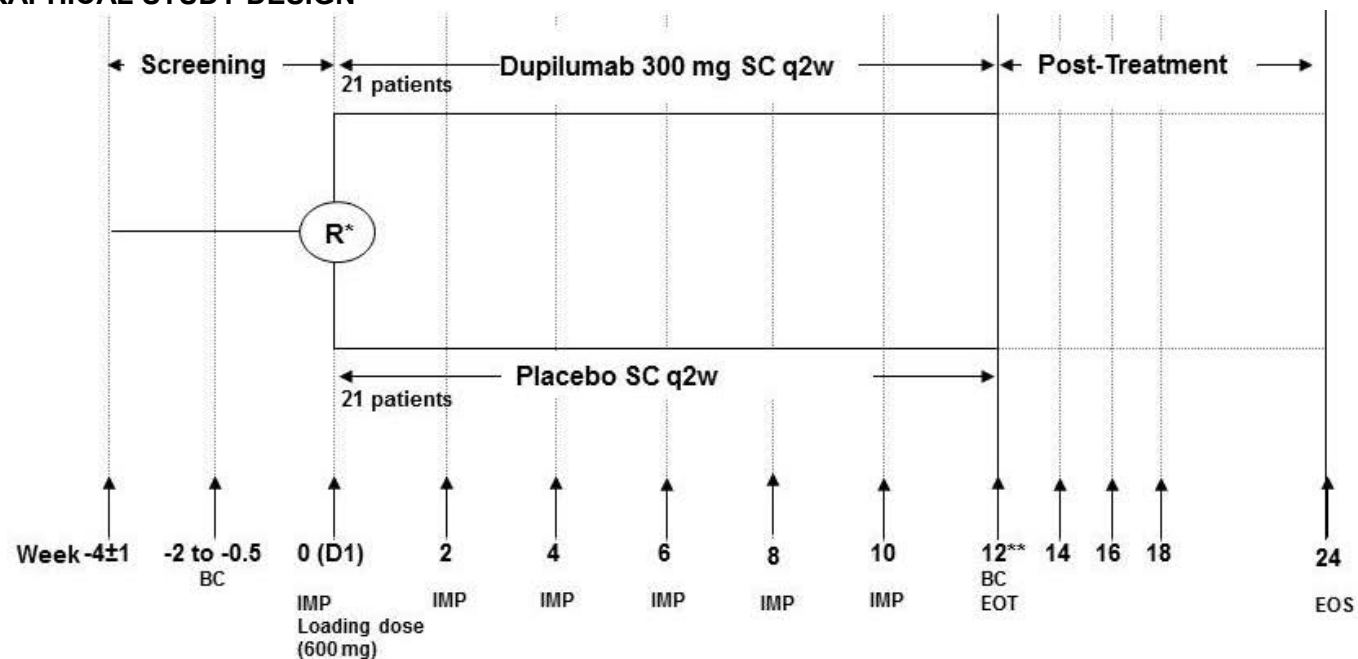
	<p>Prednisone or Prednisolone</p> <p>Following the bronchoscopy procedure, patients will receive 40 mg daily for 3 days to prevent procedure-induced asthma exacerbations. Prednisone/prednisolone treatment may be extended to 5 days as clinically indicated.</p>
ENDPOINT(S)	<p>Main Endpoints:</p> <ul style="list-style-type: none"> Change from baseline in numbers of the following inflammatory cells in the bronchial submucosa (per square millimeter) at 12 weeks: <ul style="list-style-type: none"> Eosinophils, Mast cells, Total T-lymphocytes, T-helper lymphocytes. Change from baseline in mucin-stained area in the bronchial mucosa (per square millimeter) at 12 weeks <p>Additional Endpoints:</p> <p><u>Pharmacodynamics:</u></p> <ul style="list-style-type: none"> Absolute change from baseline in fractional exhaled nitric oxide (FeNO) at 12 weeks. Absolute change from baseline in average FeNO from 6 to 12 weeks. <p><u>Pharmacokinetics:</u></p> <ul style="list-style-type: none"> Serum functional dupilumab concentrations. <p><u>Safety:</u></p> <ul style="list-style-type: none"> Adverse events (AE), Vital signs, Physical examination, Electrocardiogram (ECG), Clinical laboratory tests. Anti-drug antibodies (ADA). <p>Exploratory Endpoints and Analyses:</p> <p><u>Efficacy:</u></p> <ul style="list-style-type: none"> Lung function will be assessed by the following: <ul style="list-style-type: none"> Change from baseline in spirometry including forced expiratory volume (FEV₁), Change from baseline in AM/PM Peak Expiratory Flow (PEF). Asthma control will be assessed by the following: Patient-reported symptoms: Change from baseline in Asthma Control Questionnaire 5-question version (ACQ-5) score. <p><u>Pharmacodynamics / Pharmacogenetics / Mechanistic Analyses:</u></p> <ul style="list-style-type: none"> Peripheral blood and bronchoscopy samples, including bronchoalveolar lavage fluid (BALF), bronchial brushings and bronchial biopsies, will be collected and archived up to 15 years. Peripheral blood and bronchoscopy samples will be assessed for Th2-related biomarkers and other biomarkers of inflammation. RNA will be isolated from bronchoscopy samples to evaluate change from baseline in relative gene expression.

	<ul style="list-style-type: none"> RNA will be isolated from whole blood to evaluate baseline gene expression, including eosinophilic and type 2 / Th2-related genes. Additional inflammatory cell counts in bronchial epithelium and submucosa and basement membrane thickness will be assessed by immunohistochemistry (IHC)/histology. Inflammatory cell counts in BALF will be assessed at baseline and 12 weeks. Exploratory genetic analysis of blood deoxyribonucleic acid (DNA).
ASSESSMENT SCHEDULE	See Section 1 for details
STATISTICAL CONSIDERATIONS	<p>Sample size determination:</p> <p>Approximately 42 patients will be randomized to achieve 21 completers per group. The statistical power of the study is estimated based on the additional pharmacodynamics endpoint of FeNO as no historical data is available for the main endpoints of bronchial submucosal inflammatory cells. With 21 completers per group, the study will have an 80% power to detect a difference of 25 ppb in the change from baseline in FeNO at Week 12 between SAR231893 and placebo, assuming a pooled SD of 32, and with a T-test at 1-sided alpha=0.05.</p> <p>A patient who received treatment and prematurely ends his/her treatment prior to Week 12 may be replaced in order to have a sufficient number of patients with adequate bronchial biopsies to assess the main endpoints.</p> <p>Analysis Population:</p> <p><u>Pharmacodynamics</u></p> <p>For the main PD endpoints in bronchial submucosa, the PD population will consist of all randomized patients who underwent baseline and Week12/end-of-treatment (EOT) bronchoscopies and have adequate biopsies for analysis at both baseline and end-of-treatment.</p> <p><u>Pharmacokinetics</u></p> <p>The PK population will consist of all patients in the safety population with at least one post dose, non-missing and eligible serum concentration data. Patients will be analyzed according to the treatment actually received.</p> <p><u>Safety</u></p> <p>All patients who were exposed to study treatment, regardless of the amount of treatment administered, will be included in the safety population.</p> <p><u>ADA</u></p> <p>The ADA population will consist of all patients in the safety population with at least one qualified ADA result in the ADA assay following the first dose of the study medication. Patients will be analyzed according to the treatment actually received.</p> <p>Main Analysis:</p> <p>The main endpoints, change from baseline in the number of airway submucosal inflammatory cells per surface airway of basal lamina (cells/mm²) and mucin in the bronchial mucosa, will be analyzed by analysis of covariance (ANCOVA) with fixed terms for treatment, stratification factors of region and ICS dose, and airway submucosal inflammatory cells per surface airway of basal lamina (cells/mm²) and mucin in the bronchial mucosa at baseline as</p>

	<p>covariates. An estimate and two-sided 90% confidence interval (CI) for the difference in treatment mean changes will be calculated from the model. No multiplicity adjustment will be made for the main analyses.</p> <p>Descriptive statistics will also be performed by treatment and timepoint on raw changes and percent changes from baseline.</p> <p>Analysis of additional endpoints</p> <p><u>Pharmacodynamics:</u></p> <p>The additional PD endpoints will be analyzed similarly to the main analysis.</p> <p>Analysis of FeNO will be specified in the statistical analysis plan.</p> <p><u>Pharmacokinetics</u></p> <p>Dupilumab concentrations will be summarized by timepoint with descriptive statistics and plotted over time.</p> <p><u>Anti-drug antibodies</u></p> <p>Incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%), presented by study treatment.</p> <p><u>Safety</u></p> <p>The safety analysis will be based on the review of descriptive statistics (summary tables) and individual data for adverse events (AEs) and clinical laboratory, vital signs and ECG parameters. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and the number of patients with Treatment-Emergent Adverse Events (TEAEs) will be summarized. Potentially clinically significant abnormalities (PCSAs) for clinical laboratory, vital sign, and ECG data and out-of-normal range values for clinical laboratory data will be flagged and summarized in frequency tables.</p> <p>Analysis of exploratory endpoints</p> <p>Exploratory PD endpoints will be analyzed similarly to the main analysis.</p> <p>Associations between biomarker baseline characteristics and treatment outcome (as measured by FEV₁ and other efficacy endpoints) will be explored. Composite biomarker scores (eg, Th2-related biomarkers) may be explored as appropriate. Correlations between changes in biomarkers and treatment responses (as measured by FEV₁ and other efficacy endpoints) will be assessed.</p> <p>Descriptive statistics and, as appropriate, graphs will be provided for raw data, absolute changes and percent changes from baseline.</p>
DURATION OF STUDY PERIOD (per patient)	<p>Total study duration for each patient, is approximately 29 weeks.</p> <ul style="list-style-type: none"> • Screening: maximum of 5 weeks. • Treatment period: 12 weeks. • Follow-up period: 12 weeks.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

	Screening ^x		Treatment Period								EOT ^b	Post Treatment Period			EOS ^c
Week	-4±1	-2 to -0.5	0	2	4	6	8	10	12	14	12 (14 or 16) ^d	14 (16 or 18)	16 (18 or 20)	18 (20 or 22)	24 (26 or 28)
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V8.1 (optional) ^e	V8.2 (optional)	V9	V10	V11	V12	V13
Day ^a			D1												
Informed consent	X														
Inclusion/exclusion criteria	X	X	X ^f												
Medical/surgical history	X														
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reversibility ^g	X														
Chest radiograph	X ^h														
Chest imaging								X ^u							
Randomization			X												
Body weight	X		X								X				X
Height	X														
IMP Administration															
Dupilumab/Placebo ⁱ			X ^j	X	X	X	X	X	X	X					
Prednisone/Prednisolone ^k		X									X				
Pharmacodynamics															
FeNO ^l	X	X				X	X	X			X				X
Bronchoscopy (BALF, biopsy, brushing)		X									X				
PD Biomarkers in Blood ^{m,n}	X	X				X					X				
Whole blood RNA sample		X													
DNA sampling (optional) ^o			X												
Efficacy															
Spirometry (FEV ₁) ^p	X	X		X	X	X	X				X	X		X	X
ACQ-5 ^q	X	X			X		X				X		X		X
Pharmacokinetics															
Systemic drug concentration ^m			X	X		X	X				X			X	X
Anti-dupilumab antibody sampling ^m			X				X				X				X

	Screening ^x		Treatment Period								EOT ^b	Post Treatment Period			EOS ^c
Week	-4±1	-2 to -0.5	0	2	4	6	8	10	12	14	12 (14 or 16) ^d	14 (16 or 18)	16 (18 or 20)	18 (20 or 22)	24 (26 or 28)
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V8.1 (optional) ^e	V8.2 (optional)	V9	V10	V11	V12	V13
Day ^a			D1												
Safety															
Vital signs ^f	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Oxygen saturation		X									X				
ECG	X		X								X				
Physical examination	X										X				X
Pregnancy test ^s	X		X		X		X		X		X		X		X
Virus serology ^t	X							X ^u							
Urinalysis	X	X									X				X
Clinical laboratory testing ^{m,t}	X	X			X		X	X ^u			X		X		X
Archival serum sampling ^o		X									X				
Reliever medication pm ^v	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense or download electronic diary/PEF meter ^w	X	X	X	X	X	X	X	X	X	X	X		X		X
Call IVRS	X		X	X	X	X	X	X	X	X	X				X
AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Randomization Visit (Visit 3) is defined as Day 1. Visit windows for subsequent visits are +/- 3 days.

b Patients who permanently discontinue treatment early will complete the EOT assessments, with the exception of the bronchoscopy, and then will participate in the Post Treatment period according to the visit schedule until EOS (see [Section 10.3.4](#)).

c Patients may be asked to return to the clinic to have additional follow-up ADA samples collected after the EOS based on the overall assessment of antibody titers and clinical presentation.

d If optional visits V8.1 and/or V8.2 are done, all the following visits are postponed by 2 or 4 weeks.

e If bronchoscopy has to be postponed to week 14 or 16, then schedule additional visits with IMP injection at week 12 and/or 14 as described in [Section 10.1.9](#).

f Review suitability for dosing.

g Qualifying criteria for reversibility is based on historical data within 5 years prior to Screening. If qualifying historical data is not available for reversibility or airway hyperresponsiveness (See [1.01](#)), reversibility must be demonstrated and documented. Three attempts may be made during the Screening Period to meet the qualifying criteria for reversibility. Patients must meet the criteria for reversibility prior to Visit 2. See [Section 9.3.1.1.2](#).

h As per local standard of care, perform chest radiograph if no chest imaging (X-ray, CT, MRI) available within previous 12 months and if there is a local requirement.

i Patients must be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction. See [Section 8.1.4](#).

j Loading dose.

k Prednisone/Prednisolone is administered after bronchoscopy procedure.

- l* Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour. Three attempts may be made during the Screening Period to meet the qualifying criteria for FeNO. Patients must meet the criteria for FeNO prior to Visit 2.
- m* Samples will be collected prior to administration of investigational medicinal product during the Treatment Period.
- n* See [Section 9.3.2](#) for PD Biomarkers in blood.
- o* This is an optional sample and a separate written consent form must be signed prior to collection.
- p* Spirometry will be performed between 6:00 AM and 12:00 PM after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of ICS/LABA for 12 hours and prior to administration of investigational product, if applicable. Three attempts may be made during the Screening Period to meet the qualifying criteria for spirometry. Patients must meet the criteria for spirometry prior to Visit 2.
- q* ACQ-5 is completed in the patient's electronic diary during clinic visits.
- r* See [Section 9.2.2.3](#).
- s* For women of childbearing potential, serum pregnancy test at Visit 1 and urine pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 3 prior to randomization.
- t* See [Section 9.2.2.2](#) for details of laboratory testing.
- u* Only for patients planning to enter the open label extension study. Clinical laboratory testing includes only ANA and anti-ds DNA antibody (see [Section 9.2.2.2](#)). Chest imaging is to be performed only for those patients who have not had prior chest imaging – see [Section 10.1.8](#) for details.
- v* Patients may administer salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as needed during the study. Patients will be asked at study site visits if additional supplies are needed. Patients will record daily usage in the electronic diary.
- w* Electronic diary/PEF meter is used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, combination product ICS/LABA use, AM and PM PEF, nocturnal awakenings, and morning and evening asthma symptom scores. This device is dispensed at Visit 1 and information is reviewed and downloaded from this device on the other indicated days.
- x* If needed the screening period may be extended by a window of up to 7 days to allow (re) confirming of entry eligibility or resolving scheduling impediments for bronchoscopy (see [Section 10.1](#))

NOTE: Multiple activities scheduled for the same time will be conducted in the following sequence when applicable: urine collection, ECG, heart rate, blood pressure, body temperature, blood sampling, FeNO, spirometry, bronchoscopy and then prednisone/prednisolone or IMP administration and finally a meal

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3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ATS:	American Thoracic Society
BAL:	bronchoalveolar lavage
BALF:	bronchoalveolar lavage fluid
CPK:	creatine phosphokinase
CYP:	cytochrome P450
DMC:	Data Monitoring Committee
ECG:	electrocardiogram
e-CRF:	electronic case report form
EOT:	end-of-treatment
FeNO:	fractional exhaled nitric oxide
FEV ₁ :	forced expiratory volume in 1 second
GSO:	global safety officer
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HLT:	high level term
ICS:	inhaled corticosteroids
IgE:	Immunoglobulin E
IL-13:	interleukin-13
IL-4:	interleukin-4
IVRS:	interactive voice response system
IWRS:	interactive web response system
LABA:	long-acting beta-agonists
OLE:	open label extension
PARC:	pulmonary and activated regulated chemokine
PCSA:	potentially clinically significant abnormality
PEF:	peak expiratory flow
PT:	preferred term
q2w:	every 2 weeks
SAP:	statistical analysis plan
SOC:	system organ class
TARC:	Thymus and Activation-Regulated Chemokine
TEAE:	treatment emergent adverse event
Th2:	T-helper cell 2
ULN:	upper limit of normal

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products.

The poor response of some patients with asthma to the standard regimen of controller and reliever therapies may reflect the number of cellular and molecular mechanisms operative in asthma. Recent therapeutic approaches in asthma have been focused on trying to control the Type 2/ T-helper cell-2 (Th2) response. Up-regulation of the Th2 cell-derived cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13) has been implicated as an important inflammatory component of asthma disease progression.

Dupilumab is a fully human monoclonal antibody that binds with high affinity to human IL-4R α , a subunit of heterodimeric IL-4 receptors (Type I and Type II) that mediates signaling by IL-4 (both receptor types) and by IL-13 (Type II receptor). Dupilumab inhibits the downstream signaling of IL-4 and IL-13, thereby inhibiting receptor-mediated activation of secondary messengers such as STAT6 and downstream pro-inflammatory signaling pathways.

While IL-4 and IL-13 have overlapping pleiotropic actions, IL-4 tends to predominate in modulating immune cell functions whereas IL-13 predominates in stimulation of tissues (1, 2, 3). IL-4 is a major mediator of the polarization of T helper cells toward the Th2 phenotype, ie, cells that secrete more exclusively IL-4, IL-5 and IL-13 (4) and their proliferation. Th2 cytokines have a central role in stimulating secretion of chemotaxins that promote homing of Th2 cells, eosinophils and mast cells into the respiratory epithelium (5). Surface immunoglobulin E (IgE) receptors on mast cells and eosinophils facilitate release of stored pro-inflammatory mediators from these cells through both allergen-dependent and -independent mechanisms (6). Under conditions of asthmatic inflammation, IL-4 and IL-13 prime mast cells, enhancing their responsiveness, in part by up-regulating surface receptors for IgE, and inducing the production and storage of cytokines, including IL-4 and IL-13 (7). Th2 asthma is often associated with elevation in serum IgE and allergen sensitization (ie, atopy). IL-4 is recognized as the principle promoter of IgE class switching in B cells and is thus central to elevation in IgE and the sensitization of cells expressing IgE receptors (6). The various mediators released by these sensitized cells during exposure to allergens are major contributors to airway hyper-responsiveness and disease exacerbation.

IL-13 promotes goblet cell hyperplasia and excess mucus production, characteristic of asthma (1). Epithelial basement membrane thickening is another feature of asthmatic inflammation, and a subset of asthma patients exhibit more extensive airway remodeling, characterized by subepithelial fibrosis, submucosal gland hyperplasia, increased airway smooth muscle mass, and increased airway vascularization, which results in thickening of the airway wall and luminal

narrowing (8). The preponderance of evidence indicates that Th2 cytokines, more dominantly IL-13, have a central role in facilitating this remodeling. They stimulate the secretion of several mediators thought contributory to tissue remodeling such as periostin, thymic stromal lymphopoietin (TSLP), Pulmonary and Activated Regulated Chemokine (PARC) and various growth factors. Furthermore, IL-4 and IL-13 initiate the polarization of monocytes and macrophages toward the formation of so called “alternatively activated” M2a macrophages which promote the deposition of collagen and fibrosis (9). Thus, dupilumab has potential for preventing progression of airway remodeling in patients with severe asthma.

Asthma is a heterogeneous disease comprised of several phenotypes and endotypes (10). Dupilumab is expected to substantially suppress airway inflammation, mucus hypersecretion and airway hyperresponsiveness in patients with allergic/atopic asthma and other forms of eosinophilic asthma, collectively known as Th2 asthma, which represent roughly half the overall asthma population. The therapeutic effectiveness of dupilumab across the breadth of asthma subpopulations will be assessed during clinical trials.

For complete information regarding the preclinical and clinical evaluation of dupilumab to date, see the Investigator's Brochure.

4.2 RATIONALE

4.2.1 Study Rationale

The initial clinical study of dupilumab in eosinophilic asthma (ACT11457) and the dose-ranging study (DRI12544) in a broader population with persistent asthma both showed treatment-related suppression of fractional exhaled nitric oxide (FeNO) and IL-4-/IL-13-dependent biomarkers in peripheral blood. The current study is designed to more directly investigate the effects of dupilumab on underlying mechanisms of inflammation in the asthmatic airway utilizing bronchoscopy.

In ACT11457, 104 patients with moderate-to-severe asthma inadequately controlled with medium-to-high dose combination inhaled corticosteroids (ICS) / long-acting beta-agonists (LABA) (fluticasone/salmeterol, budesonide/formoterol, or mometasone/formoterol) and with blood eosinophils >300 cells/ μ L (101 patients) or sputum eosinophils >3% (3 patients) were studied. Patients were switched to fluticasone/salmeterol at Day 1 for 4 weeks, after which background therapy was reduced systematically. The primary endpoint was the incidence of asthma exacerbations after 12 weeks. An 87% ($p < 0.0001$) relative reduction in asthma exacerbations was observed after 12-week treatment with dupilumab (5.8%) vs placebo (44.2%).

In the Phase 2b study (DRI12544), different doses and regimens of dupilumab (up to 300 mg every 2 weeks [q2w] with a loading dose of 600 mg) have been evaluated in patients with moderate to severe, uncontrolled asthma. All patients received a stable dose of medium to high ICS/LABA in addition to their study treatment (placebo or dupilumab). An interim analysis (dated 02 November 2014) was performed after the last patients completed their Week 12 assessments. At the time of the interim report, 776 patients had been enrolled in the study and 731 patients had completed the 12-week study period. Results from the interim analysis indicated significant improvements, compared with placebo, in the change from baseline forced expiratory volume in

1 second (FEV₁) at Week 12, the primary endpoint, for 3 of 4 dose regimens, including 300 mg q2w. In addition, the majority of main secondary efficacy results (annualized rates of severe exacerbation and loss of asthma control events, and changes from baseline at Week 12 in morning and evening asthma symptom scores, ACQ-5 scores, AQLQ scores, morning and evening peak expiratory flow [PEF], and Sinonasal Outcomes Test 22-item scale total scores) demonstrated statistically significant differences (not adjusted for multiplicity) in favor of dupilumab compared with placebo across the treatment comparisons, especially for the q2w dosing regimens. A final analysis for 24 weeks of treatment demonstrated a sustained therapeutic effect.

In addition, the effects of dupilumab on several pharmacodynamic and Th2-associated biomarkers were evaluated in the ACT11457 and DRI12544 studies. Fractional exhaled nitric oxide (FeNO), a quantitative method to measure airway inflammation, decreased in dupilumab-treated patients and remained suppressed through the end of treatment. Serum levels of the Th2-associated chemokines, Thymus and Activation-Regulated Chemokine (TARC) and eotaxin-3, remained unchanged with placebo, whereas, with dupilumab, circulating TARC and eotaxin-3 levels rapidly decreased and remained significantly lower than baseline values throughout the dupilumab treatment. Serum total IgE also significantly decreased during dupilumab treatment. Thus, decreased levels of the biomarkers FeNO, eotaxin-3, TARC, and total IgE confirmed the biologic activity of dupilumab and suggest that dupilumab is impacting Th2-mediated airway inflammation. The current study has been designed to more directly evaluate the effect of dupilumab on the Th2 response and inflammation within the lung through bronchoscopy sampling.

The current study will directly assess airway inflammatory biomarkers in bronchial biopsies, brushings and alveolar lavage fluid and further correlate these assessments with various biomarkers in peripheral blood and breath and with the overall clinical condition of the patients. We now hypothesize that dupilumab, by reducing the production of potent chemotaxins, will decrease the numbers of mast cells, eosinophils, total T lymphocytes and T-helper lymphocytes in the bronchial submucosa. Dupilumab, by controlling inflammation, as further evidenced by a reduction in FeNO, will result in a decrease in mucin in the mucosa, which reflects the excess production of mucus characteristic of asthma. Exploratory analyses may show further changes in inflammatory cells in the bronchial epithelium and reversal of basement membrane thickening associated with asthma. Shifts in the transcriptome in the mucosa, biopsies, and bronchoalveolar lavage (BAL) cells, particularly in Th2 signature genes, mucin genes, and genes related to mast cells and eosinophils, may reflect the overall impact of dupilumab on underlying inflammatory processes.

4.2.2 Population rationale

In this placebo-controlled study, dupilumab will be added-on to standard of care asthma therapy (minimum of an inhaled corticosteroid in combination with LABA) in patients with persistent asthma. Patients requiring a third asthma controller are eligible. The population is comprised of patients with a physician diagnosis of asthma for ≥ 12 months, based on the Global Initiative for Asthma (GINA) 2015 Guidelines (11) and entry criteria described in [Section 7](#). A similar patient population is being evaluated in the asthma Phase 3 clinical trial (EFC13579) because in addition to suffering the symptoms associated with a lack of asthma control, such patients utilize a

disproportionate level of health care services, are at increased risk of a severe asthma exacerbation and may suffer the long term adverse effects of systemic and inhaled corticosteroids.

In this small exploratory study, to better evaluate the effects of dupilumab on airway inflammation, the study population will be enriched for patients with evidence of ongoing inflammation based on elevation in FeNO levels (≥ 26 ppb; upper limit of normal (12)). In addition, due to the bronchoscopy procedures in this study, additional restrictions will be in place for patients' safety, as detailed in the inclusion and exclusion criteria (Section 7), including more restrictive requirements for age and FEV₁ criteria, as compared to the asthma Phase 3 clinical trial.

4.2.3 Design Rationale

PDY14192 is an exploratory, randomized, double-blind, placebo-controlled, parallel group study. The clinical trial uses an add-on therapy approach to inhaled corticosteroid in combination with LABA. Patients requiring a third controller for their asthma will be considered eligible for this study.

After a screening period (5 weeks with optional additional up to 7 days) patients will be randomized in a 1:1 ratio to one of the following 12 week-treatments:

- Dupilumab 600 mg loading dose followed by 300 mg every 2 weeks (q2w).
- Placebo q2w with placebo loading dose.

During the Randomized Treatment Period, patients continue the stable (or equivalent) dose of an allowable combination product. The End-Of-Treatment (EOT) is designated as 2 weeks after the last dose of dupilumab.

Patients treated with placebo will serve as an inactive control group, to more clearly establish the effects attributed to dupilumab.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic 2 weeks after the last treatment dose for the EOT assessments, with the exception of the bronchoscopy procedure, and then participate in follow-up assessments in the Post Treatment Period as indicated in the visit schedule (see Section 1.2 and Section 10.3.4).

Eligible patients, who complete the treatment period, including the EOT assessments, will be offered the opportunity to participate in an open label extension (OLE) study with dupilumab. Patients subsequently enrolled in the OLE will not participate in the Post Treatment Period of this trial.

Patients not participating in the OLE will enter a Post Treatment Period immediately after the EOT visit (2 weeks after the last treatment dose), or otherwise after premature treatment discontinuation, and will be evaluated for an additional 12 weeks. The Post Treatment Period is designed to monitor patients on their background controller medication alone after discontinuation of the blinded treatment. During this follow-up period, patients continue treatment with the stable background dose of their background controller medication or their asthma treatment as modified based on medical judgment.

4.2.4 Dose Rationale

The dose regimen of subcutaneous (SC) dupilumab selected for this study is the highest dosing regimen that will be tested in the Phase 3 clinical trial - 300 mg every 2 weeks (q2w). All patients randomized to receive treatment with dupilumab will get an initial loading dose of 600 mg on Day 1. The administration of the loading dose of dupilumab will allow systemic concentrations to reach steady-state faster, and potentially reduce the time to onset of clinical effect.

Proof of concept for efficacy was established in the ACT11457 phase 2a study at 300 mg weekly for 12 weeks, which was generally well tolerated. The study showed unprecedented efficacy in a population of mostly severe asthmatics with poor asthma control and decreased lung function at baseline while on treatment with mostly high doses of ICS in combination with a LABA. In the subsequent phase 2b dose-ranging study, interim analysis at 12 weeks has shown the rapid effects of dupilumab on FEV₁ and FeNO which plateaued by Week 12 following repeated treatment. The treatment response was also observed to approach the maximal effect at 300 mg q2w regimen.

4.2.5 Endpoint Rationale

Commensurate with the hypothesis that dupilumab will overall suppress asthmatic airway inflammation, several endpoints have been selected for this exploratory clinical study.

First, changes from baseline in the inflammatory cells most consistently characteristic of asthmatic inflammatory infiltrates, namely eosinophils, mast cells, total T-lymphocytes and T-helper cells, will be assessed in the submucosa of bronchial biopsies. In a clinical trial with omalizumab in allergic asthma, these inflammatory cell types were evaluated by bronchial biopsies and demonstrated a response to treatment (13).

Bronchial biopsies afford a direct assessment of the effects of dupilumab on bronchial inflammation. Inflammatory cell infiltration can occur in the mucosal, submucosal and smooth muscle layers, but most abundantly in the submucosa. During asthmatic inflammation, eosinophils, mast cells, and lymphocytes, including IL-4 expressing subpopulations within each of these cell types, are all increased in bronchial biopsies from atopic asthmatic patients compared with healthy control subjects. Assessment of the abundance of these cells using immunohistochemistry or other staining techniques will characterize the type of inflammation and quantify the effects of dupilumab on immune cell infiltration.

In addition, the reported dependence of goblet hyperplasia and mucus production on IL-4R α mediated mechanisms suggests that dupilumab will markedly suppress mucin in the bronchial epithelium of asthmatic patients; therefore, the abundance of mucin in the mucosa will be quantified.

4.2.6 Risk assessment

In terms of safety, there are no significant safety findings based on current available data and dupilumab has been generally well tolerated in all clinical trials completed in healthy volunteers and in patient populations, including those with atopic dermatitis (AD), asthma, and chronic sinusitis with nasal polyposis. Local injection site reactions have been observed as the most frequent treatment emergent adverse event (TEAE) in studies conducted in healthy subjects. The

adverse event profile observed in the completed and the ongoing study in patients with AD is consistent with the profile observed in the studies in asthma patients. The most frequent TEAEs in both AD and asthma patient studies were in the system organ classes (SOCs) of Infections and Infestations (preferred term [PT]: nasopharyngitis), Nervous System Disorder (PT: headache), and General Disorders and Administration Site Conditions (high level term [HLT]: injection site reactions). Based on the results of the recently completed dose-ranging study in patients with AD (study R668-AD-1021) and of the interim analysis of the dose-ranging study in patients with asthma (study DRI12544), injection site reactions appear to be the primary dose-dependent TEAE related to dupilumab treatment, while nasopharyngitis and headache appear to be balanced across treatment groups including placebo. A few TEAEs were observed more often in dupilumab-treated patients in individual studies without contributing to a pattern for a particular dose or underlying disease; these TEAEs include nasopharyngitis, headache, oral herpes/herpes simplex, cough, oropharyngeal pain, and influenza. The majority of the TEAEs were mild-to-moderate in intensity.

In summary, the safety data observed so far in completed and currently ongoing studies in AD and asthma patients (at the same or even higher doses than that proposed for this study) have demonstrated a positive profile for dupilumab in comparison to placebo.

Bronchoscopy

Bronchoscopy will be performed prior to treatment (during screening) and at the end of treatment to allow assessment of the effects of dupilumab within the lung and provide a mechanistic understanding of the response to dupilumab in asthma. The risks of bronchoscopy include discomfort and coughing (which will be reduced through local anesthetics), wheezing (which can be reduced by premedication with beta-agonist), reduced oxygen (which will be monitored and treated as needed during the procedure), minor bleeding, infection and fever. Pneumothorax is a rare complication of bronchoscopy. Bronchoscopies will be performed at experienced centers with established standard operating procedures. Prior to the procedure, the investigator will confirm patient suitability by evaluating the patient's current lung function (eg, FEV₁), oxygen saturation and asthma control. In addition, prior to the procedure, the investigator will perform assessments, such as coagulation tests and platelets, to confirm suitability as well as any other assessments, such as a chest X-ray, at the investigator's discretion. Patients will be monitored after the procedure for at least one hour to allow detection and treatment of any complications. Another major risk of doing bronchoscopy in patients with asthma is inducing an asthma exacerbation. Because of this patients will receive prednisone/prednisolone for 3 to 5 days after the bronchoscopy to prevent procedure-induced asthma exacerbations.

4.2.7 Specific parameters rationale

Main Endpoints

Eosinophils, mast cells, total T-lymphocytes and T-helper lymphocytes will be counted in the bronchial submucosa of biopsy thin sections using quantitative histology and/or immunohistochemistry and reported as the number of cells per square millimeter.

Goblet cell hyperplasia and increased production of mucin, features of asthmatic inflammation, will also be assessed histologically.

Additional Endpoints

Percent eosinophils in bronchoalveolar lavage fluid (BALF):

Th2 mechanisms are recognized as drivers of eosinophilic airway inflammation in asthma. Assessment of eosinophilic inflammation during asthma studies is routinely achieved by conducting cytological examinations of bronchoalveolar lavage fluid or sputum and reporting the eosinophils as a percentage of total cells counted.

FeNO:

Nitric oxide (NO) is produced in the airway epithelium as a result of NO synthases, the activity of which is upregulated during inflammation. FeNO is an accepted measure of airway inflammation for which clinically meaningful changes have been defined (12). Use of FeNO measurements has been recommended by the American Thoracic Society (ATS) for the monitoring of asthmatic inflammation (12). FeNO can be readily performed in a standardized and quantitative manner using a convenient hand-held device (12). During previous studies, a significant suppression of FeNO was observed when dupilumab treatment was added onto ICS/LABA maintenance therapy.

Exploratory endpoints:

Bronchial biopsy histology

In addition, thickening of the respiratory subepithelial membrane is a common histological finding in asthma. The mechanism of this membrane thickening is not well understood, however, IL-4 and IL-13 are known to stimulate secretion of growth factors and to promote transformation of monocytes and macrophages into cell phenotypes that secrete collagen and promote remodeling. Therefore, dupilumab treatment has potential for slowing or reversing epithelial membrane thickening.

Goblet cell hyperplasia and increased production of mucin, features of asthmatic inflammation, will also be assessed histologically.

Bronchial biopsy RNA analysis:

Bronchial brushings collected during bronchoscopy will constitute a more selective sampling of the respiratory mucosa which is comprised of primarily goblet cells and ciliated epithelial cells.

Bronchoalveolar lavage cell RNA analysis:

Cells harvested from BALF are predominantly macrophages with lesser numbers of eosinophils, neutrophils and lymphocytes. Recent studies have demonstrated Th2 polarization of inflammatory cells in sputum from asthma patients. The current study will further explore this polarization in BALF cells. In a milieu dominated by IL-4, macrophages should in principle be polarized toward an M2a phenotype that overexpresses growth factors and may promote airway remodeling. Dupilumab should suppress the expression of markers associated with M2a polarization, as well as other markers of IL-4 α driven processes in BAL cells.

Allergen-specific IgE testing:

All patients will be evaluated at baseline and at EOT with a multiallergen-specific IgE panel, specific to global region for environmental allergens, which includes Staphylococcal enterotoxin (SAE) A & B IgE for all regions. This panel will be used to classify patients as atopic and, as quantitative tests to assess shifts in allergen-specific IgE titers during treatment. SAE IgE is associated with severe asthma, a diminished FEV₁ and higher intake of oral glucocorticosteroids and hospitalization due to asthma exacerbations. Enterotoxins generated by *S. aureus* can act both as nominal antigens, stimulating specific IgE responses, and as superantigens, promoting a polyclonal IgE response reflected by an increase in total IgE levels.

5 STUDY OBJECTIVES

5.1 MAIN

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

5.2 ADDITIONAL

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

5.3 EXPLORATORY

Exploratory objectives of this study include the following:

- To explore the effects of dupilumab, compared to placebo, in patients with persistent asthma on:
 - Pulmonary function and asthma control,
 - Th2-associated biomarkers in peripheral blood.
- To explore the pharmacokinetic-pharmacodynamic relationship of the inflammatory biomarkers.
- To evaluate the relationship between the baseline characteristics of patients (eg, demographics, clinical status, clinical lab values, biomarkers, and genetic profiles) and treatment responses.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This study is a Phase 2a, multicenter, exploratory, randomized, double-blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered SC for 12 weeks in patients with persistent asthma who are receiving at minimum a medium to high dose of ICS in combination with LABA. Patients requiring a third asthma controller are eligible. During the study, patients will undergo 2 bronchoscopy procedures, one at the beginning and one at the end of treatment.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

- A 5 weeks screening (not to exceed overall 6 weeks screening), potentially additional 7 days to complete eligibility assessment and to overcome impediments to baseline bronchoscopy scheduling.
- A 12-week treatment period.
- A 12-week post-treatment period for patients not participating in an open label extension (OLE) study.
 - Eligible patients participating in an OLE study will enter the OLE study after completion of the end-of-treatment visit assessments.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur when either:

- The last patient has completed the 12-week post-treatment period or,
- The last patient has completed the EOT visit and enrolled in the OLE study.

6.3 INTERIM ANALYSIS

A formal interim analysis is not planned.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

A data monitoring committee (DMC) is independent from sponsor and is commissioned for the dupilumab clinical development program. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The

primary responsibilities of the DMC are to review and evaluate the safety data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

The DMC procedures and safety data to be reviewed by the DMC are described in the DMC charter. In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patients with a physician diagnosis of asthma for ≥ 12 months, based on the Global Initiative for Asthma (GINA) 2015 Guidelines (11) and the following criteria:

- Existing treatment with medium to high dose ICS (≥ 250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a LABA for at least 3 months with a stable dose ≥ 1 month prior to Visit 1.
 - Existing treatment with a third asthma controller (eg, long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA]) for at least 3 months with a stable dose ≥ 1 month prior to Visit 1 is also allowed.
- Pre-bronchodilator forced expiratory volume in 1 second (FEV₁) 55 to 85% of predicted normal at Visit 1.

Documented reversibility from historical data within 5 years of Visit 1 of at least 12% and 200 mL in FEV₁ after the administration of 200 to 400 mcg albuterol/salbutamol (2 to 4 inhalations of albuterol/salbutamol or of a nebulized solution of albuterol/salbutamol, if considered as a standard office practice) **OR** documented airway hyperresponsiveness (methacholine PC₂₀ < 8 mg/mL [or PC₂₀ < 16 mg/mL on ICS]) within 5 years of Visit 1. If historical data is not available, reversibility must be demonstrated and documented before baseline bronchoscopy (reversibility can be demonstrated at any time prior to baseline bronchoscopy (Visit 2) and randomization and does not have to occur in the same spirometry assessment of a compliant FEV₁ test.

I 02. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in [Section 7.1](#) will be screened for the following exclusion criteria which are sorted and numbered in the following sub-sections:

7.2.1 Exclusion criteria related to study methodology

E 01. Patients <18 years or >65 years old.

E 02. Fractional exhaled nitric oxide (FeNO) <26 ppb at Visit 1.

E 03. Chronic obstructive pulmonary disease or other lung diseases (eg, idiopathic pulmonary fibrosis, eosinophilic granulomatosis with polyangiitis [Churg-Strauss Syndrome], etc) which may impair lung function.

- E 04. A patient who experiences an asthma exacerbation that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to Visit 1.
- E 05. Evidence of lung disease(s) other than asthma, either clinical evidence or imaging (chest X-ray, computed tomography [CT], magnetic resonance imaging [MRI]) within 12 months of Visit 1 or at the screening visit, as per local standard of care.
- E 06. A patient who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to Visit 1.
- E 07. Previous smoker (smoking history >10 pack-years) or current smoker (within 6 months prior to Visit 1).
- E 08. Comorbid disease that might interfere with the evaluation of IMP or conduct of study procedures (eg, bronchoscopy).
- E 09. Known or suspected alcohol and/or drug abuse.
- E 10. Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures (eg, due to language problems or psychological disorders).
- E 11. Patients requiring non-selective beta-adrenergic receptor blockers for any reason and initiation or dose change of a selective beta-1 adrenergic receptor blocker within 3 months prior to Visit 1.
- E 12. Anti-immunoglobulin E (IgE) therapy (omalizumab) or any other biologic therapy within 130 days of Visit 1.
- E 13. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or plan to begin therapy during the Screening Period or the Randomized Treatment Period.
- E 14. Patients who received bronchial thermoplasty within 3 years of Visit 1 **OR** patients who plan to begin therapy during the Screening Period or the Randomized Treatment Period.
- E 15. Exposure to another investigative study medication within a time period prior to Visit 1 that is less than 5 half-lives of the study medication. For an investigative antibody, in case the half-life is not known, then the minimum interval since exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 1.
- E 16. Patients receiving medications or therapy that are prohibited as concomitant medications (See [Section 8.8](#)).
- E 17. Patients who have previously been treated with dupilumab in any clinical trial of dupilumab.

- E 18. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.
- E 19. Intubation for asthma within 6 months prior to Visit 1.
- E 20. Patient with a history of a life-threatening asthma attack within 5 years of Visit 1.
- E 21. Patient who has a contraindication to or is otherwise ineligible to undergo a bronchoscopy, as per the Investigator's assessment (eg, coagulopathy, adverse reaction to bronchoscopy medications).
- E 22. Use of anticoagulants (eg, warfarin, clopidogrel). Note: regular aspirin use is permitted. See [Section 8.8](#).

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

- E 23. Non-compliance with use of the mandatory background therapy, eg ICS/LABA combination, during the screening period, as defined as:
 - <80% of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient electronic diary during the screening period.
- E 24. A patient with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to insulin-dependent diabetes, uncontrolled hypertension, active hepatitis, active or latent untreated tuberculosis, bronchiectasis. Other conditions that are well controlled and stable will not prohibit participation if deemed appropriate per the investigator's judgment.
- E 25. Treatment with systemic (oral or injectable) corticosteroids within 28 days of Visit 1

7.2.3 Exclusion criteria related to the current knowledge of dupilumab

- E 26. Pregnant or breast-feeding women.
- E 27. Women of childbearing potential (pre-menopausal female biologically capable of becoming pregnant) who:
 - Do not have a confirmed negative serum beta-human chorionic gonadotropin test at Visit 1
 - Are not protected by one of the following acceptable forms of effective contraception during the study:
 - Established use of oral, injected, implanted or inserted hormonal contraceptive,
 - Intrauterine device (IUD) with copper or intrauterine system (IUS) with progestogen,

- Contraceptive barrier (condom, diaphragm or cervical/vault caps) used with spermicide (foam, gel, film, cream or suppository), if allowed by local regulations,
 - Female sterilization (eg, tubal occlusion, hysterectomy or bilateral salpingectomy),
 - For the patient's partner: Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; the vasectomized male partner should be the sole partner for the patient,
 - True abstinence in keeping with the preferred and usual lifestyle and if allowed by local regulation; periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) is not an acceptable method of contraception.
- Menopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception
- E 28. Diagnosed active parasitic infection (helminths), suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.
- E 29. History of HIV infection or positive HIV serology at Visit 1.
- E 30. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per investigator's judgment. Tuberculosis testing would be performed on a country by country basis according to local guidelines if required by regulatory authorities or ethics committees.
- E 31. Evidence of acute or chronic infection requiring treatment with systemic antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1, significant viral infections within 4 weeks before Visit 1 that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment). Exceptions may be considered for uncomplicated mild viral or fungal infections requiring antiviral or antifungal therapy respectively only after discussion with the Investigator and approval by the Sponsor.
- E 32. Live attenuated vaccinations within 12 weeks prior to Visit 1 or planned live, attenuated vaccinations during the study; see [Appendix A](#) for list of prohibited live attenuated vaccines.
- E 33. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc).
- E 34. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

- E 35. Patients with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.
- E 36. Active hepatitis or patients with positive or indeterminate hepatitis B surface antigen (HBsAg), positive IgM hepatitis B core antibody (IgM-HBcAb) or positive hepatitis C antibody (confirmed with hepatitis C virus [HCV] RNA) at Visit 1. Patients who are HBcAb positive and HBsAg negative at Visit 1 must undergo hepatitis B virus (HBV) DNA testing prior to randomization to determine eligibility (refer to [Table 1](#) for eligibility interpretation of hepatitis serology results).
- E 37. Drug induced liver injury related criteria at Visit 1:
- Underlying, active hepatobiliary disease **OR**
 - Alanine Aminotransferase (ALT) >3 Upper Limit of Normal (ULN)
- E 38. Abnormal lab values at Visit 1:
- Creatine phosphokinase (CPK) >10 ULN **OR**
 - Platelets <100,000 cells/mm³ **OR**
 - Eosinophils >1500 cells/mm³

7.2.4 Additional exclusion criteria during or at the end of screening before randomization

- E 39. Patient who has withdrawn consent before enrollment/randomization.
- E 40. Prisoners or persons who are legally institutionalized.
- E 41. Patient with known hypersensitivity to any component of the dupilumab formulation (See the Investigator's Brochure for details on the formulation).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S) (IMP)

8.1.1 Dupilumab

Sterile dupilumab will be provided in 150 mg/mL in glass pre-filled syringe to deliver 300 mg in 2 mL.

8.1.2 Placebo

Sterile placebo for dupilumab will be provided in identically matched glass pre-filled syringe to deliver 2 mL.

8.1.3 Preparation of investigational product

Dupilumab or matching placebo in glass pre-filled syringes will be supplied to the investigational site. Additional information will be provided in the Pharmacy manual.

8.1.4 Dosing schedule

The IMP is administered every 14 ± 3 days (q2w). The doses of investigational product must be separated by ≥ 11 days to avoid an overdose.

The IMP will be administered at the clinical site following clinic procedures and blood collection. Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.

Subcutaneous injection sites should be alternated among the 4 quadrants of the abdomen (avoiding navel and waist areas), the upper thighs or the upper arms, so that the same site is not injected twice consecutively. This instruction pertains to the day that the loading dose is injected as well as the administration of q2w injections. For each injection, the anatomic site of administration will be recorded in the electronic case report form (e-CRF).

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Inhaled corticosteroid in combination with LABA

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

8.2.1.1 Screening period

Prior to screening, patients must be on a stable background therapy of a medium to high dose of ICS (≥ 250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a long-acting beta agonist [LABA] for at least 3 months with a stable dose ≥ 1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥ 1 month prior to Visit 1 (patients requiring oral steroids as controller medication or biologics are excluded). If patients take two different ICS, the total daily dose of ICS should be calculated to evaluate the eligibility criteria on daily dose of ICS which will be still considered as one controller. Please refer to medium and high dose of ICS in [Appendix B](#). Please note that the dose of ICS means the delivered dose from inhaler. For example, 110 mcg of fluticasone propionate MDI could deliver 125 mcg of fluticasone propionate, and 125 mcg will be used to calculate the ICS dose for eligibility.

If the Study Investigator based on their medical judgment, decides to optimize use of asthma medications prior to Visit 1 irrespective of potential participation in the study, note that changes in ongoing asthma medications must occur at least 1 month prior to Visit 1. The introduction of new controller medications must occur at least 3 months prior to Visit 1 with a stable dose for at least 1 month prior to Visit 1.

8.2.1.2 Randomized treatment period

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

8.2.1.3 Post-treatment period

Upon completing the randomized treatment period, patients not continuing with the open label extension will proceed to be treated with the controller medication regimen and dose used during the randomized treatment period, which could be adjusted based on the medical judgment of the investigator of the patients' asthma control status.

8.2.2 Albuterol or levalbuterol reliever medication

The reliever medication will not be dispensed or supplied by the sponsor.

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

All other reliever medications rather than albuterol/salbutamol or levalbuterol/levosalbutamol should be avoided.

8.2.3 Prednisone / Prednisolone

After the bronchoscopy procedure, patients will receive prednisone/prednisolone 40 mg po daily for 3 days. Treatment may be extended up to a total of 5 days if clinically indicated. If a patient requires treatment with prednisone/prednisolone for more than 5 days after the first bronchoscopy, the patient will not be included in the study due to the bronchoscopy requirement at the end-of-treatment.

Prednisone/prednisolone will not be dispensed or supplied by the sponsor.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched 2.25 mL pre-filled syringes. To protect the blind, each treatment kit of 2.25 mL (dupilumab / placebo) glass pre-filled syringes will be prepared such that the treatments (dupilumab and its matching placebo according to its dose) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Study patients, Investigators, and study site personnel will not have access to the randomization (treatment codes) except under circumstances described in [Section 8.3.2](#).

Refer to [Section 10.5](#) for suspected unexpected adverse drug reaction unblinding by the Sponsor.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS)/interactive web response system (IWRS) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking.

Patient withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the investigator (ie, at the site level), then the patient will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the patient will not be withdrawn from treatment.

At the facilities where the systemic drug concentration measurements, anti-drug antibodies and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

Patients, investigators and site personnel will not have access to assay results for eotaxin-3, antigen-specific IgE, total IgE, Eosinophil Cationic Protein (ECP), TARC and periostin while the study is ongoing, as the related data are not essential for patient care and have the potential for unblinding.

The Data Monitoring Committee will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

A randomized treatment kit number list will be generated centrally by Sanofi. The investigational product (dupilumab or placebo) will be packaged in accordance with this list.

The Sanofi Clinical Supplies team will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system. This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the treatments to the patients.

Patients who meet the entry criteria will be randomized to receive either dupilumab or placebo.

Patients who failed screening for transient entry criteria may be re-screened once more if the study enrolment is still open; a different patient identification will be issued. Re-screening is not permitted if the patient failed screening after baseline bronchoscopy was already performed. There is no requirement for a waiting period between the screen-failure date and the re-screening date. The IVRS/IWRS report will flag re-screened patients. Patients that are re-screened must sign a new consent form and all Visit 1 procedures must be repeated unless a prior assessment is performed within the time frame permitted prior to study entry.

The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via an IVRS/IWRS that will be available 24 hours a day.

Patients will be randomized using a 1:1 randomization ratio for dupilumab 300 mg q2w and placebo q2w in 2 mL. Randomization will be stratified by ICS dose (medium and high) and region (North America and Europe).

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

8.5 PACKAGING AND LABELING

Dupilumab and placebo will be supplied as one glass pre-filled syringe packed in a patient kit box. Both glass pre-filled syringe and box will be labeled.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

All investigational products should be stored at a temperature between 2°C and 8°C in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (eg, pharmacists) in accordance with local regulations, policies and procedures.

Control of investigational product storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the IMP should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP dispensed, used and unused. The IMP tracking log and inventory form is to be updated each time investigational product is dispensed. The study monitor will periodically check the supplies of the IMP held by the Investigator or pharmacist to verify accountability.

Treatment kit number has to be recorded on the appropriate page of the e-CRF and also on the IMP tracking log and inventory log form.

An electronic diary is used by the patient for the daily recording of salbutamol/albuterol or levosalbutamol/levoalbuterol use as well as daily combination product ICS/LABA use and recording of oral steroids use after bronchoscopy and in case of an exacerbation event. Site personnel will review and download the eDiary data at each clinic visit and will follow up with the patient accordingly.

The Monitoring Team in charge of the study will have to check case report form data comparing them with the centralized treatment allocation system information, the IMP kit and IMP tracking log and inventory form.

For NIMP not provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator and must be captured in standard site documents and records (eg, medical notes).

8.7.2 Return and/or destruction of treatments

All used, partially-used or unused treatments will be retrieved by the Sponsor or destroyed at study site.

The IMP tracking log and inventory form will be used by the Investigator (or the pharmacist) to document destroyed IMP. The form will be countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

For NIMP not provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator and must be captured in standard site documents and records (eg, medical notes).

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

8.8.1 Prohibited Concomitant Medication

The following concomitant treatments are not permitted during the Screening Period or the Randomized Treatment Period:

- Systemic steroids (steroids can only be used to treat an asthma exacerbation and after bronchoscopy as described in [Section 8.2.3](#)).
- Anti-immunoglobulin E (IgE) therapy (eg, omalizumab).
- Biologic therapy.
- Immunosuppressant.
- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker initiated more than 3 months prior to Visit 1 with stable dose for at least 3 months prior to Visit 1).
- Allergen immunotherapy (except if initiated more than 3 months prior to Visit 1 with stable dose for at least 1 month prior to Visit 1).
- Bronchial thermoplasty.
- Intravenous immunoglobulin (IVIG) therapy.
- Live, Attenuated Vaccines: Refer to [Appendix A](#).
- Anticoagulants: clopidogrel, warfarin, rivaroxaban, dabigatran, apixaban.
- Other investigational drugs.

8.8.2 Permitted concomitant medication

- Antihistamines are permitted as concomitant medication.
- Topical, ocular or intranasal corticosteroids are permitted during the study.
- Aspirin.
- Selective beta-1 adrenergic receptor blockers, if patient has been on a stable dose for at least 3 months prior to Visit 1.

8.8.3 CYP substrates

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized. However, interleukin-4 (IL-4) was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (14, 15). Human peripheral blood mononuclear cells (PBMC) incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (16). Since the clinical significance of the limited in vitro findings for IL-4 and IL-13 involvement in CYP regulation and the impact of dupilumab on CYP enzymes are not fully understood, during the study treatment and at least up to the end of follow-up, caution should be used for drugs which are metabolized via these CYP isoforms and which have a narrow therapeutic index. This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal if needed. Some examples of CYP450 substrates with narrow therapeutic indices are provided in [Appendix C](#).

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 MAIN ENDPOINT

9.1.1 Main Pharmacodynamic Endpoints

There are multiple main pharmacodynamic endpoints in this exploratory study. These endpoints will be assessed on bronchial biopsies taken at baseline and the end of treatment (12 weeks) and include the following:

- Change from baseline in numbers of the following inflammatory cells in the bronchial submucosa (per square millimeter) at 12 weeks:
 - Eosinophils,
 - Mast cells,
 - Total T-lymphocytes,
 - T-helper lymphocytes.
- Change from baseline in mucin-stained area in the bronchial mucosa (per square millimeter) at 12 weeks.
 - Mucin will be identified by staining with Alcian-blue periodic acid-Schiff and/or immunostaining for MUC5AC and then the mucin-positive area will be measured and expressed per square millimeter.

9.2 ADDITIONAL ENDPOINTS

9.2.1 Additional Pharmacodynamic Endpoints

- Absolute and relative change from baseline in FeNO at 12 weeks.
- Absolute and relative change from baseline in the average FeNO from 6 to 12 weeks.

9.2.1.1 Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour. Further details on the procedure for measuring exhaled nitric oxide with NIOX will be provided in a separate instruction manual. FeNO will be performed at multiple times during the study as specified in the study flowchart ([Section 1.2](#)).

Treatment effect on FeNO will be assessed at the end of treatment (12 weeks) as both an absolute and relative change from baseline. In addition, FeNO will be assessed at multiple time points during the treatment period and the change from baseline in average FeNO from 6 to 12 weeks will be assessed.

9.2.2 Safety endpoints

The same safety assessments will be applied across all arms. Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI), will be collected at every visit. The Investigator will ask the patient how he/she has felt since the last study visit. The study specific and general safety criteria are detailed in [Section 10.4](#). To assure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in [Section 6.4.1](#).

Safety observations

- The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow up the outcome of SAEs /AESI until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- In case of any SAE/AESI with immediate notification brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor.

9.2.2.1 Adverse events

Adverse events for each patient will be monitored and documented from the time the patient gives informed consent at Visit 1 until the End-of Study Visit or till the rollover to the extension study except for SAEs and AESIs.

Adverse events, adverse events with special interest (AESI) and serious adverse events (SAEs) will be reported as described in [Section 10.4](#).

Refer to [Section 10.4](#) to [Section 10.7](#) for details.

9.2.2.2 Laboratory safety variables

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

The clinical laboratory tests will be conducted by an accredited (College of American Pathologists or equivalent) central laboratory with national and regional clinical licenses as required for diagnostic testing and must provide evidence of participation in proficiency testing, as appropriate. After reviewing the laboratory report and evaluating any results that are outside the normal range, the Investigator must sign and date the laboratory report. Abnormal laboratory values that are considered to be clinically significant by the Investigator must be repeated as soon

as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of the persistent abnormality is determined.

Refer to [Section 1.2](#) Study Flow Chart for the description of the clinical laboratory evaluations and the schedule of laboratory evaluations performed throughout this study.

The **clinical laboratory testing** parameters that will be measured are:

- **Hematology:** hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count (neutrophils, eosinophils, basophils, monocytes and lymphocytes), and total red blood cell count.
- **Coagulation:** Prothrombin time, partial thromboplastin time (PTT) at Visit 1 only
- **Serum chemistry:** creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase (LDH), electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. The blood sample must be taken with the patient in fasting state which means no intake of any food or drink except for water for at least 8 hours. (If the visit can only be done during the day and the patient is not under fasting conditions, the patient should eat light food and the site should document that serum chemistry is not taken under fasting conditions).
- **Anti-nuclear antibody (ANA)** at Visit 1 for all patients and at Visit 8 only for patients planned to participate in the OLE. Note: Anti-ds DNA antibody will be tested if ANA is positive ($\geq 1:160$ titer).

Other laboratory safety testing that will be measured includes:

- **Urinalysis:** Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin. A quantitative measurement for glucose, protein, erythrocytes, and leucocytes will be performed in the event that the urine dipstick is positive for any of the above parameters. If the urine dipstick is positive for proteins, a microscopic analysis will be performed.
- **Virus serology testing:** (at Visit 1 for all patients and at Visit 8 only for patients planned to participate in the OLE) hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb [total and IgM]) and hepatitis C virus antibodies (HCV Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies). Patients who are Total-HBcAb positive and HBsAg negative at Visit 1 must undergo HBV DNA testing prior to randomization to determine eligibility. In case of results showing HCV Ab positive, HCV RNA testing must be performed prior to randomization to determine eligibility. At Visit 8, the follow-up testing noted above (HBV DNA or HCV RNA) must be done as needed to determine eligibility for the OLE study. Refer to [Table 1](#) for eligibility interpretation of hepatitis serology results.

Table 1 - Hepatitis Serology Eligibility Interpretation

Hepatitis Serology Result	Protocol Action
HBsAg positive or indeterminate	Excluded
IgM-HBcAb positive	Excluded
total-HBcAb positive (with or without HBsAb positive)	Test for HBV DNA <ul style="list-style-type: none"> • If HBV DNA positive/detected: Excluded. • If HBV DNA negative/not detected: Eligible^a.
HBsAb positive, HBsAg negative, HBcAb negative	Eligible
HCV Ab positive	Test for HCV RNA <ul style="list-style-type: none"> • If HCV RNA positive/detected: Excluded. • If HCV RNA negative/not detected: Eligible.

^a It is recommended that patients who are receiving potentially immunosuppressive therapy and are HBcAb positive and HBV DNA negative undergo surveillance HBV DNA studies every 1-3 months depending upon the individual potential therapeutic risk and comorbidities. Repeat HBV DNA testing should be considered at Visit 8 for these patients. If necessary, a hepatologist should be consulted on a case-by-case basis.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix D](#).

9.2.2.3 Vital signs

Vital signs include: blood pressure (mmHg), heart rate (beats per minute), respiration rate (breaths per minute) and body temperature (degrees Celsius). 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. Body temperature may be measured as oral or auricular, but at a clinical site, temperature must be measured consistently with the same method throughout the study. Refer to [Section 1.2](#) Study Flow Chart for the schedule of vital signs performed throughout this study.

9.2.2.4 Oxygen saturation

On Visits 2 and 9, oxygen saturation will be measured by pulse oximetry before the bronchoscopy procedure to ensure patient suitability (See [Section 10.1.2](#) and [Section 10.1.10](#)). The pre-bronchoscopy oxygen saturation (%) will be recorded in the eCRF. In addition, during and after the bronchoscopy procedure, the patient's oxygen saturation will be monitored for safety, as per the clinical site's standard procedures.

9.2.2.5 Physical Examination

Physical examinations 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. Refer to [Section 1.2](#) for the schedule of physical examinations performed throughout this study.

9.2.2.6 Electrocardiogram (ECG) variables

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 investigator should review the ECG and document his/her interpretation signed and dated on the ECG print out. The original trace is kept as source data. Electrocardiogram tracings are also read manually by independent, certified and “centralized” cardiologists, who determine ECG parameters and who in addition alert the Investigator and the Sponsor of any clinically significant findings or changes. These manually read tracings are the ECG tracing of record for this clinical trial. A specific written manual regarding the procedures related to the centralized ECG reading are provided to each investigator. Refer to the ECG manual for further details.

Note: Any abnormal ECG parameter should be immediately rechecked for confirmation before making a decision of permanent discontinuation of treatment with dupilumab for the concerned patient.

9.2.2.7 Pregnancy test

A serum pregnancy test (β -human chorionic gonadotrophin) will be performed at screening (Visit 1) in women of childbearing potential, and a urine dipstick pregnancy test will be performed at Visit 3 prior to randomization and other visits. A negative result must be obtained at Visits 1 and 3 prior to randomization. Refer to [Section 1.2](#) Study Flow Chart for the schedule of pregnancy test performed throughout this study.

9.2.3 Systemic drug concentration and anti-drug antibodies

9.2.3.1 Sampling time

Predose blood samples will be collected for determination of serum functional dupilumab and anti-dupilumab antibodies as designated in the study flow chart (see [Section 1.2](#)). The date of collection should be recorded in the patient e-CRF. The date and time also will be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

If an SAE occurs in a patient, blood samples should be collected for determination of functional dupilumab concentration, and anti-dupilumab antibody assessment at or near the onset and completion of the occurrence of the event, if possible. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled systemic drug concentration page in the e-CRF must be completed as well.

Patients who discontinue early from treatment or patients who choose not to participate in the OLE study 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. Patients may be scheduled for additional follow-up ADA assessments after the EOS visit if necessary based on the overall assessment of antibody titers and clinical presentation.

9.2.3.2 Handling procedure

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of systemic drug concentration and anti-drug antibodies is provided in [Table 2](#).

Table 2 - Summary of handling procedures for dupilumab and anti-dupilumab antibody

Sample type	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Blood sample volume	5 mL	5 mL
Anticoagulant	None	None
Blood handling procedures	See Operational Manual	See Operational Manual
Serum aliquot split	Two aliquots	Two aliquots
Storage conditions	<6 months: below -20°C <24 months: below -80°C (preferred)	<6 months: below -20°C <24 months: below -80°C (preferred)
Serum shipment condition	In dry ice	In dry ice

9.2.3.3 Bioanalytical method

Serum samples will be assayed using validated methods as described in [Table 3](#).

Table 3 - Summary of bioanalytical methods for dupilumab and anti-dupilumab antibody

Analyte	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	Electrochemiluminescence
Site of bioanalysis	Regeneron	Regeneron

9.2.3.4 Systemic drug concentrations and Anti-drug antibody parameters

Predose serum dupilumab concentrations at Visit 3 (Day 1), dupilumab trough levels at Week 2, Week 6, and Week 8 and Week 12 and follow-up serum dupilumab at Week 18 and Week 24 (EOS) will be provided.

Anti-dupilumab antibody status (negative or titer value, if positive in the ADA assay) at Visit 3 (Day 1), Week 8, Week 12 and Week 24 (EOS) will be provided.

Unused samples collected for drug concentration or ADA analyses may be used for exploratory biomarker research, to investigate unexpected AEs or for drug concentration assessments.

9.3 EXPLORATORY ENDPOINTS

9.3.1 Exploratory Efficacy endpoints

- Change from baseline in spirometry including FEV₁
 - Absolute change from baseline in pre-bronchodilator FEV₁ at Weeks 2, 4, 6, 8 and 12,
 - Percent change from baseline in pre-bronchodilator FEV₁ at Weeks 2, 4, 6, 8 and 12,
 - Change from baseline in other lung function measurements (% predicted FEV₁, forced vital capacity [FVC], forced expiratory flow [FEF]_{25-75%}) at Weeks 2, 4, 6, 8 and 12.
- Change from baseline in morning [AM]/evening [PM] peak expiratory flow [PEF] at Weeks 2, 4, 6, 8 and 12.
- Change from baseline in Asthma Control Questionnaire 5-question version [ACQ-5] score at Weeks 4, 8 and 12.

9.3.1.1 Disease-specific efficacy measures

9.3.1.1.1 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with the ATS/ ERS guidelines (17). For pre-bronchodilator measured parameters, including FEV₁, PEF, FVC, FEV₁/FVC and FEV 25-75%, spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of long-acting muscarinic antagonist (LAMA) for at least 24 hours.

At all visits, spirometry should be performed between 6:00 AM and 12:00 PM. 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 patient standing or in another position, this should be noted on the spirometry report. For any patient, the position should be consistent throughout the study.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria.

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 test).

Automated best efforts, which combine FEV₁ and FVC are not acceptable.

The spirometer must be calibrated following the principles of the ATS/ERS guidelines every day that a study patient is seen and spirometry is carried out. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (ie, 3-liter syringe) that is used to calibrate the spirometer be subjected to a validated calibration according to the manufacturer's specifications.

Further details on spirometry will be available in a separate operational manual provided to the sites.

9.3.1.1.2 *Reversibility*

If not documented within 5 years of screening, a reversibility test may be administered during screening following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Reversibility in this circumstance could be demonstrated and recorded in a spirometry assessment regardless of FEV₁ compliance with entry criterion at that visit. Patients will receive two to up to four puffs of albuterol/salbutamol from a primed MDI. Alternatively and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. Reversibility, which is defined as an increase in absolute FEV₁ of 12% over the baseline value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of bronchodilator administration. If the patient does not meet the reversibility at Visit 1, up to 3 repeat assessments can be performed at any time (ie, unscheduled visits) prior to Visit 2.

9.3.1.1.3 *ACQ-5 (Asthma Control Questionnaire, 5-question version)*

The ACQ-5 was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment) (see [Appendix G](#)).

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

Measurement properties such as reliability and ability to detect change have been documented in the literature ([18](#)).

9.3.1.2 Disease-specific, daily efficacy assessments

9.3.1.2.1 Electronic diary/ PEF meter

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

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

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

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

Baseline AM PEF will be the mean AM measurement recorded for the 7 days prior to Visit 2, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to Visit 2. Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Visit 2.

Information derived from the electronic PEF meter will be evaluated by the Investigator at study visits.

9.3.2 Exploratory Pharmacodynamic Analyses

To evaluate the mechanism of action of dupilumab, biomarkers related to asthmatic inflammation and Th2 polarization will be assessed in bronchoscopy samples, including BALF, bronchial brushings and bronchial biopsies. RNA will be isolated from these samples to characterize treatment related changes in gene expression. In addition, selected biomarkers will be assessed in peripheral blood to allow correlation with the airway and/or therapeutic responses, to document the time course of drug response, and to compare with observations in other dupilumab clinical studies.

All samples will be archived to allow further analyses related to the mechanism of action of dupilumab. More detailed information on the collection, handling, transport and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate laboratory manual.

The exploratory biomarkers include:

- **PD Biomarkers in blood (at Visits 1 , 2 [baseline], 6 [6 weeks] and 9[12 weeks] unless otherwise noted):**
 - TARC,
 - PARC,
 - Monocyte chemotactic protein-4 (MCP-4),
 - Periostin ,
 - ECP,
 - Eotaxin 3,
 - IgE: total IgE (at Visits 1, 2, 6 and 9) and multi-allergen-specific IgE panel, which includes Staphylococcal enterotoxin (SAE) A & B IgE (at Visits 2 and 9 only),
 - Cytokines: IL-4, IL-5, IL-6, IL-13, TNF- α , IFN- γ ,
 - Note: Samples taken at Visits 1 and 2 will be analyzed for the PD biomarkers listed above for all patients who are randomized. Samples from patients who are not randomized may be analyzed or stored for future use (See [Section 10.1](#)).
- BALF will be assessed for evidence of overall inflammation, eg, chemokines, inflammatory proteins and inflammatory cells, as specified in the laboratory manual.
- **RNA:** RNA will be isolated from bronchoscopy samples (biopsy, brushings, and BAL) and whole blood and will be subjected to discrete panels of PCR analyses to evaluate genes related to inflammation including eosinophils, lymphocyte subsets and macrophages. RNA will also be stored for future analyses which may include microarray analysis.
- Additional inflammatory cell counts in bronchial epithelium and submucosa will be assessed by IHC/histology, including:
 - Mast cells, eosinophils, total T lymphocytes and T helper lymphocytes in bronchial epithelium.
- Basement membrane thickness will be measured in bronchial biopsies
- Brushings will be obtained for analysis of inflammatory protein expression, as specified in the laboratory manual.
- **Inflammatory cell counts in BALF** including: eosinophils, macrophages, lymphocytes, neutrophils, epithelial cells, mast cells
 - Bronchoalveolar lavage will be performed at baseline and at the end of treatment (12 weeks) according to the study manual. Cells will be recovered by centrifugation and slides will be prepared for cellular differential. The procedure for slide preparation and staining will be described in a separate study manual. Differential cell counts will be performed by a central reader on duplicate slides for each time point (baseline and 12 weeks). The absolute number and percentage of each cell type present will be determined and the change from baseline in the percentage of each cell type (eosinophils, macrophages, lymphocytes, neutrophils, epithelial cells, mast cells) will be calculated.

9.3.3 Pharmacogenetic assessment

9.3.3.1 *Optional stored DNA sample*

For those patients who signed the optional pharmacogenetic informed consent form, blood samples for exploratory genetic analysis of DNA will be collected at the study visit as specified in the study flow chart and this sample will be stored for future analysis. Specific procedures for collection, storage and shipping of pharmacogenetic samples will be provided in a lab manual.

The DNA sample 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 single nucleotide polymorphism array analysis and/or to whole exome sequencing or whole genome analysis in order to thoroughly explore genetic associations with disease risk and/or progression or treatment response (efficacy or adverse reactions).

The blood sample will be transferred to a site that will, on behalf of Sanofi, extract DNA from the sample. The contractor site can be located outside of your country, within or outside of the European Union.

The DNA that is extracted for genetic testing will be assigned a second number, a Genetic ID (de-identification code) that is different from the Patient ID. This “double coding” is performed to separate a patient’s medical information and DNA data.

The clinical study data (coded by Patient ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Patient ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The aliquots of DNA sent to the bioanalytical laboratories for specific genetic testing will be destroyed after completion of that specific analysis and issuance of the related analytical data.

For future genetic analysis, the DNA will be stored for up to 15 years from the completion of the clinical study report in the US.

9.4 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For patients who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes (any genetic analysis subject to additional consent per [Section 9.3.3](#)). For patients who have consented to it, archival blood samples will be collected at the visit specified in the study flow chart and processed and stored as described in the laboratory manual. For patients who have consented to it, samples collected during the bronchoscopy procedure (BAL, brushings, biopsy) will also be archived.

These archived serum samples, and any residual or leftover serum, plasma, blood or bronchoscopy samples (BAL, brushings, biopsy) remaining from planned laboratory work, may be used for research purposes related to asthma (eg, exploratory biomarkers of disease or drug effect), dupilumab mechanism of action, additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol. These samples will remain labelled with the same identifiers as the ones used during the study (ie, patient ID, sample ID). Samples will be stored for up to 15 years from the completion of the clinical study report. They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see [Section 14.3](#) and [Section 14.5](#)).

9.5 APPROPRIATENESS OF MEASUREMENTS

Bronchoscopy and the associated procedures of endobronchial biopsies, BAL and bronchial brushings have been employed in numerous clinical studies in asthma to characterize the underlying airway inflammation and demonstrate treatment effects.

Richmond et al. studied the intrasubject variability with respect to inflammatory cell counts in endobronchial biopsies from patients with mild to moderate stable asthma and concluded that in order to obtain 80% power to detect a significant difference for lymphocytes (CD3+, CD4+ or CD8+) or eosinophils (EG2+), 15 subjects was an optimal minimal sample size (19). In a clinical trial with omalizumab in allergic asthma, a treatment effect on the numbers of inflammatory cells, including eosinophils, total T-lymphocytes and T-helper cells, in the submucosa of bronchial biopsies was observed with a sample size of 14 per group (13). Ward et al. studied the intrasubject variability of cellular parameters, including eosinophils, in BAL in clinically stable, symptomatic patients with mild to moderate asthma and concluded that sample sizes between 15 and 20 were adequate to detect meaningful differences in these parameters (20). More severe patients, however, may demonstrate greater variability.

The effect of dupilumab on inflammatory cell counts within BAL or bronchial biopsies has not been previously determined. Therefore, the effect of dupilumab on FeNO, a surrogate marker for airway inflammation, has been used to guide the length of treatment and sample size in this exploratory study with dupilumab. In the prior studies, dupilumab treatment resulted in a marked reduction in FeNO as early as 4 weeks after the start of treatment (21). In addition, dupilumab treatment results in a rapid decrease in soluble attractants of inflammatory cells, such as the chemokine TARC, as early as 1 week after the start of treatment with a nadir by 4 weeks after treatment initiation (21). In clinical studies of other monoclonal antibody treatments for asthma, treatment effects on inflammatory cells in bronchial biopsies can be seen at 10 weeks after treatment initiation with mepolizumab (22) and at 16 weeks of treatment with omalizumab (13).

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The clinical trial consists of three parts, using an add-on therapy approach to inhaled corticosteroid in combination with LABA:

- Screening (5 weeks and optional addition of 7 days and not to exceed 6 weeks of screening; Visits 1 & 2).
- Randomized Treatment Period (12 weeks; Visits 3-9).
- Post-treatment Period (12 weeks; Visits 10-13).

The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within the ± 3 day visit window, unless otherwise noted.

All the study visits should be scheduled in the morning, to have the spirometry performed and the patient should be fasting for serum chemistry tests. However, if the visit can only be done at a different time of the day and the patient is not fasting, then he/she should be advised to have a light meal and the site should document that serum chemistry was not obtained under fasting conditions. For spirometry, it should be performed at approximately the same time of the day at each visit throughout the study.

Patients should be reminded that sexually active female patients of reproductive potential are required to practice effective contraception during the entire study duration, while taking dupilumab and for 12 weeks post last IMP dose.

Prior to all screening assessments, after discussion of participation in the study, the written consent form (including voluntary participation in pharmacogenetic testing/future use of samples) must be signed and dated.

Although the screening assessments for this study are grouped under the headings of Visits 1 and 2 in this protocol, it is possible for them to be performed over more than 2 site visits if necessary, as long as the screening visit window prior to randomization (Day 1) is respected and all results related to inclusion/exclusion criteria are available prior to the baseline bronchoscopy procedure. If needed, in order to (re)confirm eligibility by repeating assessments and to optimize scheduling of the baseline bronchoscopy, an additional up to 7 days may be added to the screening period on the condition that: overall screening period will not exceed 6 weeks and Visit 2 (and bronchoscopy) will occur at least 3 days prior to visit 3 (day 1). Patients who failed the initial screening for certain inclusion/exclusion criteria (time-dependent and those that may be transient), may be rescreened for study eligibility one additional time if deemed appropriate at the discretion of the investigator and as long as the screening failure occurred prior to baseline bronchoscopy. Patients who are re-screened, must sign a new consent form and must repeat all of the Visit 1 procedures (refer to [Section 8.4](#) for further instructions related to rescreening) unless a prior assessment is performed within the time frame permitted prior to study entry. For patients who participate in screening visits but are subsequently not randomized into the clinical trial, further assay of stored specimens will be discontinued unless re-designated for the alternative purposes of biomarker assay development or establishment of biomarker and RNA values for patients with asthma.

10.1.1 Visit 1 (Week -4± 1, -35 to -21 days)

Following a discussion of participation in the clinical trial, informed consent must be obtained and documented. These steps precede any study procedures.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number and register screening visit.
- Interview to collect patient demographic information, asthma history (including smoking habits), other medical history and surgical history, and prior and concomitant medications.
- Inquire about AEs/SAEs and background asthma therapy tolerability.
- Review entry criteria to assess eligibility, with special attention to verify the following:
 - Prescribed treatment dosage meets the per-protocol definition of medium to high dose ICS (≥ 250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) (See [Appendix B](#)) in combination LABA for at least 3 months with a stable dose ≥ 1 month prior to Visit 1,
 - Documentation of reversibility within 5 years of Visit 1 of at least 12% and 200 mL in FEV₁ after the administration of 200 to 400 mcg albuterol/salbutamol (2 to 4 inhalations of albuterol/salbutamol or of a nebulized solution of albuterol/salbutamol. **OR** documentation of airway hyperresponsiveness (methacholine PC₂₀ < 8 mg/mL [or PC₂₀ < 16 mg/mL on ICS]) within 5 years of Visit 1,
 - If no documented reversibility or airway hyperresponsiveness, then reversibility must be assessed during screening.
- Obtain urine for urinalysis.
- Perform 12-lead electrocardiography (ECG).
- Measure vital signs [blood pressure, heart rate, respiration rate, body temperature], weight (kg), and height (cm).
- Perform blood sampling (fasting) for the following tests:
 - PD Biomarkers (refer to [Section 9.3.2](#)). During the screening period, blood collected for biomarker analysis will be stored. The planned analysis will only be conducted for patients who are randomized into the clinical trial. Blood collected from patients who are not subsequently randomized into the clinical trial may be used for biomarker assay development or establishment of biomarker values for patients with asthma, or stored for future use,
 - Clinical laboratory testing: hematology, serum chemistry, coagulation, and anti-nuclear antibody (ANA) (see [Section 9.2.2.2](#) for details),
 - Virus serology (see [Section 9.2.2.2](#) for detail),
 - For women of childbearing potential, serum β -HCG pregnancy test.
- Perform any additional laboratory testing required to confirm suitability for the bronchoscopy procedure, as per site's standard operating procedures / local requirements.
- Perform physical examination.

- Administer ACQ-5.
- Measure exhaled nitric oxide.
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour,
 - Verify $\text{FeNO} \geq 26 \text{ppb}$,
 - Three attempts may be made during the Screening Period to meet the qualifying criteria for FeNO.
- Perform spirometry
 - Entry criteria at Visit 1 include the requirement of a specific FEV_1 and demonstration of reversibility, if not previously documented, as specified in [Section 7.1](#). See below for additional directions,
 - Spirometry will be performed in the morning, 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours,
 - Pre-bronchodilator Forced expiratory volume (FEV_1) must be 55 to 85% predicted normal,
 - If a patient's FEV_1 does not qualify, then the patient may return to the site on a subsequent day to attempt to meet the spirometry criteria (3 pre-randomization attempts maximum). Patients must meet this criterion prior to the bronchoscopy procedure on Visit 2,
 - Treatment Period stability limits will be established for FEV_1 and PEF (The Treatment Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Visit 2).
- If reversibility or airway hyperresponsiveness is not documented from historical data within 5 years of screening (See Inclusion Criteria [I 01](#)), establish reversibility
 - Reversibility must be at least 12% and 200 mL in FEV_1 after 200 mcg to 400 mcg (2 to 4 inhalations of albuterol/salbutamol or of a nebulized solution of albuterol/salbutamol, if considered as a standard office practice,
 - If a patient's reversibility does not qualify, then the patient may return to the site on a subsequent day to attempt to meet the reversibility criteria (3 pre-randomization attempts maximum). Patients must meet this criterion prior to the bronchoscopy procedure on Visit 2.
- As per local standard of care, perform chest X-ray if no chest imaging (X-ray, CT, MRI) available within the previous year and if there is local requirement.
- Dispense electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule the bronchoscopy procedure (Visit 2, Week -2 to -0.5) when screening results will be available and request patient to come in fasting.

10.1.2 Visit 2 (Week -2 to -0.5, -14 to -3 days)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Compliance with use of the mandatory background therapy, ICS in combination with LABA, as defined as:
 - $\geq 80\%$ of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient electronic diary during the screening period.
- Obtain urine for urinalysis.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature).
- Measure oxygen saturation. If oxygen saturation $< 92\%$ on room air, the bronchoscopy should be postponed.
- Perform blood sampling (fasting, prior to prednisone administration) for the following tests:
 - PD Biomarkers (refer to [Section 9.3.2](#))

During the screening period, blood collected for biomarker analysis will be stored. The planned analysis will only be conducted for patients who are randomized into the clinical trial. Blood collected from patients who are not subsequently randomized into the clinical trial may be used for biomarker assay development or establishment of biomarker values for patients with asthma or stored for future use.
 - Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to [Section 9.4](#)),
 - Whole blood RNA

During the screening period, blood collected for whole blood RNA analysis will be stored. The planned analysis will only be conducted for patients who are randomized into the clinical trial. Blood collected from patients who are not subsequently randomized into the clinical trial may be used for assay development or establishment of RNA values for patients with asthma or stored for future use.
 - Clinical lab testing: hematology/chemistry (refer to [Section 9.2.2.2](#)).
- Administer ACQ-5.
- Measure exhaled nitric oxide.

- Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour.
- Perform spirometry.
 - Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product,
 - Treatment Period stability limits will be established for FEV1 and PEF (The Treatment Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Visit 2),
 - Investigator must review the spirometry results and confirm the patient is able to undergo the bronchoscopy procedure. If pre-bronchodilator FEV1 < 55% of predicted normal then bronchoscopy should be postponed.
- Review entry criteria and reconfirm eligibility based on review of Inclusion/Exclusion Criteria.

If the patient meets all inclusion and does not meet any exclusion criteria:

- Perform bronchoscopy as per separate procedure manual.
- Administer prednisone/prednisolone 40 mg po and dispense prednisone/prednisolone for continued treatment.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Schedule a site visit within a minimum of 3 days and a maximum of 2 weeks (Visit 3, Week 0).

10.1.3 Visit 3 (Week 0, Day 1)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- For women of childbearing potential, obtain urine and perform urine dipstick pregnancy test.
- Perform 12-lead electrocardiography (ECG).
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature) and weight.

- Compliance with use of the mandatory background therapy, ICS in combination with LABA, as defined as:
 - $\geq 80\%$ of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient electronic diary during the screening period.
- Review suitability for dosing. For women of childbearing potential, confirm negative urine pregnancy test.
- Call IVRS/IWRS to register visit, randomize the patient if entry criteria are met, and receive the first assignment for 2 treatment kit numbers.
 - Note: Please screen-fail the patient if entry criteria are not met.
- Perform blood sampling (prior to administration of IMP) for the following tests:
 - For those patients who have signed a specific pharmacogenetic informed consent form, collect blood sample for DNA, please refer to [Section 9.3.3](#).
 - Systemic drug concentration and ADA (refer to [Section 9.2.3](#))
- Dispense and administer IMP (See [Section 8.1.4](#)).
 - Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 2 \pm 3 days).

10.1.4 Visit 4 (Week 2)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature).
- Perform blood sampling (prior to administration of IMP) for the following tests:
 - Systemic drug concentration (refer to [Section 9.2.3](#)).
- Perform spirometry.

- Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain next treatment kit number.
- Dispense and administer IMP.
 - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 4 ± 3 days) and ask patient to come in fasting.

10.1.5 Visit 5 (Week 4)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability.
- Perform urine dipstick pregnancy test (for women of childbearing potential).
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature).
- Perform blood sampling (fasting, prior to administration of IMP) for the following tests:
 - Clinical lab testing: hematology/chemistry (refer to [Section 9.2.2.2](#)).
- Administer ACQ-5.
- Perform spirometry.
 - Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain next treatment kit number
- Dispense and administer IMP.

- Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 6 \pm 3 days).

10.1.6 Visit 6 (Week 6)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature).
- Perform blood sampling (prior to administration of IMP) for the following tests:
 - PD Biomarkers (refer to [Section 9.3.2](#)),
 - Systemic drug concentration (refer to [Section 9.2.3](#)).
- Measure exhaled nitric oxide:
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour.
- Perform spirometry:
 - Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain next treatment kit number.
- Dispense and administer IMP.
 - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later and ask patient to come in fasting.

10.1.7 Visit 7 (Week 8)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability.
- Perform urine dipstick pregnancy test (for women of childbearing potential).
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature).
- Administer ACQ-5.
- Perform blood sampling (fasting, prior to administration of IMP) for the following tests:
 - Systemic drug concentration and ADA (refer to [Section 9.2.3](#)),
 - Clinical lab testing: hematology/chemistry (refer to [Section 9.2.2.2](#)).
- Measure exhaled nitric oxide.
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour.
- Perform spirometry.
 - Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain next treatment kit number.
- Dispense and administer IMP.
 - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Schedule a site visit 2 weeks later (Week 10 \pm 3 days).

10.1.8 Visit 8 (Week 10)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature)
- If patient plans to participate in the open label extension study, obtain blood samples for virus serology and anti-nuclear antibody (ANA) (see [Section 9.2.2.2](#) for detail).
- Measure exhaled nitric oxide.
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain next treatment kit number.
- Dispense and administer IMP.
 - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- If the patient plans to participate in the open label extension study, perform chest X-ray or MRI if a chest X-ray was not performed at screening and there is no chest X-ray, MRI or high resolution computed tomography (HRCT) scan available within the 12 months prior to screening.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later and ask patient to come in fasting.

10.1.9 Visits 8.1 and 8.2 (Week 12 and 14 / Optional Treatment Visits)

- These visits are optional visits and would occur only if the bronchoscopy at EOT needs to be postponed as described in [Section 10.1.10](#).
- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability.

- Perform urine dipstick pregnancy test (for women of childbearing potential) at Visit 8.1.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature).
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain next treatment kit number.
- Dispense and administer IMP.
 - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Schedule a site visit 2 weeks later for bronchoscopy (Visit 9/EOT) or additional IMP administration (Visit 8.2).
 - If next visit will be the End-of-Treatment Visit, remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit. Ask patient to come in fasting.

10.1.10 Visit 9 (Week 12 [14 or 16] / End-of-Treatment)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Confirm suitability for bronchoscopy procedure.
 - Measure oxygen saturation. If oxygen saturation < 92% on room air, the bronchoscopy should be postponed,
 - If patient is not suitable to undergo bronchoscopy for either clinical (at the discretion of the PI) or administrative (in consultation of study management) reasons, but would be suitable within the next 4 weeks (by Week 16), then continue in study using optional visits (see [Section 10.1.9](#)) to allow continuation of every 2 week dosing and reschedule the End-of-Treatment visit. If necessary, the bronchoscopy may be postponed up to 4 weeks. If the bronchoscopy is postponed, the patient should receive an additional dose of IMP at this visit and complete assessments for Visit 8.1 and be rescheduled for the bronchoscopy. All the EOT assessments should also be postponed and performed at the time of the bronchoscopy. The bronchoscopy should be scheduled 7 – 15 days after the last IMP dose and must occur 12 – 16 weeks after Day 1. Patients may receive up to 2 additional doses to facilitate this rescheduling,
 - If patient is suitable to undergo bronchoscopy then perform the following EOT assessments.

- Obtain urine for urinalysis.
- Perform urine dipstick pregnancy test (for women of childbearing potential).
- Perform 12-lead electrocardiography (ECG).
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature) and weight.
- Perform physical examination.
- Administer ACQ-5.
- Perform blood sampling (fasting) for the following tests:
 - PD Biomarkers (refer to [Section 9.3.2](#)),
 - Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to [Section 9.4](#)),
 - Systemic drug concentration and ADA (refer to [Section 9.2.3](#)),
 - Clinical lab testing: hematology/chemistry (refer to [Section 9.2.2.2](#)).
- Measure exhaled nitric oxide
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour.
- Perform spirometry
 - Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product,
 - Investigator must review the spirometry results and confirm the patient is able to undergo the bronchoscopy procedure. If pre-bronchodilator FEV₁ < 55% of predicted normal then bronchoscopy should be postponed,
- Perform bronchoscopy as per separate procedure manual.
- Administer prednisone/prednisolone 40 mg po and dispense prednisone/prednisolone for continued treatment.
- Call IVRS/IWRS to register visit.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.

- If patient will participate in the OLE, complete assessments as described above (including bronchoscopy) and then enroll in OLE and proceed as per OLE protocol.
- Schedule a site visit 2 weeks later (Week 14 \pm 3 days) if patient will not enroll in the OLE.

10.1.11 Visit 10 (Week 14 [16 or 18]/ Post Treatment Period)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature).
- Perform spirometry.
 - Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Schedule a site visit 2 weeks later (Week 16 \pm 3 days) and ask patient to come in fasting.

10.1.12 Visit 11 (Week 16 [18 or 20] / Post Treatment Period)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Perform urine dipstick pregnancy test (for women of childbearing potential).
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature).
- Administer ACQ-5.
- Perform blood sampling (fasting) for the following tests:
 - Clinical lab testing: hematology/chemistry (refer to [Section 9.2.2.2](#)).
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 18 \pm 3 days).

10.1.13 Visit 12 (Week 18 [20 or 22] / Post Treatment Period)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Perform blood sampling for the following tests:
 - Systemic drug concentration (refer to [Section 9.2.3](#)).
- Perform spirometry
 - Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with LABA as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 6 weeks later (Week 24 \pm 3 days) and ask patient to come in fasting.

10.1.14 Visit 13 (Week 24 [26 or 28] / End-of-Study Visit)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Obtain urine for urinalysis.
- Perform urine dipstick pregnancy test (for women of childbearing potential).
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature) and weight.
- Perform physical examination.
- Administer ACQ-5.
- Perform blood sampling (fasting) for the following tests:
 - Systemic drug concentration and ADA (refer to [Section 9.2.3](#)),
 - Clinical lab testing: hematology/chemistry (refer to [Section 9.2.2.2](#)).
- Measure exhaled nitric oxide.
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour.
- Perform spirometry
 - Spirometry will be performed in the morning 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 (vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.

- Download electronic diary/PEF meter and take back the device.
- Call IVRS/IWRS to register the EOS date.

10.2 DEFINITION OF SOURCE DATA

All evaluations that are reported in the case report form must be supported by appropriately identified source documentation.

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

All the data collected in the e-CRF should be transcribed directly from source documents. Data downloaded from the study-associated central laboratories, spirometry, nitric oxide measurement, and patient electronic diary / PEF meter will be considered source data.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the AE is sufficiently resolved and unlikely to recur after resuming therapy with IMP.

In addition, the following conditions(s) will be causes for temporary treatment discontinuation:

- Infections or infestations that do not respond to medical treatment.
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per [Appendix D](#).

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients must be withdrawn from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients must be withdrawn from the treatment (ie, from any further investigational product or study procedure) for the following reasons:

- At their own request or at the request of their legally authorized representative (Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Any code breaking requested by the Investigator will lead to permanent treatment discontinuation.
- Pregnancy.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Diagnosis of a malignancy during the study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (See [Appendix F](#)).
- Serum ALT >3 ULN and Total Bilirubin >2ULN (See [Appendix D](#)).
- Serum ALT >5 ULN if baseline ALT \leq 2 ULN or ALT >8 ULN if baseline ALT >2 ULN ([Appendix D](#)).

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 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.

If possible, and after the permanent discontinuation of treatment, the patients should complete the EOT visit assessments and enter the Post Treatment Period for continued safety follow-up.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic 2 weeks after the last dose of IMP to complete the EOT assessments, with the exception of the bronchoscopy, and then participate in the Post Treatment period according to the visit schedule. For example, if a patient discontinues treatment at Visit 4, he/she would undergo assessments indicated for Visit 9 (EOT), except the bronchoscopy, 2 weeks after his/her last IMP dose and then the patient would continue in the study according to the visit schedule until the end of study visit (Visit 13). In this way, all patients would undergo 12 weeks of safety follow-up after their last IMP dose.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

If possible, the patients are assessed using the procedure normally planned for the end-of-treatment visit with the exception of the bronchoscopy procedure.

Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. If possible, the patients should be assessed using the procedures defined above.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

A patient should only be designated as lost to follow-up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.3.6 Replacement of patients

A patient who received treatment and prematurely ends his/her treatment prior to Week 12 may be replaced in order to have a sufficient number of patients with adequate bronchial biopsies to assess the main endpoints.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Since asthma exacerbations are representative of the underlying disease (persistent asthma) of the study population, these events should not be reported as AEs unless fulfilling the criteria for a serious adverse event as described in [Section 10.4.1.2](#). For this study, asthma exacerbations will be managed by the Investigators based on their medical judgment and applicable national / international asthma management guidelines.

Any surgical procedures are not considered as adverse events, including the bronchoscopy procedure, but an adverse event caused by the procedure will be reported as AE.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or

- Is a congenital anomaly/birth defect
- Is a medically important event
Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm,
 - Anaphylaxis (refer to [Appendix E](#) for Definition of Anaphylaxis),
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
 - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse,
- ALT >3 x ULN + total bilirubin >2 x ULN,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions,
- Cancers diagnosed during the study,
- Chronic neurodegenerative diseases (newly diagnosed).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described [Section 10.4.2](#), even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

- Anaphylactic reactions or - systemic allergic reactions that are related to IMP and require treatment (refer to [Appendix E](#) for Definition of Anaphylaxis).
- Severe injection site reactions that last longer than 24 hours.

- Any infection meeting at least one 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 (see [Appendix F](#)),
 - Note: antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.
- Significant ALT elevation
 - ALT >5 x the upper limit of normal (ULN) in patients with baseline ALT ≤2 x ULN;
or
 - ALT >8 x ULN if baseline ALT >2 x ULN.
- 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 one of the seriousness criteria (see [Section 10.4.1.2](#)).
 - 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 (not based on systematic pills count) and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms,
 - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the 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.

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Not applicable

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
 - Symptomatic and/or,
 - Requiring either corrective treatment or consultation, and/or,
 - Leading to IMP discontinuation or modification of dosing, and/or,
 - Fulfilling a seriousness criterion, and/or,
 - Defined as an AESI.

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team

within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.4.4](#), even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF. Instructions for AE reporting are summarized in [Table 4](#).

Table 4 - Summary of adverse event reporting instructions

Adverse event / laboratory abnormality		Reporting timeline
Serious adverse event		Within 24 hours
Pregnancy		Within 24 hours
Overdose	Symptomatic	Within 24 hours
	Asymptomatic	Routine
ALT elevation		
	ALT >5 ULN if baseline ALT is ≤2 ULN	Within 24 hours
	ALT >8 ULN if baseline ALT is >2 ULN	Within 24 hours
	ALT >3 ULN plus total bilirubin >2 ULN	Within 24 hours
Anaphylactic reactions, acute systemic allergic reactions or acute allergic reactions that require immediate treatment		Within 24 hours
Severe injection site reactions that last longer than 24 hours		Within 24 hours
Severe infections including parasitic infections		Within 24 hours

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix D](#).

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia.
- Thrombocytopenia.
- Increase in ALT.
- Acute renal insufficiency.
- Suspicion of rhabdomyolysis.

In addition, on-treatment eosinophil counts >3000 cells/ μ L (3.0 giga/L) are to be reported as AEs.

NOTE: In some clinical trials these laboratory abnormalities can be considered as AESIs. For this study, only significant ALT increase will be considered as AESIs (see [Section 10.4.1.3](#)).

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected [eg, wheezing related to asthma].

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

For safety, the treatment code will be unblinded by the Sponsor for reporting to the Health Authority of any suspected unexpected adverse drug reaction (SUSAR) and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor.

In case of a SUSAR, Sanofi Global Pharmacovigilance and Epidemiology will utilize XGRID to reveal medication assignment for regulatory reporting requirements for the particular case.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

Allergic reaction is a potential risk associated with the administration of most therapeutic monoclonal antibodies.

Acute allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Anaphylaxis may represent the most severe form of infusion reaction, but these events may also occur via non-IgE mediated mechanisms (eg, anaphylactoid reactions), or may occur via other immune-mediated mechanisms (eg, cytokine-mediated). Allergic reactions may begin within a few hours and persist up to 24 hours post dosing. Refer to Appendix E “Definition of Anaphylaxis”, which describes the clinical criteria for the diagnosis of anaphylaxis.

10.6.2 Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction in the first 12 weeks. Any anaphylactic reactions, acute systemic allergic reactions or acute allergic reactions that require immediate treatment must be reported as an AESI (within 24 hours) (for further details, see AESI definition in Section 10.4.1.3) and study medication must be permanently discontinued. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Severe injection site reactions

Based on the subcutaneous mode of administration of high doses of protein and on a higher incidence of local injection site reactions observed at the highest dose level (300 mg weekly), severe injection site reactions, are considered as a potential risk. Patients who experience an injection site reaction must be closely monitored for the possibility of a more intense injection site reaction with a future injection. Any severe injection reaction that lasts over 24 hours will be reported as an AESI with immediate notification.

If there is any consideration being given to premedicating before the next dose (for preceding systemic or local allergic symptoms of any type/severity), please contact sponsor prior to dosing patients.

10.6.3 Infections, including parasitic infections

Some biologic therapies have been associated with an increased risk of infection, including opportunistic infection. As a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness.

Any opportunistic infection requiring parenteral or prolonged (>14 days) antibiotics or antituberculosis medication should be considered serious and be reported as AESI with immediate notification. The study medication should be discontinued in case of suspicion of serious infection and a complete diagnostic work-up should be performed (ie, cultures for fungi and/or mycobacteria other than tuberculosis, histopathological or cytological evaluation, antigen detection and serum antibody titers). Patients should be referred to an infectious disease specialist if deemed necessary for diagnostic work up and appropriate treatment.

Since dupilumab binds to IL-4R α , preventing IL-4 and IL-13 activation of their respective receptors, it inhibits the T-helper 2 (Th2) cytokines production. Infections with a diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte responses. The Th2 response is characterized by production of IL-4, IL-13 and IL-5, subsequently generating IgG₁ and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a number of helminthic parasitic diseases. The eosinophilic response to helminths is determined both by the host's immune response and by the parasite, including its distribution, migration, and development within the infected host. Therefore, patients treated with dupilumab may potentially have an increased risk of parasitic infection.

In order to minimize this risk, any patient with an active parasitic infection should be excluded from the study. Similarly, patients with suspected parasitic infection, or those at high risk of parasitic infection are also excluded, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization. During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/ or residence in endemic areas, especially when conditions are conducive to infection (eg, extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc.). Subsequent medical assessments (eg, stool exam, blood tests, etc.) must be performed in order to rule out parasitic infection/infestation. Patients with confirmed parasitic infections during the study should be reported as AESI with immediate notification and will be permanently discontinued from the study.

10.6.4 Elevated liver function tests

No pre-clinical and clinical data has suggested any hepatic toxicity of dupilumab; however, as a general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity.

In order to closely follow liver function tests (LFT), assessment of total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing. Clinical laboratory testing at Visit 1 adds hepatitis screen (HBsAg, HbsAb, HBcAb [total and IgM], HCV Ab). Patients who are -Total-HBcAb positive and HBsAg negative at Visit 1 must undergo HBV DNA testing prior to randomization to determine eligibility. In case of results showing HCV Ab positive, HCV RNA testing must be performed prior to randomization to determine eligibility. At Visit 8, the

follow-up testing noted above (HBV DNA or HCV RNA) must be done as needed to determine eligibility for the OLE study. Refer to [Table 1](#) for eligibility interpretation of hepatitis serology results. Active hepatitis or patients with positive or indeterminate HBsAg, positive IgM-HBcAb or positive hepatitis C antibody (confirmed with HCV RNA) at Visit 1 are excluded from the study (See [E 36](#)). In addition, patients who are total-HBcAb positive and HBV DNA positive are excluded from the study (See [Table 1](#)).

Guidance for the investigation of elevated LFTs is provided in [Appendix D](#).

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size determination and the statistical power are estimated based on the pharmacodynamic endpoint of fractional exhaled nitric oxide (FeNO) as no historical data is available on the main endpoints of bronchial submucosal inflammatory cells. The following assumptions are used for the estimations:

- A difference of 25 ppb in the change from baseline in FeNO at Week 12 between SAR231893 and placebo, and a common standard deviation of 32 ppb (This corresponds to a hypothesized effect size of 0.78).
- A t-test at 1-sided $\alpha=0.05$.
- Not accounting for early dropout, ie, the calculated sample size refers to the size of completers. Definition of completers will be detailed in the statistical analysis plan (SAP) prior to database lock.

Based on the above assumptions, it is estimated that, with a total of 42 completers, or approximately 21 completers per group, the study will have a 80% power to detect a difference of 25 ppb in the change from baseline in FeNO at Week 12 between SAR231893 and placebo. Based on observations in other clinical trials (see [Section 9.5](#)), it is expected that this sample size will be sufficient to evaluate the main PD endpoints in bronchial submucosa.

Approximately 42 patients will be randomized to achieve 21 patients per group with adequate biopsy samples.

The calculations were made using nQuery Advisor 7.0.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

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

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

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 PD and Biomarker analyses population

For the main PD endpoints in bronchial submucosa, the PD population will consist of all randomized patients who underwent baseline and Week12/EOT bronchoscopies and have adequate biopsies for analysis at both baseline and end of treatment. The analysis will be “as-treated” or based on the treatment actually received. If a patient receives in error both placebo and dupilumab during the course of the study, the patient will be included in the dupilumab group.

Analysis population for additional PD/biomarker endpoints will be similarly defined. The details will be specified in the SAP.

11.3.2 Efficacy population

For analyses of exploratory efficacy endpoints, the efficacy population will consist of all randomized patients who have both baseline and a post-baseline spirometry data. The analysis will be “as-treated” or based on the treatment actually received. If a patient receives in error both placebo and dupilumab during the course of the study, the patient will be included in the dupilumab group. Additional exploratory efficacy analyses will be also performed using the conventional mITT population in which patients will be included in the group as randomized.

11.3.3 Safety population

The safety population will consist of all patients randomized and exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

Treatment emergent period for safety population is defined as the time between the first administration of study medication to the end of the Post-treatment Period.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For a patient receiving in error both placebo and dupilumab during the trial, the patient will be included in the dupilumab group (ie, as-treated analysis).

11.3.4 Pharmacokinetics (PK) population

The PK population will consist of all patients in the safety population with at least one non-missing and eligible serum concentration data. Patients will be analyzed according to the treatment actually received.

11.3.5 Anti-drug antibody population

The ADA population will consist of all patients in the safety population with at least one qualified ADA result in the ADA assay following the first dose of the study medication. Patients will be analyzed according to the treatment actually received.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

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

11.4.1.2 Compliance

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

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

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized. In addition, number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%], and >20% under-planned dosing administrations.

11.4.2 Analyses of main endpoints

11.4.2.1 Analysis of main endpoint(s)

The main endpoints (see [Section 9.1](#)), change from baseline in the number of airway submucosal inflammatory cells per surface airway of basal lamina (cells/mm²) and mucin in the bronchial mucosa, will be analyzed using analysis of covariance (ANCOVA) models with fixed terms for treatment, stratification factors of region and ICS dose, and airway submucosal inflammatory cells per surface airway of basal lamina (cells/mm²) and mucin in the bronchial mucosa at baseline as covariates. An estimate and two-sided 90% confidence interval (CI) for the difference in treatment

mean changes will be calculated from the model. No multiplicity adjustment will be made for the main analyses.

Due to the small sample size of the trial, secondary analyses of the main endpoints will be performed using an ANCOVA model similar as above but excluding one or both stratification factors.

Descriptive statistics will also be provided by treatment and timepoint on raw changes and percent changes from baseline.

The main analyses will be based on PD population.

11.4.2.2 Multiplicity considerations

No multiplicity procedures will be used as the study is exploratory in nature.

11.4.2.3 Analyses of exploratory efficacy endpoints

(see [Section 9.3.1](#))

The change from baseline in FEV₁ at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach based on efficacy population. The model will include change from baseline values up to week 12 as response variables, and factors (fixed effects) for treatment, pooled countries / regions, visit, treatment-by-visit interaction, FEV₁ baseline value and baseline-by-visit interaction. 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. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 90% CI and the p-value will be provided for comparisons of each dose against placebo. No imputation will be performed for the MMRM model.

11.4.3 Analyses of additional and exploratory pharmacodynamics and biomarker endpoints

(see [Section 9.2.1](#) and [Section 9.3.2](#))

The values to be used as baselines will be those collected on Visit 2. If any of the scheduled assessments on Visit 2 are technically disqualified (eg, insufficient sample), then values determined at Screening Visit 1 can be used as baseline.

For all parameters, raw data, absolute changes from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point.

Summary plots (mean +/- standard error of the mean) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment group.

11.4.4 Analyses of safety data

(See [Section 9.2.2](#))

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety population using the following common rules:

The baseline value is defined generally as the last available value before the first dose of IMP.

Treatment emergent period for safety population is defined as the time from the first administration of study medication to the end of the Post-treatment Period.

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.4.1 Adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. 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.

Proportion of patients with at least one treatment emergent adverse event (TEAE), serious TEAE and TEAE leading to discontinuation of the study will be tabulated by treatment group. In addition TEAEs will be described according to maximum intensity and relation to the study drug. None treatment emergent serious AE, None treatment emergent AE leading to study discontinuation will be summarized separately.

11.4.4.1.1 AESI

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group.
- The time-to-first event analyzed using K-M methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.

- An overview summary of the number (%) of patients with
 - Any TEAE,
 - Any serious AE (regardless of treatment-emergent status),
 - Any treatment-emergent SAE,
 - Any AE leading to death,
 - Any AESI,
 - Any TEAE leading to permanent study drug discontinuation,
 - Any TEAE by maximum intensity, corrective treatment, and final outcome.

AESI definitions and the method to identify AESIs will be specified in the SAP.

11.4.4.1.2 Death

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received.
- Death in nonrandomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Patient data listings will be provided for all AEs, TEAEs, SAE, AEs leading to study discontinuation, AESIs and deaths.

11.4.4.1.3 Clinical Laboratory Evaluation, Vital Signs and electrocardiogram data

Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, Q1, Q3, minimum and maximum.

The proportion of patients who had at least one incidence of PCSA at any time during the TEAE period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

Listings will be provided with flags indicating clinically out-of range values, as well as PCSA values.

11.4.5 Analyses of systemic drug concentration and anti-drug antibodies

(See [Section 9.2.3](#))

11.4.5.1 Drug concentration analysis

Concentrations of functional dupilumab in serum will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by treatment per visit.

Concentrations of functional dupilumab in serum will be used for population PK analysis by non-linear mixed effects modeling if warranted. Additional details of the analysis plan and the results will be provided in a separate document.

11.4.5.2 Anti-drug antibodies analysis

Incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%), presented by study cohorts. Listing of all ADA titer levels will be provided for patients positive in the ADA assay. All samples that are positive in the ADA assay will be further tested for the presence of anti-dupilumab neutralizing antibodies.

Plots of concentrations of functional dupilumab will be examined and the potential influence of ADA on individual concentration-time profiles will be evaluated. Assessment of the potential impact of ADA on safety and efficacy may be provided.

ADA at baseline will be summarized by:

- Number (%) of patients with a baseline sample negative in the ADA assay.
- Number (%) of patients with a baseline sample positive in the ADA assay.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the titer for patients positive in the ADA assay at baseline.

ADA incidence and titer will be provided for the following:

- Number (%) of patients negative in ADA assay at all times.
- Number (%) of patients positive in ADA assay at any time.
- Number (%) of patients with treatment-emergent positive response in the ADA assay.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for treatment-emergent positive patients.
- Number (%) of transient treatment-emergent positive patients.
- Number (%) of persistent treatment-emergent positive patients.

Titer values (Titer value category)

The minimum titer for samples positive in the ADA assay is based on the minimum required dilution of the assay.

Low (Titer <1000)

Moderate ($1,000 \leq \text{Titer} \leq 10,000$)

High (Titer >10,000)

Definitions:

Pre-existing anti-drug antibodies are defined as:

- An ADA positive response in the assay at baseline with all post treatment ADA results negative, **OR**
- An ADA positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.

Treatment-emergent anti-drug antibodies are defined as:

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

Treatment-boosted anti-drug antibodies are 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 ADA responses are further classified as Transient, Persistent or Indeterminate:

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

11.5 INTERIM ANALYSIS

A formal interim analysis is not planned.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the patient.

Prior to collection of blood for archiving of serum, the optional Future Use of Specimens informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the patient.

The informed consent form, the optional pharmacogenetic informed consent form and the optional Future Use of Specimens informed consent form to be used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the Health Authorities (Competent Regulatory Authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the Health Authorities (Competent Regulatory Authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the Health Authorities (Competent Regulatory Authority) and IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized

personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race or ethnicity (American Indian/Alaska Native, Asian, Black, Native Hawaiian/Pacific Islander, White, not reported, unknown, other) will be collected in this study because these data are required by several regulatory authorities (eg, on African-American population for FDA, on Japanese population for the PMDA in Japan, or on Chinese population for the CFDA in China).

Analyses of Patient genetic data will be conducted as described in the protocol as this is needed for pharmacogenetics analyses required for the purpose of the study or by regulatory authorities.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.

- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

Analysis of exploratory biomarkers not included in the study report will be included in separate technical report(s).

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of Health Authorities (Competent Regulatory Authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the Health Authorities (Competent Regulatory Authority) will be sought before implementation, as required by local regulation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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