NCT04203797

EudraCT: 2019-002742-20
IND Number: 105379

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFECT OF DUPILUMAB ON EXERCISE CAPACITY IN PATIENTS WITH MODERATE-TO-SEVERE ASTHMA

Compound:	Dupilumab
Clinical Phase:	4
Protocol Number:	R668-AS-1903
Protocol Version:	R668-AS-1903 Amendment 1 Global
Amendment 1 Global Date of Issue:	*See appended electronic signature page*
Original Date of Issue:	17 Sep 2019
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Ab	Antibody
ACCP	American College of Chest Physicians
ACQ-5	Asthma Control Questionnaire, 5-question version
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AQLQ(S)	Asthma Quality of Life Questionnaire (Self-Administered)
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BID	Twice a day
BOCF	Baseline observation carried forward
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CPET	Cardiopulmonary exercise test
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CWR	Constant work rate
CWRET	Constant work rate exercise test
Dynamic hyperinflation	An increase in end expiratory lung volumes under conditions of increased minute ventilation (ie, during exercise)
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EGPA	Eosinophilic granulomatous with polyangiitis
ERS	European Respiratory Society
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration

FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in One Second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
IC	Inspiratory capacity, defined as the maximal amount of air a person can inhale at the end of a normal exhalation
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL-13	Interleukin-13
IL-4	Interleukin-4
IL-4Rα	Interleukin-4 receptor alpha
IL5	Interleukin-5
IL-5R	Interleukin-5 receptor
IRB	Institutional Review Board
Isotime	Shortest equivalent exercise time achieved
ISR	Injection site reactions
IVRS/IWRS	Interactive voice response system/interactive web response system
IWRET	Incremental Work Rate Exercise Test
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonists
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LTRA	Leukotriene receptor antagonist

mAb	Monoclonal antibody
MCID	Minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metabolic equivalent of task
MI	Multiple imputation
OCS	Oral corticosteroid
PCSV	Potentially clinically significant value
PFT	Pulmonary function test
PGIC	Patient Global Impression of Change
PGII	Patient Global Impression of Impact
PT	Preferred term
Q1	First quartile
Q2W	Once every 2 weeks
Q3	Third quartile
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SABA	Short-acting beta agonist
SAE	Serious adverse event
SAF	Safety analysis set
SAMA	Short acting muscarinic antagonist
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
tLIM	Time to limit of tolerance
ULN	Upper limit of normal
VO_2	Oxygen consumption
W/min	Watts per minute
WBC	White blood cell
WOCBP	Women of childbearing potential

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AMENDMENT HISTORY

Amendment 1

The purpose of this amendment is to provide eligibility criteria flexibility while ensuring appropriate patients qualify for the study and to reduce the number of site visits and ensure study objectives are met during the Coronavirus Disease 2019 (COVID-19) pandemic. The following table outlines the changes made to the protocol and the rationales.

Change	Rationale	Section Changed
Inclusion criteria: • Modified FEV_1 reversibility eligibility criterion to allow documented evidence of bronchodilator reversibility or positive methacholine challenge test within 12 months of the screening visit • Pre-bronchodilator FEV_1 percent predicted has been changed from between 30% and 70% to between 30% and 75% at both the screening and baseline visits • Patients who do not meet the inclusion criteria due to a transient reason (eg, an abnormal laboratory value and judged to return to an acceptable range by the investigator within the screening period prior to day 1) may be allowed to repeat the test one additional time (up to a total of 2 attempts) on a different day during the screening period to meet the qualifying criteria. There is no need to screen fail such participants if the test finally meets the eligibility criteria.	• To provide eligibility criteria flexibility in the context of the COVID-19 pandemic while ensuring appropriate patients are enrolled in the study without impacting study objectives and study assumptions	Synopsis: Procedures and Assessments Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, criteria #3 and 4 Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events (Table 1), footnotes #5 and 6 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visits Section 9.2.2.5 Spirometry
Exclusion criteria: • Exclude treatment with a live (attenuated) vaccine within 4 weeks prior to the baseline visit (previously excluded if within 12 weeks) • Exclude patients for any reason that the investigator believes would make cardiopulmonary exercise unsafe or inadvisable (new)	• To align with current dupilumab protocols • To ensure patient safety	Section 7.2.2 Exclusion Criteria, criteria #29, 38 (new), and 45 (new)

Change	Rationale	Section Changed
• Exclude patients for country-specific exclusions (new)	• To ensure compliance with local country-specific regulations	
The run-in period constant work rate exercise test (CWRET) can be repeated twice (up to a total of 3 tests) to familiarize patients with the test and to determine the work rate that can achieve the qualifying exercise time criterion. Clarified that the same work rate must be used for the CWRET at the baseline and at the end of treatment visits.	• To provide a detailed clarification for the objective/goals of the run-in CWRET and to clarify the guidance for repeating the CWRET (if necessary) to adjust the individualized work rate that can achieve the qualifying exercise time criterion. • Clarification added to avoid confusion and to ensure the same individualized work rate established during run-in CWERT is used at the baseline and end of treatment visit CWRET to evaluate change from baseline in exercise endurance time.	Synopsis: Procedures and Assessments Section 6.1 Study Description and Duration Section 7.2.2 Exclusion Criteria, criterion #18 Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events (Table 1), footnotes #15 and 16 Section 9.2.2.4 Cardiopulmonary Exercise Testing (CPET)
Removed requirement for baseline CWRET exercise duration between 3 and 8 minutes.	• The adjustment of individualized work rate to meet the qualifying requirement of exercise duration between 3 and 8 minutes prior to randomization will be already established during the run-in CWRET and therefore, no longer necessary to repeat it at the baseline CWRET.	Section 6.1 Study Description and Duration Section 7.2.2 Exclusion Criteria, criterion #18 Section 9.2.2.4 Cardiopulmonary Exercise Testing (CPET)
Combined visits 2 and 3 into 1 visit (visit 2) during the run-in period.	• To decrease the number of in-clinic site visits in the context of the COVID-19 pandemic while ensuring all required data are collected for the study.	Synopsis: Study Duration Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 8.2 Run-in Treatment Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events (Table 1), footnote # 2
Visits 6 and 7 (in the original protocol weeks 8 and 10 and now weeks 6 and 8) changed from in-clinic to phone visits. Changed accelerometry wear reminder to phone call. Phone contacts (ie, phone visits) added at weeks 2 and 6.	• To decrease the number of in-clinic site visits in the context of the COVID-19 pandemic while ensuring all required data are collected for the study.	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events (Table 1), footnote #10
Removed exploratory endpoint of 'Change from baseline to week 12 in the weekly average of daily AM measures of FEV_1 assessed by home spirometry'.	• To ensure safety at home during the COVID-19 pandemic for an exploratory endpoint whose measurement	Synopsis: Procedures and Assessments, Statistical Plan Section 2.3 Exploratory Objectives Section 3.2.1 Rationale for Study Design

Change	Rationale	Section Changed
Changed the following exploratory endpoint from 'Change from baseline to week 12 in number of nocturnal awakenings per night measured by accelerometry' to 'Change from baseline to week 12 in number of nocturnal awakenings per night from patient diary'. Removed exploratory endpoint of 'Change from baseline to week 12 in sleep duration per night measured by accelerometry'.	requires a daily aerosol generating procedure. • This exploratory endpoint is to evaluate asthma related nocturnal awakenings; these are to be recorded by patients daily only in the patient diary and not captured by accelerometry.	Section 4.1.3 Exploratory Endpoints Section 5.2 Efficacy Variables Section 6.1 Study Description and Duration Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events (Table 1), footnotes #11 and 12 deleted in original protocol Section 9.2.2.1 Accelerometers Section 9.2.2.2 At Home Spirometer (prior section deleted) Section 11.4.2 Demography and Baseline Characteristics
Modified criteria for discontinuing study drug due to elevated AST and/or ALT values.	• To align with current dupilumab protocols	Section 8.5.2.1 Reasons for Permanent Discontinuation of Study Drug
Eliminated 2-minute time point for post-exercise spirometry.	• To rectify a previous error for this time point of post-exercise spirometry assessment (was supposed to be at 5 minutes and not at 2 minutes post-exercise).	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events (Table 1), footnote #18 Section 9.2.2.5 Spirometry
Added a Cardiopulmonary Exercise Testing (CPET) contraindication table in protocol in addition to the contraindications listed in the CPET manual.	• To further ensure patient safety for the cardiopulmonary exercise testing during the study by including the CPET contraindication table in the protocol.	Section 3.3 Risk-Benefit Section 9.2.2.4 Cardiopulmonary Exercise Testing (CPET) Table 2 Absolute and Relative Contraindications to CPET
Added text to clarify general changes to study conduct in the context of the COVID-19 pandemic (eg, to allow for study drug to be shipped to patient's home).	• To ensure study objectives continue to be met during the COVID-19 pandemic.	Section 3.3 Risk-Benefit Section 6.1 Study Description and Duration Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events (Table 1), footnotes #8 and 14 Section 11 Statistical Plan
Added an Estimand table; clarified primary and secondary efficacy analysis methods; streamlined the statistical plan section of the synopsis; updated summaries of patient disposition and AEs.	• To implement a concept estimand and treatment policy in the analysis approaches for the primary efficacy endpoint based on ICH E9 (R1) guidance. • Streamlined text for clarity and consistency without changing analysis methods and assumptions	Synopsis: Statistical Plan Section 8.4 Rescue Treatment Section 11.4.1 Patient Disposition Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
Confidentiality statement updated.	• To comply with updated sponsor standard confidentiality language.	Title page
Minor editorial changes and text reorganization.	• For clarification	Throughout the protocol.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of dupilumab on exercise capacity in patients with moderate-to-severe asthma
Site Location(s)	Global
Principal Investigator:	To be determined
Objective(s)	**Primary** • To demonstrate that dupilumab treatment improves exercise capacity in patients with moderate-to-severe asthma **Secondary** • To demonstrate that dupilumab treatment increases physical activity of daily living in patients with moderate-to-severe asthma • To demonstrate that dupilumab treatment improves pre- and post-exercise lung function in patients with moderate-to-severe asthma
Study Design	This is a phase 4, global, randomized, double-blind, placebo-controlled study to evaluate the effects of dupilumab on exercise capacity in patients with a ventilatory limitation to exercise and on activities of daily living in patients with moderate-to-severe asthma over a 12-week treatment period. Approximately 140 patients will be enrolled, with a 1:1 randomization ratio. Up to 10% of patients on maintenance oral corticosteroids (OCS; ≤10 mg/day OCS, prednisone/prednisolone or dose equivalent) will be allowed to participate in the study. Randomization will be stratified by baseline Forced Expiratory Volume in One Second (FEV_1, <50% vs. ≥50% predicted), use of maintenance OCS use (yes/no), and age (<35 vs. ≥35 years) to balance effects these variables may have on exercise performance.
Study Duration	The duration of the study for a patient is approximately 14 weeks, excluding the screening and run-in periods. The entire study consists of an up to 4-week screening period, up to 4-week run-in period, a 12-week treatment period, and a 2-week post-treatment follow-up period.
End of Study Definition	The end of study is defined as the last study visit of the last patient.
Population	
Sample Size:	Approximately 140 patients will be enrolled (approximately 70 per arm)
Target Population:	Male and female adult patients ≥18 to ≤55 years of age at screening with moderate- to-severe asthma

Treatment(s)	
Study Drug	Dupilumab, as 150 mg/mL solution in a pre-filled syringe for SC injection.
Dose/Route/Schedule:	A 600 mg loading dose SC on study day 1 and 300 mg once every 2 weeks (Q2W) SC from week 2 to week 10
Placebo	Placebo matching dupilumab dose in a pre-filled syringe for SC injection
Route/Schedule:	Administered SC, Q2W
Background Treatment	Patients should be on a stable dose of medium-to-high dose inhaled corticosteroid (ICS) – inhaled fluticasone propionate ≥250 µg to 1000 µg twice a day (BID) or equivalent and a second controller medication (eg, long-acting beta agonist [LABA]) throughout the study. Patients who are also on a stable dose of a third, non-corticosteroid asthma controller medication eg, leukotriene receptor antagonist (LTRA) at screening are allowed to participate as long as they can be maintained on a stable dose throughout the study duration. Up to 10% of patients on maintenance OCS at screening and baseline (≤10 mg/day of oral corticosteroids, prednisone/prednisolone or dose equivalent) are allowed.
Dose/Route/Schedule:	
Endpoint(s)	
Primary:	Change from baseline to week 12 in constant work rate exercise endurance time
Secondary:	• Change from baseline to week 12 in average number of steps walked per day (based on accelerometry data) • Change from baseline to week 12 in total energy expenditure (metabolic equivalents of tasks [METs]) (based on accelerometry data) • Change from baseline to week 12 in the mean duration of moderate-to-vigorous physical activity (defined as ≥3 METs) (based on accelerometry data) • Change from baseline to week 12 in pre- and post-exercise FEV_1 (based on spirometry data)
Procedures and Assessments	Efficacy procedures and assessments include the following: • Cardiopulmonary Exercise Testing (CPET): A medically well-accepted and standardized test that has been utilized to assess degree of exercise impairment in a variety of pulmonary diseases. o Qualifying Maximal Incremental Work Rate Exercise Test (IWRET): Will be performed at screening to determine the peak work rate to use in calculating 80% of maximum work rate for the Constant Work Rate Exercise Testing (CWRET).

The IWRET can be performed up to a total of 3 times during the screening period to determine study eligibility.

- CWRET: Will be performed during run-in, at baseline, and at week 12. The run-in CWRET will be performed to acquaint patients with the test and to determine the maximal individualized work rate that the patient can tolerate to achieve an exercise duration between 3 to 8 minutes (180 to 480 seconds), (ie, time to limit of tolerance [tLIM]). At the baseline visit, and at the end of treatment visit, CWRET must be performed utilizing the same constant work rate established for an individual patient at the qualifying run-in CWRET to evaluate change in exercise endurance time from baseline. The following will be obtained during the baseline CWRET: exercise endurance time, inspiratory capacity (IC), perception of dyspnea measured by the Borg Dyspnea Scale, perception of leg fatigue measured by the Borg Leg Fatigue Scale, and oxygen consumption (VO_2).

- Spirometry: A spirometer that meets the American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations will be used. Spirometry will be performed locally and read centrally in accordance with the ATS/ ERS guidelines. Spirometry will be performed at the screening and baseline visits to determine study eligibility, and at other time points as specified in the schedule of events.
- Accelerometers: Wearable sensors which objectively record and measure physical activity, and energy expenditure in a "free living" environment, reflecting activities of daily living. Patients will be instructed to wear an accelerometer day and night during the weeks per the schedule of events in the protocol. The following data will be obtained from the accelerometer recording: number of steps walked per day, total energy expenditure (metabolic equivalents of task [METs]), and mean duration of moderate-to-vigorous physical activity (defined as ≥3 METs).
- Fractional Exhaled Nitric Oxide (FeNO) Level: A marker of airway inflammation. FeNO levels will be assessed in accordance with ATS/ERS guidelines using the standardized nitric oxide measuring equipment (eg, Circassia NIOX VERO®).
- Asthma Control Questionnaire, 5-question version (ACQ-5): A patient-reported outcome measure used to assess asthma symptom control among patients with asthma.
- Asthma Quality of Life Questionnaire with Standardized Activities (Self-Administered) [AQLQ(S)]: A patient-reported disease-specific health-related quality of life instrument that measures both physical and emotional impact of asthma.
- Patient Global Impression of Change (PGIC): A patient-reported measure that assesses patients' impression about the change in their ability to exercise since study treatment initiation. Patients will be asked to recall the change in their ability to exercise since the baseline visit.

	• Patient Global Impression of Impact (PGII): A patient-reported measure that assesses patients' impression about the impact of asthma on their ability to exercise during the past week. Safety procedures and assessments include the following: monitoring and recording of adverse events (AEs); measurements of vital signs, including body temperature (°C), sitting systolic and diastolic blood pressure (mm Hg), pulse rate (beats per minute), and respiratory rate; physical examination; electrocardiogram (ECG); laboratory testing including hematology, blood chemistry, urinalysis, and pregnancy testing.
Statistical Plan	The **null hypothesis and alternative** to be tested: • Null hypothesis: The mean change from baseline in the constant work-rate exercise endurance time at week 12 is the same between dupilumab and placebo. • Alternative hypothesis: The mean change from baseline in the constant work rate exercise endurance time at week 12 differs between dupilumab and placebo. **Justification for the sample size:** The planned sample size of approximately 70 patients per treatment group will provide >85% power to detect a 105-second mean change in constant work rate exercise endurance time, with a standard deviation of 190 seconds, 2-sided $\alpha = 5\%$, and 10% drop out rate. **Analysis Sets:** • The full analysis set (FAS) includes all randomized patients. • The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). **Baseline Definition** Baseline for singular-value assessments, such as measurements from the CWRET, FEV_1, and FVC from spirometry, will be the latest valid measurement taken prior to the first administration of study drug. Baseline for the 14-day average values of measurements from accelerometry is defined as the average of the non-missing values during the 14 days prior to the first administration of study drug. **Primary Efficacy Analysis:** The primary endpoint of change from baseline in constant work rate exercise endurance time at week 12 will be analyzed using an analysis of covariance (ANCOVA) model for the FAS population. The ANCOVA model will include terms for treatment group, randomization stratification factors and the baseline value for the constant work rate exercise endurance time. The intercurrent events handling strategy for systemic corticosteroid use or an increase in systemic corticosteroids for an asthma exacerbation during last 4-weeks of the treatment period and for treatment discontinuation is specified in the Estimand table provided in the section for Primary Efficacy Analysis. The imputation method for missing data based on the reasons for study discontinuation is defined below:

- Missing data due to:
  - AE or lack of efficacy will be imputed by baseline observation carried forward (BOCF).
  - Other reasons will be imputed using multiple imputation (MI) rules under a missing at random assumption. A detailed imputation model will be specified in the SAP.

Subgroup analysis may be performed for age, sex, weight, baseline FEV_1, baseline constant work rate endurance time and baseline ACQ-5. Subgroup analyses may not be performed if the primary efficacy result is not statistically significant.

Secondary Efficacy Analysis:

The secondary efficacy endpoint of change from baseline to week 12 in pre-/post-exercise FEV_1 will be analyzed using the same method as for the primary analysis.

Other secondary endpoints measured by accelerometry (ie. change from baseline to week 12 in: average number of steps walked per day, total energy expenditure, and mean duration of moderate-to-vigorous physical activity) will be analyzed using a method similar to that for the primary endpoint, except that patients who initiate corticosteroids for the treatment of an asthma exacerbation within the last 4 weeks of the treatment period (or corticosteroid dose increase for those on maintenance OCS) will be included in the analysis.

Multiplicity adjustment will be applied for testing of multiple endpoints. Type I error rate will be controlled using a hierarchical testing procedure for the primary and then key secondary endpoints at the 2-sided 0.05 level. The order of the endpoints for hierarchical testing will be specified in the SAP.

Safety analysis will be based on the SAF. This includes reported treatment-emergent AEs (TEAEs), adverse events of special interest (AESIs), and other safety data (eg, clinical laboratory evaluations, vital signs, and 12-lead ECG results). A descriptive summary of safety results will be presented by treatment group.

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 therapeutic response of some patients with asthma may reflect a number of cellular and molecular mechanisms operative in asthma. Up-regulation of interleukin-4 (IL-4) and interleukin-13 (IL-13) activity has been implicated as an important type 2 inflammatory component of asthma pathophysiology.

It is well-established that exercise intolerance and difficulties engaging in physical activity are common complaints of patients with asthma, reported by at least 66% of patients (Fuhlbrigge, 2002). In a survey in 1300 European patients, 70% of severe asthmatics receiving asthma medication reported limitation in physical activity (Dockrell, 2007). Additionally, exercise capacity evaluated by cycle ergometry is known to be reduced in asthmatics when lung function is impaired. Chronic expiratory flow limitation in patients with moderate-to-severe asthma may be a contributing factor to exercise intolerance. Use of bronchodilators prior to exercise, though useful for blunting decrease in forced expiratory volume in one second (FEV_1), does not reliably improve exercise capacity (Vermeulen, 2016). A high unmet need exists to improve exercise capacity and activity levels in patients with asthma.

Patients with obstructive lung disease, often develop dynamic hyperinflation (defined as an increase in end expiratory lung volume under conditions of increased minute ventilation [ie, during exercise]) due to expiratory air-flow limitation in the face of decreased time for exhalation with increasing respiratory rate. This results in a decrease in inspiratory capacity (IC). Dynamic hyperinflation increases inspiratory mechanical load and thereby results in sense of breathlessness and exercise intolerance in patients with obstructive lung disease. Severity of dyspnea correlates with degree of expiratory flow limitation (measured by FEV_1) and peripheral airway resistance (Mahler, 1991).

There are no published, rigorously designed studies assessing the effects of pharmacotherapeutic intervention on assessing either maximal exercise capacity or activities of daily living in patients with asthma. Dupilumab therapy has demonstrated improvement in lung function and asthma control. Inhibition of IL-4/-13 is known to improve lung function and reduce airway inflammation (Gandhi, 2016) (Vatrella, 2014) (Castro, 2018) (Wenzel, 2016). It is therefore hypothesized that dupilumab treatment may improve exercise capacity and increase physical activity in patients with moderate-to-severe asthma.

Dupilumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and immunoglobulin E (IgE).

Dupilumab (brand name DUPIXENT®) has been approved in the United States as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with

an eosinophilic phenotype or with oral corticosteroid (OCS) dependent asthma and in the European Union (EU) for patients aged 12 years and older with severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fractional exhaled nitric oxide (FeNO) who are inadequately controlled with high dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment. Dupilumab has been approved in the United States for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and in EU for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 6 years and older who are candidates for systemic therapy. Dupilumab has also been approved in the United States as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP) and in the EU for adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. Dupilumab has shown efficacy in a proof of concept study in patients with eosinophilic esophagitis.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to demonstrate that dupilumab treatment improves exercise capacity in patients with moderate-to-severe asthma.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To demonstrate that dupilumab treatment increases physical activity of daily living in patients with moderate-to-severe asthma
- To demonstrate that dupilumab treatment improves pre- and post-exercise lung function in patients with moderate-to-severe asthma

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To demonstrate that dupilumab treatment decreases dynamic hyperinflation during constant work rate exercise in patients with moderate-to-severe asthma
- To demonstrate that dupilumab treatment improves perception of dyspnea
- To demonstrate that dupilumab treatment improves perception of leg fatigue
- To demonstrate that dupilumab treatment increases oxygen consumption during the constant work rate exercise test (CWRET)

- To demonstrate that dupilumab treatment improves asthma control in patients with moderate-to-severe asthma
- To demonstrate that dupilumab treatment improves asthma-related quality of life in patients with moderate-to-severe asthma
- To demonstrate that dupilumab treatment improves patients' impression of ability to carry out exercise
- To demonstrate that dupilumab treatment improves patients' impression of the impact that asthma has on the ability to perform exercise
- To demonstrate that dupilumab treatment decreases pre- and post-exercise FeNO
- To measure nocturnal awakenings due to asthma measured by patient diary

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Patients with moderate-to-severe asthma treated with dupilumab show improvement in exercise capacity and increase in physical activity of daily living.

3.2. Rationale

3.2.1. Rationale for Study Design

It has been shown that dupilumab treatment significantly improves FEV_1, asthma control and reduces type 2 mediated inflammation in patients with moderate-to-severe asthma (Castro, 2018) (Rabe, 2018) (Wenzel, 2016). This study will determine whether these improvements translate into (1) an increase in exercise capacity as measured by cycle ergometry and constant work rate exercise endurance time, and (2) an increase in physical activities of daily living assessed by accelerometry.

Effects of pharmacotherapy on exercise capacity and physical activity in patients with asthma have not been rigorously examined in clinical studies. Small studies in asthma with bronchodilators or bronchodilator + ICS intervention have shown inconsistent results regarding improvement in exercise capacity (Haverkamp, 2007) (Robertson, 1994). A 6-week study of patients with mild-to-moderate asthma treated with high dose fluticasone showed improvement in exercise endurance time and FEV_1 (Haverkamp, 2007). However, other studies in patients with asthma treated with bronchodilators demonstrated increases in FEV_1 without consistent improvement in exercise capacity (Freeman, 1989). An unblinded, small study of omalizumab in 20 consecutive patients with severe allergic asthma (10 receiving omalizumab and 10 placebo) demonstrated significant improvement in both FEV_1 and exercise capacity after 16 weeks of omalizumab treatment (Schaper, 2011).

Small, non-interventional, cross-sectional studies using various accelerometers worn at the wrist or hip have shown that patients with severe asthma walk approximately 27% to 30% fewer steps per day compared to age and gender matched healthy volunteers (mean steps/day severe asthma =

5362; range 3999 to 7817 vs. healthy controls 7817; range 6072 to 10014) (Cordova-Rivera, 2018). Studies evaluating FEV_1 as a marker of physical activity have shown conflicting results. Bahmer et al reported that FEV_1 and peak expiratory flow were poor markers of physical activity in asthma patients showing no significant correlation between FEV_1 and steps walked per day (Bahmer, 2017), whereas Hennegrave, et al showed significant correlation between steps walked and FEV_1 (Hennegrave, 2018).

Dupilumab has been shown to increase lung function and improve asthma control. It is hypothesized that this demonstrated efficacy may result in improvements in exercise capacity and physical activity of daily living. Pulmonary limitation to exercise will be identified by demonstrating a decrease in IC from pre-exercise to the value during the maximal incremental exercise test performed at screening.

This phase 4, randomized, placebo-controlled study is designed to evaluate whether treatment with dupilumab increases exercise endurance time evaluated using constant work rate exercise testing (CWRET). Additionally, physical activities of daily living (steps walked per day, energy expenditure, and time spent in moderate-to-vigorous activity) will be assessed using accelerometry.

A blinded, randomized design is chosen to minimize bias in data collection and result interpretation. The presence of a placebo arm is appropriate for the objectives of this study since it will provide the most robust assessment of the efficacy of dupilumab. A run-in period is planned to stabilize background asthma treatment, familiarize patients with the CWRET, determine an individualized work rate that a patient can tolerate for 3 to 8 minutes (180 to 480 seconds), and to collect pre-treatment accelerometry data. A 12-week treatment period is selected based on the findings in dupilumab clinical studies in moderate-to-severe asthma patients where near-maximal improvements in lung function occurred by approximately 8 to 12 weeks after treatment initiation. A 2-week post-treatment follow-up period is chosen to ensure clinical stability of patients after the treatment period is complete.

Cardiopulmonary exercise testing (CPET) has been utilized in several interventional studies to assess the degree of dynamic hyperinflation in patients with obstructive lung diseases, and its impact on exercise capacity (Benfante, 2018) (Casaburi, 2014) (Maltais, 2011) (O'Donnell, 2004). CPET can be performed on a stationary bicycle or a treadmill. Cycle ergometry has been selected over a treadmill protocol because it requires relatively little patient practice (unlike treadmill exercise) and the external power output is accurately known. A constant work-rate protocol is chosen to assess the primary endpoint versus a maximal incremental exercise test, as the former is more sensitive to discriminate change in exercise capacity. To minimize variability in the measurements, the CPET will be done using a standardized CPET protocol, and only at sites proficient in CPET and pulmonary function testing.

3.2.2. Rationale for Dose Selection

The dose regimen selected for this study is dupilumab 300 mg administered subcutaneously (SC) every other week (Q2W) with a 600 mg loading dose for the first dose. This dosing regimen is chosen as it has been shown to be efficacious, with an acceptable safety profile in asthma pivotal studies and is approved for the treatment of moderate-to-severe asthma, the patient population under study.

3.3. Risk-Benefit

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any new patients in this study unless the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable continuation of study sites for this study, as allowed by local laws and regulations.

Dupilumab has shown a favorable risk-benefit profile in patients with atopic dermatitis, asthma, and CRSwNP (see details in the DUPIXENT label and Dupilumab Investigator's Brochure).

The study population consists of a moderate-to-severe asthma patient population studied in the phase 3 studies of the dupilumab asthma clinical program, and for which dupilumab has been shown to have a positive risk-benefit profile. The safety data available to date across multiple indications and risk-reducing measures planned in this study, in conjunction with the clinical benefit of dupilumab demonstrated in asthma patients, support a favorable risk-benefit profile for dupilumab for this study population.

Multiple studies have shown that patients with obstructive lung disease and decreased lung function can perform a CPET safely. A number of procedures are required to assure patient safety when performing a CPET. At screening, patients will be carefully evaluated to determine appropriateness for a CPET; those not appropriate for the test will be excluded from the study. Both relative and absolute contraindications including, but not limited to, uncontrolled arrhythmia, uncontrolled elevated blood pressure (systolic blood pressure >180 mm Hg or diastolic blood pressure >95 mm Hg), clinically significant coronary artery disease, unstable angina, etc, preclude participation in this study (a detailed list of absolute and relative contraindications for performing CPET is provided in Section 9.2.2.4, Table 2). Any patient who the investigator judges to be unsuitable for exercise regardless of CPET contraindications cannot enroll or continue in the study. A CPET will be performed only at pulmonary function test (PFT) labs experienced in performing CPET and according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) recommendations. Professionals experienced in performing CPET in patients with abnormal lung function, certified in advanced cardiac life support and experienced in interpreting physiologic responses to exercise will closely monitor each patient during the CPET. A number of physiologic responses are assessed repeatedly during CPET, including electrocardiogram (ECG) parameters, oxygen saturation, blood pressure, pulmonary ventilation, oxygen uptake, and respiratory rate. A medical doctor must be present in the room in which the initial incremental work rate exercise test (IWRET) is conducted and readily available for medical intervention, if needed, at all subsequent exercise tests. Resuscitation equipment must be immediately available in the PFT lab where the exercise testing is performed. A CPET laboratory manual, providing detailed instructions, including relative and absolute contraindications to testing and indications for exercise termination, will be distributed to each study site.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The primary endpoint is change from baseline to week 12 in constant work rate exercise endurance time.

4.1.2. Secondary Endpoints

The secondary endpoints are:

- Change from baseline to week 12 in average number of steps walked per day (based on accelerometry data)
- Change from baseline to week 12 in total energy expenditure (metabolic equivalents of tasks [METs]) (based on accelerometry data)
- Change from baseline to week 12 in the mean duration of moderate-to-vigorous physical activity (defined as ≥3 METs) (based on accelerometry data)
- Change from baseline to week 12 in pre- and post-exercise FEV_1 (based on spirometry data)

4.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Change from baseline to week 12 in isotime IC
  (Note: isotime is defined as the shortest equivalent exercise time achieved)
- Change from baseline to week 12 in perception of dyspnea measured by the Borg Dyspnea Scale at isotime
- Change from baseline to week 12 in perception of leg fatigue measured by the Borg Leg Fatigue Scale at isotime
- Change from baseline to week 12 in end-exercise oxygen consumption (VO_2)
- Change from baseline in total ACQ-5 score (Asthma Control Questionnaire, 5-question version) at week 12
- Change from baseline to week 12 in total AQLQ(S) score (Asthma Quality of Life Questionnaire Standardized Version)
- Proportion of patients responding with an improvement on the Patient Global Impression of Change (PGIC) at weeks 4 and 12
- Proportion of patients responding with no or limited impact on the Patient Global Impression of Impact (PGII) at weeks 4 and 12
- Change from baseline to week 12 in FeNO, pre- and post-exercise

- Change from baseline to week 12 in forced vital capacity (FVC) pre- and post-exercise
- Change from baseline in FEV_1 and FVC at week 4
- Change from baseline to week 12 in the maximal percent fall in post-exercise FEV_1 in patients with exercise-induced asthma (defined as patients who had a ≥20% fall in post-exercise FEV_1 from pre-exercise value on the IWRET)
- Change from baseline to week 12 in number of nocturnal awakenings per night due to asthma from patient diary

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, weight, height, sex, race, etc), disease characteristics, medical history, and medication history for each patient.

5.2. Efficacy Variables

The efficacy variables include measurements or scores for individual patients of the following:

- Exercise endurance time measured from the CWRET
- IC, perception of dyspnea, and leg fatigue during exercise measured by the Borg Dyspnea Scale and Borg Leg Fatigue Scale, and VO_2 measured from the CWRET
- Pre- and post-exercise FEV_1 and FVC measured by in-clinic spirometry
- FEV_1 and FVC measured by in-clinic spirometry at the visit(s) when exercise testing is not performed
- Number of steps walked per day, total energy expenditure per day (in METs), and mean duration of moderate-to-vigorous physical activity per day defined as ≥3 METs assessed by accelerometry
- Nocturnal awakenings due to asthma
- ACQ-5
- AQLQ(S)
- FeNO
- PGIC
- PGII

5.3. Safety Variables

Safety variables include recording, measurements or laboratory test results for individual patients of the following: adverse events (AEs), vital signs, physical examination findings, hematology, blood chemistry, urinary analysis, and ECG findings.

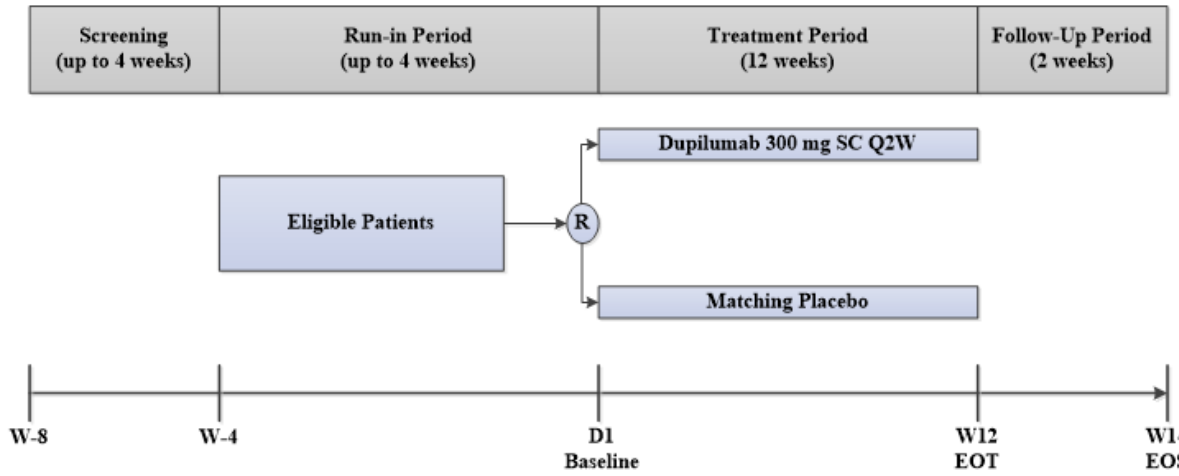
6. STUDY DESIGN

6.1. Study Description and Duration

This phase 4, global, randomized, double-blind study of dupilumab vs. placebo is designed to evaluate the effects of dupilumab on exercise capacity and daily activity in patients with moderate-to-severe asthma over a 12-week treatment period. Approximately 140 patients will be enrolled in the study, approximately 70 per treatment group with a 1:1 randomization ratio. Up to 10% of patients on maintenance OCS at screening and baseline (≤10 mg/day OCS, prednisone/prednisolone or dose equivalent) will be allowed to participate in the study. Randomization will be stratified by baseline FEV_1 (<50% vs. ≥50% predicted) and age (<35 vs. ≥35 years) to balance effects these variables may have on exercise performance.

The study consists of an up to 4-week screening period, an up to 4-week run-in period, a 12-week treatment period, and a 2-week post-treatment follow-up period (see Figure 1).

Figure 1: Study Flow Diagram



D = study day; R = randomization; EOS = end of study; EOT = end of treatment; W = study week
Note: The study drug dosing regimen is dupilumab 600 mg loading dose on study day 1 and 300 mg Q2W from week 2 to week 10 or matching placebo.

Screening Period (Up to 4 Weeks/Visit 1):

After providing informed consent, the patients will be assessed for study eligibility at the screening visit. During the screening period, patients will perform qualifying ACQ-5, spirometry, bronchodilator reversibility testing (if applicable) , and laboratory assessments.

Patients must meet all screening eligibility requirements prior to conducting incremental work rate exercise testing (IWRET). Patients who meet these eligibility requirements will undergo a symptom-limited, incremental, maximal effort, cycle cardiopulmonary exercise test (IWRET) to determine the maximum work rate he/she can achieve. During the IWRET, work rate will be set to increase at either 10, 15, 20, or 25 W/min depending on the investigator's assessment of the patient's ability to exercise. The primary goals of the IWRET are to determine peak work rate patients can endure, to assess development of dynamic hyperinflation and determine the patient's exercise endurance time. Patients must exercise until exhaustion, for between 4 and 16 minutes inclusive, and must have documented dynamic hyperinflation defined as decrease in IC during the IWRET of more than 100 mL from the pre-exercise value . If the exercise time is outside of the 4 to 16 minute required window or IC does not decrease by >100 mL, the test may be repeated with a change in the work rate from that previously used by ±10% or 5 W/min, whichever is greater. The IWRET can be repeated twice (up to a total of 3 times) to determine study eligibility. A patient who exercises <4 or >16 minutes or who does not drop IC by >100 mL after 3 IWRET attempts will be considered a screen failure.

The IWRET (to be performed at screening) and the CWRET (to be performed during the run-in period, at baseline and at the end of the treatment period) will be administered according to guidelines for CPET published in the Joint Statement of the ATS and the American College of Chest Physicians (ACCP) (American Thoracic Society, 2003). CPET is a non-invasive, well-accepted, standard protocol-driven method to assess the performance of the heart and lungs during exercise (Puente-Maestu, 2016). The test will be performed on an electromagnetically-braked cycle ergometer in an exercise physiology laboratory overseen by a trained pulmonologist or medical doctor designee. A medical doctor must be present in the room in which the initial IWRET is conducted and readily available for medical intervention, at all subsequent exercise tests. Resuscitation equipment must be immediately available in the PFT lab (ie, in the room) in which the exercise testing is performed. Patients will exercise until exhaustion (time to limit of tolerance [tLIM]) breathing through a mouthpiece with noseclip in place or while wearing a mask.

Run-in Period (Up to 4 Weeks/Visit 2):

During the run-in period patients must maintain a stable dose of background asthma controller medication including OCS, if applicable, for at least 4 weeks prior to the baseline visit. Patients will perform a run-in CWRET using a standardized CWRET protocol on an electromagnetically-braked cycle ergometer. The CWRET will be performed at 80% of the maximal work rate previously determined from the IWRET. The goal of the run-in CWRET is to determine the individualized work rate the patient can tolerate to achieve an exercise duration time between 3 to 8 minutes, and to familiarize the patient with the test. For those achieving exercise times outside of these limits (ie, <3 to >8 minutes) a second CWRET may be performed after a work rate adjustment by ±10% or 5 W/min, whichever is greater. In rare cases, a third test may need to be performed after a further work rate adjustment to achieve a 3 to 8 minute exercise endurance time. Patients who are unable to achieve an exercise endurance duration between 3 to 8 minutes (180 to 480 seconds) after 3 attempts will be considered screen failures.

At visit 2, patients will be given the accelerometer and instructed on its proper use. Patients will be instructed to wear the accelerometer on their wrist, 24 hours/day, 7 days/week (except during charging time, bathing, and any other water activities) for a total of 3 weeks during the run-in period and record daily how much time spent bathing or swimming, total time charging the device, physical activity (eg, walking, moderate physical activities, and vigorous physical activities), and nocturnal awakenings due to asthma in the patient diary. The first week is a training period for the patient to become familiar with the accelerometer. The subsequent 2 weeks of daily accelerometry are to obtain the pre-treatment baseline data.

Baseline and Treatment Period (12 Weeks/Visits 3 to 9):

Eligible patients will be randomized 1:1 on day 1 to receive dupilumab or placebo. Background asthma controller medication must remain constant throughout the treatment period. Patients will be asked to wear an accelerometer on their wrist 24 hours/day, 7 days/week for 14 consecutive days prior to visit 3/randomization, and for 14 consecutive days prior to visit 9/end of treatment Visit (except during charging time, bathing, and any other water activities). The CWRET will be performed at baseline and week 12 to assess the change in constant work rate exercise endurance time from baseline, the primary endpoint for the study. In-clinic spirometry will be assessed pre- and post-exercise as part of the CWRET per the schedule of events. Note: The same exercise work rate established at the qualifying run-in CWRET which achieves an exercise time between 3 and 8 minutes must also be applied for the baseline and end of treatment CWRET. Pulmonary ventilation, breathing pattern, gas exchange (all assessed from the respired gases by a metabolic cart), arterial oxygen saturation (assessed by pulse oximetry), ECG parameters, IC, perceived dyspnea and perceived leg fatigue (by Borg Dyspnea and Leg Fatigue Scales, respectively) will be assessed during the CWRET. Details of cardiopulmonary exercise testing procedures including absolute and relative contraindications for performing exercise testing are provided in Table 2 and will also be provided to each site in the CPET laboratory manual. Asthma control, asthma quality of life, nocturnal awakenings due to asthma, and airway inflammation will be assessed at baseline and during the treatment period using the ACQ-5, AQLQ, PGII, and PGIC questionnaires, patient diary and FeNO measurements, respectively. Additional in-clinic spirometry will be performed at week 4 using the same equipment utilized to perform spirometry pre- and post-exercise testing.

Safety, including adverse events, will be assessed throughout the study.

Post-treatment Follow-up Period: (2 Weeks/Visit 10)

All patients will have a follow up visit 2 weeks after completing the treatment period.

NOTE: If there are restrictions to the clinical study as a result of the COVID-19 pandemic, it may be necessary to adjust the visit schedule, convert in-person visits to telephone contacts, and postpone study procedures until the next available study visit. All visits when CPET is performed must occur in the clinic including the randomization visit. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency. Once local COVID-19 conditions resolve, all study visits and procedures should follow the schedule of events as specified in Table 1.

6.1.1. End of Study Definition

The end of study is defined as the last study visit of the last patient.

6.2. Planned Interim Analysis

No interim analysis is planned for this study.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 140 patients (approximately 70 per arm) are planned to be enrolled in the study.

7.2. Study Population

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male and female ≥18 to ≤55 years of age at screening
2. A physician diagnosis of asthma according to Global Initiative for Asthma (GINA) 2018 step 4 or 5 asthma for at least 12 months prior to the screening visit
3. Pre-bronchodilator FEV_1 between 30% and 75% predicted (the Third National Health and Nutrition Examination Survey [NHANES III] reference values) at both the screening and baseline visits
4. Bronchodilator reversibility defined as >200 mL and 12% increase in FEV_1 post-administration of a short-acting beta agonist (SABA)*. A patient may also qualify if there is a documented history of bronchodilator reversibility or positive methacholine challenge test within 12 months prior to the screening visit.

   *Dose of SABA: 200 to 400 µg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized

solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice)

5. Demonstrate dynamic hyperinflation as defined by a decrease in IC of >100 mL during the IWRET at screening
6. Stable background therapy for at least 3 months with a stable dose ≥4 weeks prior to the baseline visit of a medium-to-high dose ICS (fluticasone propionate ≥250 to 1000 μg twice daily [BID] or equivalent) in combination with at least a second controller medication (eg, long-acting beta agonist [LABA], long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA], theophylline, etc); a third controller is allowed and with the same stabilization requirements.

   Note: Up to 10% of patients on maintenance OCS at screening and baseline (≤10 mg/day OCS, prednisone/prednisolone or dose equivalent) will be allowed to participate in the study. Patients must be on a stable dose of OCS for at least 4 weeks prior to the screening visit and between the screening and baseline/randomization visits and throughout the study.
7. Blood eosinophil count ≥300 cells/μL for patients not on maintenance OCS at the screening visit
8. ACQ-5 score ≥1.5 at the screening and baseline visits
9. Able to provide signed informed consent
10. Willing and able to comply with clinic visits and study-related procedures

NOTE: Patients who do not meet the inclusion criteria for a reason that could be transient (eg, an abnormal laboratory value and judged to return to an acceptable range by the investigator within the screening period prior to day 1) may be allowed to repeat the test one additional time (up to a total of 2 attempts) on a different day to meet the qualifying criteria. There is no need to screen fail such participants if the test finally meets the eligibility criteria.

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Body mass index >35 kg/m^2 at screening
2. Current smoking, vaping or tobacco chewing or cessation of any of these within 6 months prior to randomization, or >10 pack-years smoking history
3. Asthma exacerbation requiring systemic corticosteroids within 8 weeks prior to screening or between screening and baseline visits
4. Upper or lower respiratory tract infection within 4 weeks prior to screening (visit 1) or between screening and baseline visit
5. History of life-threatening asthma (eg, severe exacerbation that required intubation within the last 5 years)

6. On or initiation of bronchial thermoplasty within 3 years prior to visit 1 or plan to begin therapy during the screening period or during the study after screening
7. Significant chronic pulmonary disease other than asthma (eg, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, interstitial lung disease, chronic obstructive pulmonary disease (COPD), eosinophilic granulomatous with polyangiitis (EGPA), also called Churg-Strauss Syndrome) or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts at screening
8. Pulmonary embolus or pulmonary infarction within 1 year of screening or thrombosis of lower extremities unless previously treated with at least 3 months of anti-coagulant therapy or patient has an inferior vena cava filter
9. Diagnosis/history of pulmonary hypertension
10. Patients who require supplemental oxygen at screening
11. Clinically significant cardiac disease (eg, history or presence of left or right sided heart failure, active endocarditis, current myocarditis or pericarditis, moderate or severe valvular heart disease, history of hypertrophic cardiomyopathy, or suspected dissecting aneurysm)
    a. Myocardial infarction within 6 months prior to screening
    b. Clinically significant coronary artery disease or a history of angina within the last 3 years, unless the patients has a negative cardiac stress test within 1 year prior to randomization
12. History of uncontrolled arrhythmias causing symptoms or hemodynamic compromise within 6 months of screening or history of clinically significant tachyarrhythmias or bradyarrhythmias
13. Any clinically significant abnormality on screening ECG
14. Syncope within 6 months of screening
15. Uncontrolled hypertension (>180 mm Hg systolic, >95 mm Hg diastolic) at screening or baseline.
16. Participation in exercise or physical rehabilitation program within last 6 months prior to screening or planned during the study
17. Patients who exercised <4 minutes or >16 minutes during the screening IWRET
18. Patients unable to achieve a constant work rate exercise time between 3 and 8 minutes during run-in CWRET, despite work rate adjustments
19. History of clinically significant renal, hepatic, 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
20. Known or suspected history of immunosuppression or immunodeficiency disorder including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis), despite infection resolution; or unusually frequent,

recurrent, or prolonged infections, suggesting an immune-compromised status, as judged by the investigator

21. 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)
22. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
23. Initiation, discontinuation, or change in the dosage regimen of allergen immunotherapy (ie, subcutaneous or sublingual) within 3 months prior to screening (visit 1)
    - Patients on a stable dose of these medications for at least 3 months prior to visit 1 may be included in the study, but must not change the dose during the study.
24. Previous use of dupilumab.
25. Use of any investigational drugs (other than the study drug) within 3 months or at least 5 half-lives prior to visit 1, whichever is longer
26. Anti-IgE therapy (eg, omalizumab [Xolair®]) within 130 days prior to visit 1 or any other biologic therapy (including anti-IL5, anti-IL-5R, anti-IL4Rα, anti-IL-13 mAb) or systemic immunosuppressant (eg, methotrexate, any anti-tumor necrosis factor mAbs, Janus kinase inhibitors, B- and/or T-cell targeted immunosuppressive therapies) to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) and other diseases, within 3 months or 5 half-lives prior to screening, whichever is longer
27. Exposure to another investigative drug (monoclonal antibodies as well as small molecules) within a period prior to screening, of <3 months or <5 half-lives (whichever is longer)
28. History of systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients
29. Treatment with a live (attenuated) vaccine within 4 weeks prior to the baseline visit or planned live attenuated vaccinations during the study
30. Patients with active tuberculosis or non-tuberculous mycobacterial infection, latent untreated tuberculosis, or a history of incompletely treated tuberculosis will be excluded from the study unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the investigator and/or infectious disease specialist. *(Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethic committees.)*
31. 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

32. Human immunodeficiency virus (HIV) by clinical or serological history
33. Established diagnosis of hepatitis B viral (HBV) infection at the time of screening or positive for hepatitis B surface antigen (HBsAg) at the time of screening
    - Patients who have gained immunity for hepatitis B virus infection after vaccination (patients who are HBsAg negative, hepatitis B surface antibody [HBsAb] positive, and hepatitis B core antibody [HBcAb] negative) are eligible for the study.
    - Patients with positive HBcAb are eligible for the study only if hepatitis B viral DNA level is undetectable.
34. Established diagnosis of hepatitis C viral (HCV) infection at the time of screening. Patients positive for hepatitis C Ab are eligible for the study only if HCV RNA test is negative prior to randomization.
35. Liver injury-related criteria:
    - Clinically significant/active hepatobiliary disease or evidence of liver disease as indicated by persistent (confirmed by repeated tests ≥2 weeks apart) elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal [ULN] during the screening).
36. Any of the following abnormal lab values at screening:
    - Creatine phosphokinase (CPK) >10×ULN or
    - Platelets <100,000 cells/mm^3
    - Clinically significant electrolyte abnormalities in the opinion of the principal investigator

    NOTE: If an abnormal value is detected at screening, a repeat test should be performed to confirm the abnormality. Only if the repeat test confirms the abnormality would the patient be categorized as a screen failure.
37. Known or suspected alcohol and/or drug abuse OR positive pre-study drug/alcohol screen
38. Any relative or absolute contraindication to CPET listed in Table 2 or any other reason not provided in the list of relative or absolute contraindications to CPET (Table 2) that the investigator believes would make CPET unsafe or inadvisable.
39. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this study, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents.
40. Inability to follow instructions or complete study-related procedures (eg, due to language problems or psychological disorders)
41. Individuals accommodated in an institution because of regulatory or legal order; prisoners or patients who are legally institutionalized

42. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor
43. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
44. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure)
    e. and/or sexual abstinence†, ‡.

    *Women of child bearing potential are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

    †Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

    ‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.
45. Any country-specific regulation that would prevent the participant from entering the study

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patient who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.5.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study or study drug will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The study drug dosing regimen is dupilumab 600 mg loading dose on study day 1 and 300 mg Q2W from week 2 to week 10 or matching placebo.

Dupilumab drug product is supplied for this study in the following concentration:

- Dupilumab 150 mg/mL: Each 2.0 mL single-use prefilled glass syringe with snap-off cap delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution)

Placebo matching dupilumab is prepared in the same formulation without the addition of protein (ie, active substance, anti-IL-4Rα mAb).

Study drug will be administered by SC injections. Subcutaneous injection sites of study drug should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations. To allow for adequate assessment of possible injection site reactions (ISRs), study drug should be administered only into areas of normal looking skin. Instructions for recording and reporting ISRs will be provided in the study binder.

Patients and/or caregivers who are willing and able to self-administer some dupilumab doses outside of the clinic will be trained on injecting the study drug.

The procedure for preparing and administering dupilumab will be provided in the pharmacy manual.

8.2. Run-in Treatment

Patients' background asthma controller medication will be stabilized during the up to 4-week run-in period.

8.3. Background Treatments

Patients must be on a stable dose of medium-to-high dose ICS – inhaled fluticasone propionate ≥250 µg to 1000 µg BID or equivalent and a second controller medication (eg, LABA) throughout the study. Patients who are also on a stable dose of a third, non-corticosteroid asthma controller medication, eg, LTRA, at screening are allowed to participate as long as they can be maintained on a stable dose throughout the study duration. For the up to 10% of patients who are on maintenance OCS (≤10 mg/day OCS, prednisone/prednisolone or dose equivalent) at screening and baseline; their OCS dose must remain constant during the study

8.4. Rescue Treatments

Short-acting bronchodilators (either SABA or short acting muscarinic antagonists [SAMAs]) are permitted as rescue therapy throughout the study, except within 6 hours of exercise testing or spirometry. In the event that a SABA is required within 6 hours (or 8 hours for SAMA) prior to exercise on the day of exercise testing or spirometry, the exercise test and/or spirometry must be rescheduled within the time window per the schedule of events (Table 1).

Systemic corticosteroids are allowed as rescue treatment for asthma exacerbations. Need for rescue therapy, dosage, and corticosteroid taper regimen will be determined by the site principal investigator and/or the patient's personal physician.

Patients who experience an asthma exacerbation in the last 4 weeks of the double blind treatment period and require treatment with systemic corticosteroids or an increase in systemic corticosteroids (for those patients on OCS) will not undergo CWRET at week 12, but the patient will be followed to perform other efficacy assessments including accelerometry, spirometry and safety assessments.

8.5. Dose Modification and Study Treatment Discontinuation Rules

8.5.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.5.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2.

8.5.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction (eg, Hy's law is met (Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation FDA, 2009))
- Patient withdraws consent
- If, in the investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- In the event of a protocol deviation, at the discretion of the investigator or the Sponsor
- Any patient unblinding requested by the investigator will lead to permanent treatment discontinuation
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Other intercurrent illnesses or major surgery which could, in the opinion of the investigator, present an unreasonable risk to the patient as a result of his/her continued participation in the study
- Development of a condition that precludes exercise
- Infections or infestations that do not respond to medical treatment
- Any opportunistic infection, or other infections whose nature or course may suggest an immunocompromised status
- Serum ALT and/or AST >3×ULN with total bilirubin >2×ULN , excluding confirmed Gilbert's syndrome
- Confirmed AST and/or ALT >5×ULN (for more than 2 weeks)
- Neutrophils <1500/mm^3
- Platelets <100000/mm^3
- Suspicion of rhabdomyolysis or CPK >10×ULN

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

8.5.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing will be temporarily discontinued in the event of:

- Surgical procedure
- Hospitalization

- Severe laboratory abnormalities (as noted in Section 8.5.2.1) where a causal relationship to study drug can be reasonably excluded, (ie, an alternative cause is evident): study drug will be discontinued but may be resumed when the laboratory abnormality is sufficiently normalized. At minimum, the laboratory value(s) must return to a level that no longer meets the specified criteria for discontinuation, as defined in Section 8.5.2.1. A decision to resume study treatment will be made jointly by the investigator and medical monitor (medical monitor's written approval is required).
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal agents, or requires oral treatment with such agents for longer than 2 weeks

After the condition leading to temporary discontinuation of study drug resolves, study drug dosing may resume. A decision to temporarily discontinue study drug and/or resume study drug dosing should be discussed with the Regeneron medical monitor.

The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the Regeneron medical monitor should be contacted as soon as possible. Resumption of study drug dosing requires consultation and agreement between the investigator and the Regeneron medical monitor.

If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor (except for illness or medical circumstance requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.6. Management of Acute Reactions

8.6.1. Acute Injection Reactions

8.6.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4.

Acute systemic reactions following injection of study drug (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.6.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4.

8.7. Method of Treatment Assignment

Approximately 140 patients will be randomized in a 1:1 ratio to receive either dupilumab or placebo according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or

qualified designee). Up to 10% of patients on maintenance OCS at screening and baseline (≤10 mg/day OCS, prednisone/prednisolone or dose equivalent) will be allowed to participate in the study. Randomization will be stratified by baseline FEV_1 (<50% vs. ≥50% predicted), use of maintenance OCS use (yes/no), and age (<35 vs. ≥35 years).

8.8. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Medical/Study Director, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

8.9. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded (Section 8.5.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.10. Treatment Logistics and Accountability

8.10.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.10.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

8.10.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.10.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

Patient will complete a paper diary to record dosing information.

8.11. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to final study visit will be recorded. This includes medications that were started before the study and are ongoing during the study. Any treatment administered from the time of first dose of study drug to the final study visit will be considered concomitant treatment.

8.11.1. Prohibited Medications and Procedures

The following concomitant treatments are not permitted during the study (from screening to end of study visit):

- Biologic therapy (biologic therapy is not allowed to be used from 3 months or at least 5 half-lives prior to visit 1, whichever is longer, and during the study).
- Chronic immunosuppressants (immunosuppressants are not allowed to be used from 3 months or at least 5 half-lives prior to visit 1, whichever is longer, and during the study) except maintenance OCS (≤10 mg/day of oral corticosteroids prednisone/prednisolone or dose equivalent) in up to 10% of patients.
- Allergen immunotherapy (except if initiated more than 3 months prior to visit 1 and dose stabilized 1 month prior to visit 1).

- Bronchial thermoplasty
- Exercise or physical rehabilitation program
- Intravenous immunoglobulin (IVIG) therapy
- Live Attenuated Vaccines

Chickenpox (varicella)	Oral typhoid
FluMist-Influenza	Rubella
Intranasal influenza	Smallpox (vaccinia)
Measles (rubeola)	Yellow fever
Measles-mumps-rubella combination	Bacille Calmette-Guerin
Measles-mumps-rubella-varicella combination	Rotavirus
Mumps	Varicella zoster (shingles)
Oral polio (Sabin)	

- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with dose stabilized at least 4 weeks prior to visit 1)
- Any investigational drugs (other than the study drug)

8.11.2. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 8.11.1, treatment with concomitant medications are permitted during the study:

If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

8.12. Poststudy Treatments

No poststudy treatments are required or planned. Patients may continue dupilumab treatment with commercial supplies per product label. Patients should continue their background asthma medication as prescribed by their personal physician.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Table 1 Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to

COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 1: Schedule of Events

	Screening and Run-in Period		Treatment Period							Follow-up	Early Termination Visit	Unscheduled Visit(s)[28]
	Screening[1]	Run-in period[1,2]										
Study Procedure	**Visit 1**	**Visit 2**	**Baseline[1,2] Visit 3**	**Ph Visit 4**	**Visit 5**	**Ph Visit 6**	**Ph Visit 7**	**Ph Visit 8**	**End of Treatment Visit 9**	**End of Study Visit 10**		
Week	-8 to -4	-4 to 0	1	2	4	6	8	10	12	14		
Day	-56 to -28	-27 to -1	1	15	29	43	57	71	85	99		
Window (day)	±7	±7	±3	±3	±3	±3	±3	±3	±3	±5		
Screening/Baseline												
Inclusion/Exclusion	X	X	X									
Informed Consent	X											
Medical/Surgical History	X											
Demographics	X											
Qualifying ACQ-5[3]	X		X									
Qualifying ECG (central reading)[4]	X											
Qualifying bronchodilator reversibility testing[5]	X											
Qualifying spirometry for FEV_1% predicted[6]	X		X									
Qualifying IWRET[4,7]	X											
Randomization			X									
Treatment												
Training on self-administration of study drug			X									
Administer study drug[8]			X	X	X	X	X	X				
Patient diary recording dosing information[9]			X	X	X	X	X	X				
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X

	Screening and Run-in Period		Treatment Period							Follow-up	Early Termination Visit	Unscheduled Visit(s)[28]
	Screening[1]	Run-in period[1,2]										
Study Procedure	**Visit 1**	**Visit 2**	**Baseline[1,2] Visit 3**	**Ph Visit 4**	**Visit 5**	**Ph Visit 6**	**Ph Visit 7**	**Ph Visit 8**	**End of Treatment Visit 9**	**End of Study Visit 10**		
Week	-8 to -4	-4 to 0	1	2	4	6	8	10	12	14		
Day	-56 to -28	-27 to -1	1	15	29	43	57	71	85	99		
Window (day)	±7	±7	±3	±3	±3	±3	±3	±3	±3	±5		
Efficacy												
Accelerometry[10]		X	X					X	X			
ACQ-5			X						X			
Patient diary to record removal of the accelerometer, nocturnal awakening due to asthma, physical activity[11]		X						X	X			
AQLQ(S)[12]			X						X			
Patient Global Impression of Change (PGIC)[13]					X				X			
Patient Global Impression of Impact (PGII)[14]			X		X				X			
CWRET[4]		X[15]	X[16]						X[17]			
Spirometry (pre- and post-exercise)[18]			X						X			
Exercise serial IC			X						X			
Borg dyspnea scale[19]			X						X			
Borg leg fatigue scale[19]			X						X			
VO_2			X						X			
Spirometry not associated with CPET[20]					X				X			
Safety												
Vital Signs[21]	X	X	X		X				X	X	X	
Physical Examination[22]	X		X						X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X

	Screening and Run-in Period		Treatment Period							Follow-up	Early Termination Visit	Unscheduled Visit(s)[28]
	Screening[1]	Run-in period[1,2]										
Study Procedure	**Visit 1**	**Visit 2**	**Baseline[1,2] Visit 3**	**Ph Visit 4**	**Visit 5**	**Ph Visit 6**	**Ph Visit 7**	**Ph Visit 8**	**End of Treatment Visit 9**	**End of Study Visit 10**		
Week	-8 to -4	-4 to 0	1	2	4	6	8	10	12	14		
Day	-56 to -28	-27 to -1	1	15	29	43	57	71	85	99		
Window (day)	±7	±7	±3	±3	±3	±3	±3	±3	±3	±5		
Laboratory Testing												
Hematology	X		X							X	X	
Blood Chemistry	X									X	X[29]	
Pregnancy Test (beta HCG)[23]	X[ser]		X[Ur]		X[Ur]				X[Ur]	X[Ur]	X[Ur]	
Urinalysis	X								X		X[29]	
Hepatitis and HIV Serology[24]	X											
Tuberculosis testing: QuantiFERON gold testing, or PPD per local regulations[25]	X											
Biomarkers and pharmacogenomics												
FeNO Measurement[26]	X		X						X			
Future biomarker research serum and plasma (optional)			X						X			
DNA[27] (optional)			X									

9.1.1. Footnotes for the Schedule of Events Table (Table 1)

1. Prior to baseline, patients must be on a medium-to-high dose ICS and at least a second asthma controller agent (eg, LABA, LAMA, or LTRA) or maintenance OCS if applicable for at least 3 months with a stable dose for at least 4 weeks prior to the baseline visit. A third controller is allowed and with the same stabilization requirements. The screening period can be completed once a patient passes ALL screening assessments/procedures. The patient can then proceed to the run-in period ensuring that the asthma background medication stabilization of at least 4 weeks has been met prior to the baseline visit (visit 3).
2. The run-in period (visit 2) may be completed and a patient can proceed to baseline once the following occurs:
   - Run-in CWRET achieved an exercise time between 3 to 8 minutes
   - Patient performs 1 week of accelerometry training followed by 2 consecutive weeks of accelerometry wear time. During the entire 3 week period, the accelerometer must be worn continuously (24 hours/day, 7 days/week) on the patient's wrist except during charging time, bathing, and any other water activities.
   - All other run-in assessments/procedures have been performed
   - Background asthma medication remains stable for at least 4 weeks (which can include the screening period) prior to the baseline visit (visit 3)
3. The Asthma Control Questionnaire-5 (ACQ-5) will be performed prior to spirometry.

   * ACQ is a patient-reported outcome measure used to assess asthma symptom control among patients with asthma. The 5-item version of the ACQ (ACQ-5) is composed of the 5 patient-reported items on awakening at night due to symptoms, awakening in the morning with symptoms, limitation of daily activities, shortness of breath, and wheezing.
4. In addition to the centrally read screening ECG performed at visit 1 for qualification, a locally performed ECG must be done prior to every CPET and demonstrate no clinically significant abnormalities, as evaluated by the investigator, to be eligible to continue in the study.
5. Patients are required to demonstrate FEV_1 reversibility of at least 12% and 200 mL after the administration of 200 to 400 µg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) during the screening period to qualify. Assessment may be performed up to a total of 2 times to qualify. Patients may also qualify if there is documented evidence of bronchodilator reversibility or positive methacholine challenge test within 12 months prior to the screening visit.
6. In-clinic spirometry - Patients must demonstrate a pre-bronchodilator FEV_1 between 30% and 75% predicted at both the screening and baseline visits to qualify. This assessment may be repeated once during the screening period and once at the baseline visit to qualify NOTE: Spirometry and all CPETs should ideally be conducted in the morning and at

approximately the same time of day at each visit. Spirometry will be done locally, and read centrally, according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidance. Spirometry and all CPETs will be performed during a trough period of bronchodilators according to their duration of action, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of ipratropium for at least 8 hours, withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for 48 hours. This will be verified before performing the measurements.

If bronchodilators have not been withheld, the CPET or spirometry, as applicable, must be rescheduled to occur within the time window of the assessment per the schedule of events.

7. The IWRET will be performed during the screening period to determine study eligibility. Exercise testing with continuous ECG, pulse oximetry and blood pressure monitoring will be performed during a trough period of bronchodilators according to their duration of action (see footnote #6). This will be verified before performing the exercise test. If the above has not occurred, the exercise test must be rescheduled to occur within the time window of the assessment per the schedule of events. IWRET can be performed up to a total of 3 times during the screening period to determine patient eligibility.

   NOTE: Prior to performing the IWRET, the patient must meet all other eligibility criteria.

8. Every 2 weeks (Q2W) study drug administrations must be separated by at least 11 days. Treatment can be administered Q2W in office at scheduled visits or at home (by patient, caregiver, or health care professional). Patients/caregivers, if preferred, may choose to have injections administered in the clinic. Due to the COVID-19 pandemic, study drug may be shipped from the clinical site to the patient's home if necessary.
9. When study drug is administered outside of the clinic, the patient (or caregiver) will record administration in the paper patient diary. He/she will return the study box kit at each subsequent in-clinic visit where drug accountability will be performed.
10. At visit 2, patients will be trained on the proper use of and wear an accelerometer on his/her wrist for a 1-week period, in order to get acclimated to the device. Patients will be instructed to wear the accelerometer continuously for 3 consecutive weeks (up until the baseline visit [visit 3]). The first week will be the training period on accelerometer use. The subsequent next 2 weeks will be to determine baseline pre-treatment daily physical activity. The study site will utilize the phone call at visit 7 to remind patients to also wear the accelerometer continuously starting 2 weeks prior to the end of treatment visit (visit 9) (ie, from week 10 to week 12). The accelerometer must be worn 24 hours/day, 7 days/week on the patient's wrist during both pre-treatment and end-of-treatment wear periods except during charging time, bathing, and any other water activities.
11. During the 2 consecutive weeks prior to baseline visit and the 2 consecutive weeks prior to week 12 visit, patients will record daily how much time spent bathing or swimming,

total time charging the device, physical activity (eg, walking, moderate physical activities, and vigorous physical activities), and nocturnal awakenings due to asthma in the patient diary.

12. The Asthma Quality of Life Questionnaire (AQLQ) will be performed prior to spirometry.* The AQLQ comprises 32 items across 4 domains: symptoms (12 items), activity limitations (11 items), environmental stimuli (4 items), and emotional function (5 items).
13. The Patient Global Impression of Change (PGIC) will be performed prior to spirometry.* PGIC is a single item patient-reported measure, which will assess patient's impression about the change in their ability to carry out exercise since study treatment initiation.
14. The Patient Global Impression of Impact (PGII) will be performed prior to spirometry.* The PGII is a single item patient-reported measure, to assess the patient's impression of the impact of asthma on their ability to carry out exercise during the past week.

    *Patient questionnaires: If COVID-19 restrictions limit the availability of staff or the patient to have in-clinic visits, site staff should make every effort to conduct telephone interviews to complete these questionnaires. Site staff should conduct the telephone interviews on the date of the scheduled site visit by following an interview guide provided by the sponsor. Patient responses from the interviewer administered questionnaires will be captured by the site staff.
15. Run-in CWRET at 80% of the previously determined individualized maximal work rate from the IWRET will be performed during run-in (visit 2) to familiarize patients with the test procedure and to determine work rate to meet the 3 to 8 minute exercise endurance time requirement. Run-in CWRET may be repeated twice (up to total of 3 tests) during the run-in period to determine work rate that achieves the qualifying criteria for exercise duration. ECG, pulse oximetry, and blood pressure monitoring are performed throughout the exercise test. Exercise tests will be performed during a trough period of bronchodilators according to their duration of action (see footnote #6).
16. The baseline CWRET will be performed utilizing the work rate established at the qualifying run-in CWRET. The same constant work rate established for an individual patient at the qualifying run-in CWRET must also be applied at the baseline and end of treatment visit.
17. Patients who require systemic corticosteroids or an increase in systemic corticosteroid dose for those receiving maintenance OCS for the treatment of an asthma exacerbation within the last 4 weeks of the double-blind treatment period will not perform a CWRET at week 12 (visit 9) but will have all other efficacy procedures performed (ie, accelerometry and spirometry without CWRET).
18. Spirometry will be performed within 15 minutes prior to exercise and at minutes 5±1, 10±1, and 20±1 post-exercise (CWRET) at baseline (visit 3) and end of study treatment (visit 9). Pre-exercise spirometry will be conducted prior to the patient sitting on the cycle ergometer and post-exercise spirometry once the patient has dismounted from the cycle ergometer. Details of the pre- and post-exercise spirometry procedures will be

detailed in the eRT user manual. The same in-clinic spirometry equipment will be used throughout the study.

19. Borg dyspnea and Borg leg fatigue will be assessed by the patient pre-exercise, every 2 minutes during exercise, and at peak exercise.
20. At visit 5 (week 4) when exercise testing is not performed, spirometry will be performed to assess FEV_1 and FVC. At visit 9, in the event that CWRET is not performed due to an exacerbation, spirometry will still be performed at the investigator's discretion.
21. Vital signs, including sitting systolic and diastolic blood pressure (mm Hg), pulse rate (beats per minute), body temperature (°C), and respiratory rate will be measured at screening, and predose at baseline and at every subsequent scheduled on-site visit. Height (cm) will be measured at screening (visit 1) only. Body weight (kg) will be measured at screening (visit 1) and at end of treatment and end of study visits.
22. Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.
23. Beta human chorionic gonadotropin (HCG) serum (Ser) pregnancy test at visit 1 and urine dipstick (Ur) pregnancy tests at other visits. A negative result must be obtained at visits 1 and 3 prior to randomization.
24. Clinical laboratory testing at screening visit 1 will include hepatitis screen covering hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C virus antibodies (HCV Ab), and human immunodeficiency virus (HIV) screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg (negative), and HBcAb (positive), an HBV DNA testing will be performed prior to randomization to rule out a false positivity if the investigator believes the patient's test is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the investigator believes the patient has a false positive result.
25. Tuberculosis testing (QuantiFERON gold testing or purified protein derivative [PPD]) will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethic committees.
26. Fractional exhaled nitric oxide (FeNO) assessment should be conducted prior to exercise testing, prior to spirometry, and after administering ACQ-5, AQLQ, and PGII questionnaires following a fast of ≥1 hour. Ensure the FeNO device is ready to use. After completing the exercise test the patient should sit comfortably in a chair to prepare for the post-exercise FeNO and serial spirometry measurements.

    NOTE: When the patient is ready to perform the post-exercise FeNO assessment, the study staff will start a stopwatch and record the starting time. This will start the timer for the post-exercise serial spirometry measurements. The post-exercise FeNO measurements should be started as soon as the time has been entered.

27. Optional DNA sample is to be collected prior to study drug administration at baseline, but can be collected at a later study visit.
28. For unscheduled visit, besides the required recording of AEs and concomitant medications/procedures, other assessments may be performed at the discretion of the investigator and based on patients' condition (eg, laboratory test monitoring an AE).
29. Optional assessment at the early termination visit.

9.1.2. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 12) will be asked to return to the clinic once for an early termination visit consisting of the end of study assessments described in Table 1.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

9.2. Study Procedures

Patient-reported outcome scales should be completed by the patient, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The scales should be completed by the patients before the consultation and/or clinical tests, in a quiet place.

9.2.1. Procedures Performed Only at the Screening/Baseline Visits

The following assessments are performed only at the screening, run-in, or baseline visits.

Procedures Performed Only at the Screening Visit

After signing informed consent, the following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Medical/surgical history
- Demographics
- Bronchodilator reversibility testing (see description in Section 9.2.2.5) or documented evidence of bronchodilator reversibility or positive methacholine challenge test within 12 months of the screening visit
- Qualifying IWRET (may be performed up to total of 3 times)
- Qualifying ECG with central reading
- Height
- Beta HCG serum pregnancy test

- TB testing: QuantiFERON gold testing, or purified protein derivative (PPD) as required. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethic committees.
- Hepatitis serology: HBsAg, HBsAb, HBcAb, and HCV Ab. In case of results showing HBsAg (negative), and HBcAb (positive), an HBV DNA testing will be performed prior to randomization to rule out a false positivity if the investigator believes the patient's test is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the investigator believes the patient is a false positive.
- Human Immunodeficiency Virus (HIV) screen (including anti-HIV-1 and HIV-2 antibodies)
- Blood eosinophil count for patients not on maintenance OCS at the screening visit

Procedures Performed Only at the Baseline Visit

- Randomization
- Training on self-administration of study drug
- DNA sample (optional) (see Section 9.2.5)

Procedures Performed Only at the Screening and Baseline Visits

- Qualifying % predicted FEV_1
- Qualifying ACQ-5

Procedures Performed Only at the Screening, Run-In, and Baseline Visits

- Review of inclusion/exclusion criteria

9.2.2. Efficacy Procedures

All procedures, eg, ACQ-5, AQLQ, PGII, PGIC, and FeNO, must be performed prior to the CPET and all patient-reported outcome assessments (eg, ACQ-5, AQLQ, etc) must be performed prior to spirometry in the order listed and specified in the schedule of events. FeNO measurement will also be done pre- and post-exercise as detailed in the eRT user manual. Every effort should be made to have patients perform study procedures in the morning. In the event this is not possible, procedures can be performed in the afternoon. Regardless, procedures must be performed at approximately the same time of day at each study visit, ie, if the baseline testing is performed in the morning, all subsequent study procedures must be performed in the morning.

9.2.2.1. Accelerometers

Accelerometers are wearable sensors which objectively record and measure physical activity and energy expenditure in a "free living" environment, reflecting activities of daily living (Attal, 2015) (Kim, 2012). Accelerometers can record steps walked, energy expenditure, and time spent performing physical activities of various intensity based on energy expenditure.

Patients will be instructed to wear an accelerometer on their wrist day and night during the 3 weeks prior to the baseline visit and for the 2 weeks prior to the end of treatment visit (24 hours per day, 7 days/week [except during charging time, bathing, and any other water activities]) per the schedule in Table 1. The following data will be obtained from the accelerometer recording:

- Number of steps walked per day
- Total Energy Expenditure (metabolic equivalents [METs])
- Mean duration of moderate-to-vigorous physical activity (defined as ≥3 METs)

Accelerometers will be provided to sites and appropriate training will be provided to the investigator regarding patient use.

Patients will complete a diary to record removal of the accelerometer, nocturnal awakenings due to asthma and physical activities.

9.2.2.2. Patient-Reported Outcomes

Patient-reported outcome assessments must occur prior to other visit procedures.

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

The ACQ-5 is a patient-reported outcome measure used to assess asthma symptom control among patients with asthma. The instrument has 5 questions that assess the most common asthma symptoms: 1. frequency awoken by asthma during the night, 2. severity of asthma symptoms in the morning, 3. limitation of daily activities due to asthma, 4. shortness of breath due to asthma, and 5. wheeze. 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). The ACQ-5 score is the mean score of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). A higher score indicates lower asthma control. A score below 1.5 reflects adequately controlled asthma and a score above 1.5 reflects 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 (Juniper, 2005).

ACQ-5 will be completed prior to spirometry during clinic visits per the schedule in Table 1.

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

The AQLQ(S) is designed as a self-administered patient-reported disease-specific health-related quality of life instrument that measures both physical and emotional impact of asthma in adults and adolescents ≥12 years of age. The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items)

- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental stimuli (4 items)

A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life.

The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The MCID for AQLQ(S) is 0.5 (Juniper, 1994).

Patient Global Impression of Change (PGIC)

The Patient Global Impression of Change (PGIC) is a patient-reported measure that assesses patients' impression about the change in their ability to exercise since study treatment initiation. Patients will be asked to recall the change in their ability to exercise since the baseline visit. The PGIC will be administered at site visits per the schedule in Table 1.

Patient Global Impression of Impact (PGII)

The Patient Global Impression of Impact (PGII) is a patient-reported measure that assesses patients' impression about the impact of asthma on their ability to exercise during the past week. The PGII will be administered at baseline and at site visits per the schedule in Table 1.

9.2.2.3. Fractional Exhaled Nitric Oxide (FeNO) Level

Measurement of FeNO level in asthmatic patients is used as a marker of airway inflammation. FeNO levels will be assessed in accordance with ATS/ERS guidelines using the standardized nitric oxide measuring equipment (eg, Circassia NIOX VERO®). Patients will be instructed to refrain from eating and drinking for at least 1 hour prior to FeNO measurements. FeNO measurements should be made prior to any spirometry. During the study, patients will be required to undergo FeNO measurement at study visits per the schedule in Table 1. Sites will be provided with equipment and instructions regarding FeNO measurement.

9.2.2.4. Cardiopulmonary Exercise Testing (CPET)

Tests will be performed on an electromagnetically-braked cycle ergometer in an exercise physiology laboratory overseen by a trained pulmonologist or medical doctor designee. A medical doctor must be present in the room in which the initial IWRET is conducted and readily available for medical intervention, at all subsequent exercise tests. Resuscitation equipment must be immediately available in the PFT lab where the exercise testing is performed. Patients will exercise until exhaustion breathing through a mouthpiece with noseclip in place or while wearing a mask.

A CPET is a medically well-accepted and standardized test that has been utilized to assess degree of exercise impairment in a variety of pulmonary diseases, including pulmonary arterial hypertension, COPD, and interstitial lung diseases, as well as in asthma (Puente-Maestu, 2016). It is frequently performed clinically in specialized centers with proper exercise equipment and training. For safety purposes, physiologic responses are assessed repeatedly during CPET, including ECG parameters, oxygen saturation, blood pressure, pulmonary ventilation, oxygen

uptake, and respiratory rate. Heart rate and blood pressure must be measured just prior to all CPETs with the patient seated on the cycle ergometer (eg, at rest). Patients must have a heart rate <100 bpm and a systolic blood pressure ≤180 mm Hg and diastolic blood pressure ≤95 mm Hg measured just prior to performing exercise.

CPET testing performed according to standardized procedures can employ either an incremental or constant work rate protocol. A maximal incremental test involves exercise to exhaustion under conditions of increasing work rate. A constant work rate protocol in this study is performed at 80% of the maximal work rate attained from the incremental maximal test and involves exercising until exhaustion. A constant work rate protocol is chosen for this study as opposed to a maximal incremental exercise test, as the former has been shown to be more sensitive to discriminate change in exercise capacity. Also, use of a constant work rate test allows measurement of a well-understood variable: cycling endurance time. To minimize variability in measurements, CPET will be done using a standardized CPET protocol, with site quality control and only at sites proficient in CPET testing (American Thoracic Society, 2003).

Relative and absolute contraindications to CPET are listed in Table 2 and the CPET laboratory manual distributed to each study site.

Table 2: Absolute and Relative Contraindications to CPET

Absolute	Relative
• Acute myocardial infarction (3 to 5 days) • Unstable angina • Uncontrolled arrhythmias causing symptoms or hemodynamic compromise • Syncope • Active endocarditis • Acute myocarditis or pericarditis • Symptomatic severe aortic stenosis • Uncontrolled heart failure • Acute pulmonary embolus or pulmonary infarction • Thrombosis of lower extremities • Suspected dissecting aneurysm • Acute asthma exacerbation • Pulmonary edema • Room air oxygen desaturation at rest <85%* • Respiratory failure • Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (ie, infection, renal failure, thyrotoxicosis) • Mental impairment leading to inability to cooperate	• Left main coronary stenosis or its equivalent • Moderate stenotic valvular heart disease • Severe untreated arterial hypertension at rest (>200 mm Hg systolic, >120 mm Hg diastolic) • Tachyarrhythmias or bradyarrhythmias • High-degree atrioventricular block • Hypertrophic cardiomyopathy • Significant pulmonary hypertension • Advanced or complicated pregnancy • Electrolyte abnormalities • Orthopedic impairment that compromises exercise performance

*Exercise patient with supplemental O2.
Source: Adapted from Amj J Respir Crit Care Med 2003;167:211-277 (American Thoracic Society, 2003).

Qualifying Maximal Incremental Work Rate Exercise Test (IWRET)

Qualifying IWRET (American Thoracic Society, 2003) will be performed only at screening (see Table 1) to determine the peak work rate to use in calculating 80% of maximal work rate for the CWRET. The procedure is as follows:

Medical history and screening ECG are performed directly prior to testing to ensure patients do not have a contraindication to exercise testing. Patients deemed eligible, are familiarized with the bicycle (stationary electromagnetically-braked cycle ergometer). Subsequently, patients will have 3 minutes of rest on the cycle, 3 minutes of unloaded pedaling, and then the work rate will be increased continuously under computer control in ramp-like fashion (ramp protocol) until the patient reaches volitional exhaustion or the supervising clinician terminates the test for safety reasons. It is important that prior to exercise the patient is informed that the test requires exercise until exhaustion. The individual supervising the exercise test should provide verbal encouragement to the patient during the test to help ensure maximal patient effort.

The peak work rate is that at which the patient reaches volitional exhaustion, usually marked by inability to maintain pedaling cadence >50 rpm. The work rate should be set to increase at either 10, 15, 20, or 25 W/min depending on the investigator's assessment of the patient's ability to exercise, with the goal of having the patient exercise between 4 and 16 minutes. Patients must develop dynamic hyperinflation defined as more than 100 mL decrease in IC from the pre-exercise value. If the exercise time is outside of the 4 to 16 minute window, the test may be repeated with a change in the work rate from that previously used by ±10% or 5 W/min, whichever is greater to achieve an exercise duration between 4 and 16 minutes. The IWRET can be performed up to a total of 3 times during the screening period to determine study eligibility. A repeated test must be performed at least 2 hours after the previous one. A patient who exercises <4 or >16 minutes or does not have a decrease in IC >100 ml during the third qualifying IWRET will be considered a screen failure.

Constant Work Rate Exercise Testing (CWRET)

CWRET will be performed on an electromagnetically-braked cycle ergometer in an exercise physiology laboratory overseen by a trained pulmonologist or medical doctor designee. While sitting on the cycle ergometer, patients will have 3 minutes of rest, 3 minutes of unloaded pedaling, and then an immediate increase in work rate to approximately 80% of the previously determined individualized peak work rate value from the incremental test. Exercise will continue until volitional exhaustion. It is important that prior to exercise the patient is informed that the test requires exercise until exhaustion. The individual supervising the exercise test should provide strong verbal encouragement to the patient during the test to obtain maximal patient effort.

If at the run-in CWRET, the patient's exercise duration is not within the range of 3 to 8 minutes, the test can be repeated 2 more times with the wattage changed by ±10% or 5 W/min, whichever is greater. If CWRET needs to be repeated, the repeat test must be performed at least 2 hours after the previous one. The exercise endurance time will be collected at time points per the schedule of events in Table 1.

During the CWRET, other measurements including serial IC, perception of dyspnea measured by the Borg Dyspnea Scale, perception of leg fatigue measured by the Borg Leg Fatigue Scale, and VO_2 will be obtained.

Note: The same exercise work rate applied at the qualifying run-in CWRET test that achieves an exercise time between 3 and 8 minutes must also be applied at the baseline and end of treatment CWRET.

Borg Dyspnea and Leg Fatigue Scales

Borg Dyspnea and Leg Fatigue Scales are validated scales to assess perceived symptoms of dyspnea and leg fatigue respectively when undergoing strenuous exercise (Borg, 2010) (Borg, 1982). The scales are from 0 (nothing at all) to 10 (very, very strong). Patients will report their Borg dyspnea and Borg leg fatigue scores at rest, every 2 minutes during exercise and at peak exercise.

The Borg Dyspnea and Leg Fatigue Scales will be performed at time points per the schedule in Table 1.

Details of all exercise-related testing procedures will be provided in the exercise testing procedure manual.

9.2.2.5. Spirometry

A spirometer that meets the ATS/ERS recommendations will be used. Spirometry will be performed locally, and read centrally, in accordance with the ATS/ERS guidelines (Miller, 2005).

Screening Spirometry to Determine FEV_1% Predicted and Bronchodilator Reversibility

Up to 2 spirometry attempts may be made during the screening period until the baseline visit to meet the qualifying criteria for FEV_1 % predicted and establish bronchodilator reversibility. Note: patients may qualify if they have documented evidence of bronchodilator reversibility or a positive methacholine challenge test within 12 months of the screening visit. Spirometry will be done locally at the site, and read centrally, according to ATS/ERS guidelines. Spirometry at all visits will be performed during a trough period of bronchodilators according to their duration of action, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of ipratropium for at least 8 hours, withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for 48 hours. This will be verified by the principal investigator or designee before performing the measurements.

Pre- and Post-Exercise (CWRET) FEV_1

For pre-exercise FEV_1, spirometry will be performed during a trough period of bronchodilators according to their duration of action, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of ipratropium for at least 8 hours, withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for 48 hours. This will be verified by the principal investigator or designee before performing the measurements.

Pre-exercise FEV_1 will be assessed within 15 minutes prior to the start of the exercise testing and post-exercise FEV_1 will be performed at minutes 5±1, 10±1, and 20±1 post-exercise at visits per the schedule in Table 1.

Pre- and post-exercise FVC will also be assessed.

Details of the spirometry procedures will be provided in the eRT user manual.

Patients who require systemic corticosteroids or an increase in systemic corticosteroid dose for those receiving maintenance OCS for the treatment of an asthma exacerbation within the last 4 weeks of the double-blind treatment period will not undergo a CWRET at week 12 (visit 9) but will have FEV_1 and FVC assessed by spirometry at rest.

The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits, at approximately the same time of day and, whenever possible, the same person should perform the measurements.

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.

Spirometry Not Associated with Exercise (at Visit 5)

At week 4 (visit 5) when exercise testing is not performed, spirometry will be performed to assess FEV_1 and FVC. At visit 9, in the event that CWRET is not performed due to an exacerbation, spirometry will still be performed at the investigator's discretion.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including body temperature (°C), sitting systolic and diastolic blood pressure (mm Hg), pulse rate (beats per minute), and respiratory rate, will be collected predose at time points according to Table 1.

Body weight and height will be measured at time points according to Table 1.

9.2.3.2. Physical Examination

A thorough and complete physical examination, including skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems, will be performed at time points according to Table 1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.3. Electrocardiogram

An ECG will be performed just prior to CPET to ensure that the patient does not have a contraindication to CPET (see Section 9.2.2.4). An ECG will be performed throughout the exercise tests as indicated in the schedule of events (Table 1). Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source documentation, and the results will be documented in the electronic case report form (eCRF).

The results of the qualifying ECG will be interpreted by a central reading center. All other ECGs will be read locally. Instructions for performing the qualifying ECG and transmitting ECG data are provided in the eRT user manual.

9.2.3.4. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Samples will be collected predose at time points listed in Table 1. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen	Low-density lipoprotein (LDL)
Carbon dioxide	Aspartate aminotransferase (AST)	High-density lipoprotein (HDL)
Calcium	Alanine aminotransferase (ALT)	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	Creatine phosphokinase (CPK); CPK isoenzymes will be measured when CPK >5 × ULN

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Pregnancy testing will be performed for all women of childbearing potential. Serum or urine pregnancy testing will be performed at time points listed in Table 1.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. In these patients, samples for FBR will be collected per Table 1. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the clinical study report (CSR).

9.2.5. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline, but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of asthma and other related inflammatory diseases. These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to dupilumab, other asthma clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of asthma as well as related allergic/atopic/type 2 inflammation diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or asthma and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the

course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period, from the time of signing the informed consent form (ICF) to the end of study. Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on serious adverse events (SAEs) and adverse events of special interest [AESIs]) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the follow-up period) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE case report form (CRF). Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Anaphylactic reactions
  - Systemic or severe hypersensitivity reactions
  - Severe injection site reactions lasting for >24 hours
  - Helminthic infections
  - Any severe type of conjunctivitis or blepharitis
  - Keratitis
  - Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female , during the study or within 12 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards For Expedited Reporting (E2A), 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger)
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions)
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions

The severity of injection site reactions (ISRs) will be graded according to the following scale (semi-colon indicates "or" within description of grade):

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires an emergency room (ER) visit or hospitalization; necrosis or exfoliative dermatitis

10.2.5. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction

- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis and periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (dupilumab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Event expectedness for study drug (dupilumab) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IECs/IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

Data collected through the implementation of CRFs regarding the impact of the COVID-19 pandemic on patients will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 on the efficacy (eg, missing data due to COVID-19) and safety evaluation will be specified in the SAP.

11.1. Statistical Hypothesis

The following null hypothesis and alternative will be tested:

- Null hypothesis: The mean change from baseline in the constant work-rate exercise endurance time at week 12 is the same between dupilumab and placebo.
- Alternative hypothesis: The mean change from baseline in the constant work rate exercise endurance time at week 12 differs between dupilumab and placebo.

11.2. Justification of Sample Size

The planned sample size of approximately 70 patients per treatment group will provide >85% power to detect a 105-second mean change in constant work rate exercise endurance time, with a standard deviation of 190 seconds, 2-sided $\alpha = 5\%$, and 10% drop out rate.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Set

The full analysis set (FAS) includes all randomized patients. It will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). All efficacy endpoints will be analyzed using the FAS.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients who signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

Baseline Definitions:

Baseline for singular-value assessments, such as measurements from the CWRET, FEV_1 and FVC from spirometry, will be the latest valid measurement taken prior to the first administration of study drug.

Baseline for the 14-day average values of measurements from accelerometry is defined as the average of the non-missing values during the 14 days prior to the first administration of study drug.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The primary endpoint of change from baseline in constant work rate exercise endurance time at week 12 will be analyzed using an analysis of covariance (ANCOVA) model for the FAS population. The ANCOVA model will include terms for treatment group, randomization stratification factors and the baseline value for the constant work rate exercise endurance time.

The intercurrent events handling strategy for systemic corticosteroid use for an asthma exacerbation or an increase in systemic corticosteroids during last 4-week of the treatment period and for treatment discontinuation is specified in Table 3 (Primary Estimands). The imputation method for missing data based on the reasons for study discontinuation is defined below:

- Missing data due to:
  - AE or lack of efficacy will be imputed by baseline observation carried forward (BOCF).
  - Other reasons will be imputed using multiple imputation (MI) rules under a missing at random assumption. A detailed imputation model will be specified in the SAP.

The primary estimands of interest for the primary endpoint, definitions of intercurrent events and corresponding strategies, and missing data handling approaches are provided in Table 3:

Table 3: Primary Estimands

	Estimands			
Endpoint category	**Endpoints**	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary/Analysis method**
Primary (Continuous)	Change from baseline to week 12 in constant work rate exercise endurance time	FAS	The intercurrent events will be handled as follows: • Initiation of systemic corticosteroids for the treatment of an asthma exacerbation or increase in systemic corticosteroid dose for those receiving maintenance OCS, within the last 4 weeks of the double-blind treatment period: Constant work rate exercise endurance time for each patient at week 12 will be assigned by his/her baseline values of constant work rate exercise endurance time (Hypothetical strategy) • Asthma exacerbation prior to week 8 of the double-blind treatment period requiring systemic corticosteroids or an increase in systemic corticosteroid dose for those receiving maintenance OCS: Data collected after the intercurrent event will be included in the analyses (Treatment policy strategy). • Initiation of prohibited medications: Data collected after the intercurrent event will be included in the analyses (Treatment policy strategy). • Treatment discontinuation: Data collected after the intercurrent event will be included in the analyses (Treatment policy strategy). Missing data imputation rules: • BOCF will be used to impute the missing values for discontinuation of the study either due to AE or lack of efficacy. • Missing data due to any other reason including COVID-19 will be imputed using multiple imputation (MI)	Mean change from baseline/The ANCOVA model with treatment group, randomization stratification factors and the baseline value for the constant work rate exercise endurance time as covariates.

Subgroup analysis may be performed for age, sex, weight, baseline FEV_1, baseline constant work rate endurance time and baseline ACQ-5. Subgroup analyses may not be performed if the primary efficacy result is not statistically significant.

11.4.3.2. Secondary Efficacy Analysis

The secondary efficacy endpoint of change from baseline to week 12 in pre-/post-exercise FEV_1 will be analyzed using the same method as for the primary analysis.

Other secondary endpoints measured by accelerometry (ie, change from baseline to week 12 in: average number of steps walked per day, total energy expenditure, and mean duration of moderate-to-vigorous physical activity) will be analyzed using a method similar to that for the primary endpoint, except that patients who initiate corticosteroids for the treatment of an asthma

exacerbation within the last 4 weeks of the treatment period (or corticosteroid dose increase for those on maintenance OCS) will be included in the analysis.

11.4.4. Control of Multiplicity

Multiplicity adjustment will be applied for testing of multiple endpoints. Type I error rate will be controlled using a hierarchical testing procedure for the primary and then key secondary endpoints at the 2-sided 0.05 level. The order of the endpoints for hierarchical testing will be specified in the SAP.

11.4.5. Safety Analysis

Safety analysis will be based on the SAF. This includes reported treatment-emergent AEs (TEAEs), AESIs, and other safety information (eg, clinical laboratory evaluations, vital signs, and 12-lead ECG results). A summary of safety results for each treatment group will be presented.

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the days from the date of the first dose of study drug to the week 12 visit date (study day 85 starting from the first dose of study drug if week 12 visit date is unavailable) or early termination date, whichever comes first.
- The post-treatment period or follow-up period is defined as the days from the date after week 12 visit date (study day 85 starting from first dose of study drug if week 12 visit date is unavailable) to end of study.

The treatment-emergent period is defined as the day from first dose of study drug to end of study. Treatment-emergent AEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment-emergent period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group during the overall study period, during the treatment-emergent period, during the 12-week treatment period, and during the follow-up period will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. The number and percentage of patients with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each vital sign variable. The criteria for treatment emergent PCSV will be defined in the SAP.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a PCSV at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

The number and percentage of patients with a treatment-emergent PCSV will be summarized for each clinical laboratory test. The criteria for treatment-emergent PCSVs will be defined in the SAP.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

11.4.5.3. Treatment Exposure

The duration of exposure during the study will be presented by treatment group and calculated as:

Date of last study drug injection – date of first study drug injection + 14 days

The number (%) of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, standard deviation, minimums, Q1, medians, Q3, and maximums.

A summary of the number of doses by treatment group will be provided.

11.4.5.4. Treatment Compliance

The compliance with protocol-defined investigational product will be calculated as follows:

Treatment Compliance = (Number of study drug injections during exposure period)/ (Number of planned study drug injections during exposure period) x 100%

The treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

11.5. Interim Analysis

No interim analysis is planned.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan, specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing), will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC).

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and is accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection

- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF/eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRF/eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible

- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: R668-AS-1903, a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of dupilumab on exercise capacity in patients with moderate-to-severe asthma with type 2 inflammation and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of dupilumab on exercise capacity in patients with moderate-to-severe asthma with type 2 inflammation

Protocol Number: R668-AS-1903

Protocol Version: Amendment 1 Global

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

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Sponsor's Responsible Regulatory Liaison

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Sponsor's Responsible Clinical Study Lead

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Sponsor's Responsible Biostatistician

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ESig Approval	[redacted] 16-Jun-2021 15:36:16 GMT+0000
ESig Approval	[redacted] 16-Jun-2021 15:57:40 GMT+0000
ESig Approval	[redacted] 17-Jun-2021 12:23:16 GMT+0000
ESig Approval	[redacted] 17-Jun-2021 13:27:45 GMT+0000

Signature Page for VV-RIM-00147293 v1.0 Approved