NCT04203797

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol 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
Compound:	Dupilumab
Protocol Number:	R668-AS-1903
Clinical Phase:	Phase 4
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Original Statistical Analysis Plan / April 30, 2023

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION 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 and/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
FEV1	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
VO2	Oxygen consumption
W/min	Watts per minute
WBC	White blood cell
WOCBP	Women of childbearing potential

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the data analysis of R668-AS-1903

1.1. Background

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 (FEV1), 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 FEV1) 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).

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

1.2. Study Objectives

In this section, primary, secondary and exploratory objectives are specified. However, all the objectives are for exploratory and hypothesis-generating purposes only. **There will be no formal hypothesis testing of any of the listed objectives.**

1.2.1. Primary Objective

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

1.2.2. 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

1.2.3. Exploratory Objectives

The exploratory objectives of the study are to:

- 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

1.3. Hypothesis and Rationale

The study is exploratory and hypothesis-generating only. **There will be no formal statistical testing of any of the hypotheses listed.**

1.3.1. Hypothesis

The pre-defined hypothesis was that patients with moderate-to-severe asthma treated with dupilumab would show improvement in exercise capacity and increase in physical activity of daily living. However, due to under enrollment, study is not sufficiently powered for the primary endpoint. Therefore, there will be no formal hypothesis testing for any of the specified endpoints in the study.

1.3.2. Rationale

1.3.2.1. Rationale for Study Design

It has been shown that dupilumab treatment significantly improves FEV1, 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 FEV1 (Haverkamp, 2007). However, other studies in patients with asthma treated with

bronchodilators demonstrated increases in FEV1 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 FEV1 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 FEV1 as a marker of physical activity have shown conflicting results. Bahmer et. al. reported that FEV1 and peak expiratory flow were poor markers of physical activity in asthma patients showing no significant correlation between FEV1 and steps walked per day (Bahmer, 2017), whereas Hennegrave et. al. showed significant correlation between steps walked and FEV1 (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 was designed to evaluate whether treatment with dupilumab increases exercise endurance time evaluated using constant work rate exercise testing (CWRET). Additionally, assessment of physical activities of daily living (steps walked per day, energy expenditure, and time spent in moderate-to-vigorous activity) was planned using accelerometry.

A blinded, randomized design was chosen to minimize bias in data collection and result interpretation. The presence of a placebo arm was considered appropriate for the objectives of this study to explore the efficacy of dupilumab. A run-in period was planned to stabilize background asthma treatment, to 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 was 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 was 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 was

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 was to be done using a standardized CPET protocol, and only at sites proficient in CPET and pulmonary function testing.

1.3.2.2. 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.

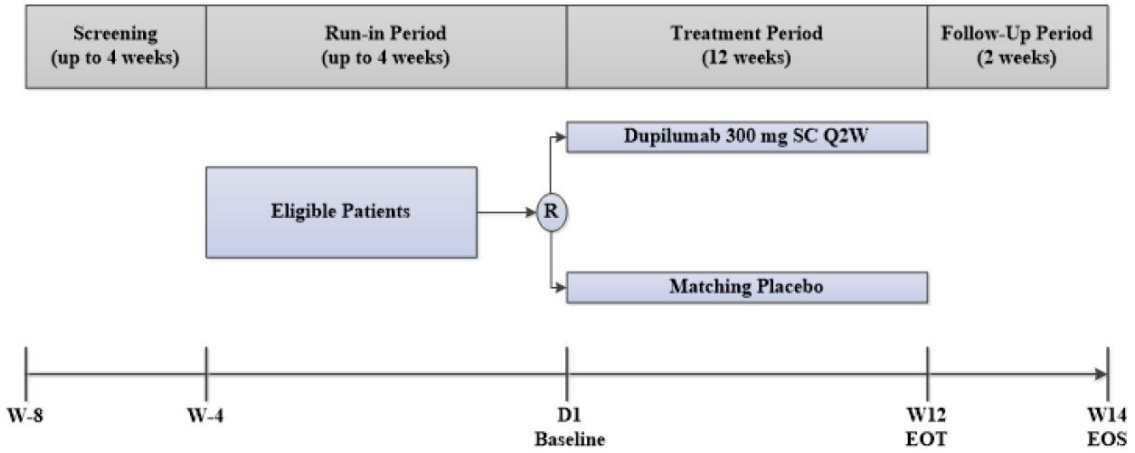
2. INVESTIGATION PLAN

2.1. Study Design and Duration

This phase 4, global, randomized, double-blind study of dupilumab vs. placebo was originally 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 were planned to be enrolled in the study, approximately 70 per treatment group with a 1:1 randomization ratio. Due to enrollment challenges, the study is going to be terminated early with approximately 40 patients enrolled. 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 FEV1 (<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. 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.

2.1.1. End of Study Definition

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

2.2. Statistical Hypothesis

The following null and alternative hypotheses are specified for reference. There is no formal hypothesis testing. All p-values will be nominal and for exploratory and hypothesis-generating purposes only.

- 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.

2.3. Sample Size and Power Considerations

The originally planned sample size of approximately 70 patients per treatment group (N=140 total) was to provide >85% power to detect a 105-second mean change in exercise endurance time, with a standard deviation of 190 seconds, 2-sided $\alpha = 5\%$, and 10% drop out rate. However, due to enrollment challenges, the study will be terminated early at a smaller-than-planned sample size, and all the analyses will be exploratory (with no alpha control).

2.4. Study Plan

2.4.1. Schedule of Events

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

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									

2.4.2. 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 .

2.4.3. 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.

3. ANALYSIS POPULATIONS

3.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients. The FAS is based on the treatment allocated (as randomized). All efficacy endpoints will be analyzed using the FAS.

3.2. Safety Analysis Set (SAF)

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

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Age at screening in years
- Sex (Male, Female)
- Ethnicity (Hispanic/Latino or not)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- ACQ-5
- Qualifying IWRET information including exercise duration, end exercise VO2, inspiratory capacity at rest, inspiratory capacity at peak exercise, and rest-peak exercise inspiratory capacity
- Qualifying ECG
- Pre-exercise ECG during IWRET
- Exercise ECG during IWRET
- Bronchodilator reversibility
- Pre-bronchodilator FEV_1 (L)
- Post-bronchodilator FEV_1 (L)
- FEV_1 Percent Predicated (%)
- Blood eosinophil count (cells/uL)
- Pre-bronchodilator Forced Vital Capacity (FVC)
- Post-bronchodilator Forced Vital Capacity (FVC)

4.2. Medical History

General medical history and surgical medical history are collected.

General medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA.

4.3. Pre-treatment/ Concomitant Medications and Procedures

Medications/Procedures were recorded from the day of informed consent to final study visit. Medications will be coded to the anatomical therapeutic chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available

version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken, or procedures performed prior to administration of the study drug will be summarized.

Concomitant medications/procedures: any treatment administered from the time of first dose of study drug until last study visit will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study drug and will continue during the study, as well as any therapies started in the follow-up period to treat a study drug related AE. All concomitant treatments must be recorded in the study case report form (CRF) with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

4.4. Efficacy Variables

This section provides more details on the primary, secondary and exploratory endpoints. However, **no endpoints listed will be formally tested and all p-values are nominal**. Additional endpoints and analytical methods may be used for exploratory and hypothesis-generating purposes.

4.4.1. Primary Efficacy Variable

The primary endpoint is change from baseline to week 12 in constant work rate exercise endurance time measured from the CWRET (refer to Protocol Section 9.2.2.4 for definition).

4.4.2. Secondary Efficacy Variables

The **secondary** endpoints are:

- Change from baseline to week 12 in pre- and post-exercise (5 seconds, 10 seconds and 20 seconds, respectively) FEV_1 (based on spirometry data; refer to Protocol Section 9.2.2.5 for detailed definition)
- Change from baseline to week 12 in average number of steps walked per day (based on accelerometry data; refer to Protocol Section 9.2.2.1 for detailed definition.)
- 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)

4.4.3. Exploratory Variables

- 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. Refer to Protocol Section 9.2.2.2 for detailed definition.
- Change from baseline to week 12 in perception of leg fatigue measured by the Borg Leg Fatigue Scale at isotime. Refer to Protocol Section 9.2.2.2 for detailed definition.
- Change from baseline to week 12 in end-exercise oxygen consumption (VO_2)
- 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 FEV1 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
- 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). Refer to Protocol Section 9.2.2.2 for detailed definition.
- Proportion of patients responding with an improvement on the Patient Global Impression of Change (PGIC) at weeks 4 and 12. Refer to Protocol Section 9.2.2.4 for detailed definition.
- Proportion of patients responding with no or limited impact on the Patient Global Impression of Impact (PGII) at weeks 4 and 12. Refer to Protocol Section 9.2.2.4 for detailed definition.

4.5. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG and physical exam. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of study treatment.

4.5.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a

Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA).

An Adverse Event (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.

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).

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.

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

4.5.2. 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.

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Helminthic infections
- Any severe type of Conjunctivitis, Blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Severe injection site reactions lasting for >24 hours

4.5.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, and urinalysis. Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables using SI units. The same set of analysis will also be prepared in US units.

Functions are defined as follows:

- Chemistry
- Hematology
- Urinalysis
- Serology

4.5.4. Vital Signs

Vital signs will be collected at time points specified in the study protocol:

- Diastolic Blood Pressure
- Systolic Blood Pressure
- Heart Rate
- Respiratory Rate
- Height
- Weight
- Body Mass Index
- Temperature

4.5.5. Electrocardiography (ECG)

An ECG will be be performed just prior to CPET to ensure that the patient does not have a contraindication to CPET. An ECG will be performed throughout the exercise tests as indicated in the schedule of events (Table 1). The results of the qualifying ECG will be interpreted by a central reading center. All other ECGs will be read locally.

- ECG Mean Heart Rate
- PR Interval, Aggregate
- QRS Duration, Aggregate
- QT Interval, Aggregate
- QTcB Interval, Aggregate
- QTcF Interval, Aggregate
- RR Interval, Aggregate

4.5.6. Physical Examination Variables

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.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: 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.

5.1. 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 (as randomized)
- The total number of patients in the SAF
- The total number of patients in the FAS
- 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 treatment discontinuation
- Summary table will be provided if applicable

5.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined based on the FAS population.

Baseline for singular-value assessments, such as measurements from the CWRET, FEV1 and FVC from spirometry, will be the latest valid measurement taken prior to the first administration of study drug.

Baseline for the 7-day average values of measurements from accelerometry is defined as the average of the valid values during the 7 days prior to the first administration of study drug.

5.3. Medical History

Medical history will be summarized based on the SAF population.

Summary tables will be sorted by decreasing frequency of SOC followed by PT.

5.4. Prior/Conconcomitant Medications and Procedures

The prior and concomitant medications will be presented for FAS. Number and proportion of subjects taking concomitant medications, prohibited medications/procedures and rescue medications/procedures will be summarized based on FAS, sorted by decreasing frequency of ATC Level 2 and ATC level 4 according to the World Health Organization Drug Dictionary.

5.5. Measurement of Compliance

Compliance will be assessed and summarized by actual treatment within SAF. 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 percentage of subjects who have <70%, and >=70% compliance will be summarized for each group.

5.6. Extent of Study Treatment Exposure

The extent of treatment exposure will be assessed and summarized by actual treatment within SAF. Exposure to study treatment will be examined for each subject and the following variables will be summarized:

- The total number of study doses administered
- Duration of treatment exposure (in weeks) calculated as:
- (Date of last study drug injection – date of first study drug injection + 14 days)/7

The number of subjects exposed to study drug will be presented by specific time point periods for each group. The time periods of interest are weeks 2, 4, 6, 8, 12.

5.7. Analysis of Efficacy Data

The efficacy analyses will be performed based on the FAS according to assigned treatment group.

5.7.1. Analysis of Primary Efficacy Variable

The primary endpoint of change from baseline in constant work rate exercise endurance time at week 12 will be descriptively summarized.

Please note that the primary endpoint of change from baseline in constant work rate exercise endurance time at week 12 was originally planned to be analyzed using ANCOVA model for the

FAS with treatment group, randomization stratification factor, and relevant baseline measurement as covariates included in the model.

5.7.2. Analysis of Key Secondary Efficacy Variable

Pre-exercise FEV1 will be assessed within 15 minutes prior to the start of the exercise testing and post-exercise FEV1 will be performed at minutes 5±1, 10±1, and 20±1 post-exercise. Pre-exercise FEV1 and Post-exercise FEV1 will be analyzed descriptively.

Continuous secondary efficacy endpoints that are to be measured by accelerometry will be summarized. 7-day average values of measurements from accelerometry are calculated for baseline and week 12 if days with a wear time of at least 22 hours (accounting for non-wear periods as permissible in protocol) and at least 5 valid days per week are available.

5.7.3. Analysis of Exploratory Variables

5.7.3.1. Measurements associated with CPET

Continuous secondary efficacy endpoints that are to be measured associated with CPET will be analyzed in the same fashion as the primary endpoint.

5.7.3.2. Patient Diary

7-day average values of measurements from patient diary are calculated for baseline and week 12 and will be summarized descriptively if at least 5 valid days per week are available. Additionally, the same analysis is repeated for patients with at least 4 valid days per week.

- Change from baseline to week 12 in number of nocturnal awakenings per night due to asthma from patient diary

5.7.3.3. Spirometry not associated with CPET

Pre-exercise FEV1 and FVC at baseline will be used as baseline value. Change from baseline in FEV1 and FVC at week 4 will be summarized.

5.7.3.4. Patient-Reported Outcomes

PRO data (ACQ-5, AQLQ(S), PGIC, PGII) will be summarized descriptively, as described in Section 4

5.8. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF. The summary of safety results will be presented by treatment group and in overall total.

5.8.1. Adverse Events

The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be displayed in subject listings. Summaries that include number and proportions of patients reporting AEs will include the PTs and the SOCs.

Period of observation: The observation period will be divided into three periods: pre-treatment, on-treatment and post-treatment.

- The pre-treatment period is defined as the time between signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the time 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 is defined as 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.

Treatment-emergent AEs are defined as AEs that developed or worsened during the on-treatment period and post-treatment period.

Summaries of all TEAEs by treatment group 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, presented by SOC and PT
- Treatment related TEAEs, presented by SOC and PT
- Serious and treatment related serious TEAEs, presented by SOC and PT
- TEAEs leading to permanent treatment discontinuation, presented by SOC and PT
- TEAEs leading to death, presented by SOC and PT

For each TEAE summary presented by SOC and PT, the summary table will be sorted by decreasing frequency of SOC and PT. For TEAE summary presented by PT, the summary table will be sorted by decreasing frequency of PT of the dupilumab arm.

Counts will be provided for each patient within each SOC and PT. Percentages will be calculated using the number of patients from the SAF in each group.

For details on handling missing data and partial dates, see Section 6.

5.8.2. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology, and urinalysis results, and will be converted to values in standard international units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit, if applicable.
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs. This summary will be provided based on all patients in the SAF as well as in the subgroup of SAF patients who did not meet the PCSV criterion at baseline (normal or missing).
- Shift tables based on baseline normal/abnormal will be presented

5.8.3. Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be listed and 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.

5.8.4. Electrocardiography (ECG)

ECG status (i.e., normal, abnormal but not clinically significant, abnormal and clinically significant) will be reported.

5.8.5. Physical Exams

Physical examination findings at baseline as well as post-treatment abnormal findings by body system and status (normal, abnormal and not done) will be provided with Listing and Tables if applicable.

6. DATA HANDLING CONVENTIONS

6.1. Data Handling Convention for Missing Data

No missing data imputation is planned in this study unless specified otherwise.

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

6.1.1. Medication

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use the last visit study date instead. Imputation flag is ‘D’.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead. Imputation flag is ‘M’.

If end year is missing: Impute date using the end of last study visit date. Imputation flag is ‘Y’.

6.1.2. PCSV

Patients who had post-baseline PCSV, but missing baseline value will be regarded as having treatment emergent PCSV. Refer to Appendix for PCSV table.

6.2. Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the computation of baseline, worst values, and PCSVs, if applicable.

7. INTERIM ANALYSIS

No interim analysis was planned for this study.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

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10. APPENDIX

10.1. Criteria for Potentially Clinically Significant Values (PCSV)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VALUES (PCSV)		
Parameter	**PCSV**	**Comments**
	Clinical Chemistry	
ALT	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
(ALT or AST) and Total Bilirubin	((ALT ≤3 × ULN and AST ≤3 × ULN) or TBILI ≤2 × ULN) at baseline and ((ALT >3 × ULN or AST >3 × ULN) and TBILI >2 × ULN) post-baseline	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VALUES (PCSV)		
Parameter	**PCSV**	**Comments**
CPK	>3 ULN	FDA Feb 2005.
	>10 ULN	Am J Cardiol April 2006.
		Categories are cumulative.
		First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
	≥15 - <30 (severe decrease in GFR)	
	≥30 - < 60 (moderate decrease in GFR)	
	≥60 - <90 (mild decrease in GFR)	
	≥ 90 (normal GFR)	
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
	≥15 - <30 (severe decrease in GFR)	
	≥30 - < 60 (moderate decrease in GFR)	
	≥60 - <90 (mild decrease in GFR)	
	≥ 90 (normal GFR)	
Creatinine	≥150 µmol/L (Adults)	Benichou C., 1994.
	≥30% change from baseline	
	≥100% change from baseline	
Uric Acid		Harrison- Principles of internal Medicine 17th Ed., 2008.
Hyperuricemia	>408 µmol/L	
Hypouricemia	<120 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L	
	>115 mmol/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VALUES (PCSV)		
Parameter	**PCSV**	**Comments**
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VALUES (PCSV)		
Parameter	**PCSV**	**Comments**
Hemoglobin	>115 g/L at baseline and ≤115 g/L post-baseline for Male; >95 g/L at baseline and ≤95 g/L post-baseline for Female <185 g/L at baseline and ≥185 g/L post-baseline for Male; <165 g/L at baseline and ≥165 g/L post-baseline for Female Decrease from baseline by ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than those based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	>0.37 v/v at baseline and ≤0.37 v/v post-baseline for Male; >0.32 v/v at baseline and ≤0.32 v/v post-baseline for Female <0.55 v/v at baseline and ≥0.55 v/v post-baseline for Male; <0.5 v/v at baseline and ≥0.5 v/v post-baseline for Female	
RBC	≥4 Tera/L at baseline and <4 Tera/L post-baseline for Male; ≥3 Tera/L at baseline and <3 Tera/L post-baseline for Female <7 Tera/L at baseline and ≥7 Tera/L post-baseline for Male; <6 Tera/L at baseline and ≥6 Tera/L post-baseline for Female	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VALUES (PCSV)		
Parameter	**PCSV**	**Comments**
	Vital signs	
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
Respiratory rate	≥12 breaths per minute at baseline and <12 breaths per minute post-baseline ≤20 breaths per minute at baseline and >20 breaths per minute post-baseline	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VALUES (PCSV)		
Parameter	**PCSV**	**Comments**
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007
ECG	Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)	
HR	≤50 bpm post-baseline and decrease from baseline by ≥20 bpm ≥120 bpm post-baseline and increase from baseline by ≥20 bpm	Categories are cumulative Ref.: CPMP 1997 guideline
PR	≥220 ms post-baseline and increase from baseline by ≥20 ms	Ref.: CPMP 1997 guideline.
QRS	<120 ms at baseline and ≥120 ms post-baseline	Ref.: CPMP 1997 guideline.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VALUES (PCSV)

Parameter	PCSV	Comments
QTcB/QTcF	Borderline: <431 ms at baseline and 431-450 ms post-baseline for Male; <451 ms at baseline and 451-470 ms post-baseline for Female Prolonged: ≤450 ms at baseline and >450 to <500 ms post-baseline for Male; ≤470 ms at baseline and >470 to <500 ms post-baseline for Female <500 ms at baseline and ≥500 ms post-baseline Increase from baseline Borderline: Increase from baseline by 30-60 ms Prolonged: Increase from baseline by >60 ms	Ref.: CPMP 1997 guideline. 5 independent criteria

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