STATISTICAL ANALYSIS PLAN

A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Pivotal Study to Assess the Efficacy, Safety, and Tolerability of Dupilumab in Patients With Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) with Type 2 inflammation

SAR231893 (REGN668)-EFC15804

STATISTICIAN: [redacted]

DATE OF ISSUE: 23-Mar-2020

Total number of pages: 104

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic Dermatitis
ADA	Anti-drug Antibodies
AE	Adverse Event
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AM	Ante Meridiem
ANA	Antinuclear Antibodies
ATS	American Thoracic Society
BODE	Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CRFs	Case Report Forms
CV	Coefficient of Variation
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DPI	Dry Powder Inhaler
ECG	Electrocardiography
e-CRF	Electronic Case Report Form
e-diary	Electronic Diary
EQ-5D	European Quality of Life-5D Scale
EOS	End-of-Study
EOT	End-of-Treatment
ERS	European Respiratory Society
E-RS: COPD	Evaluating Respiratory Symptoms (E-RS) in COPD
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FEF 25-75	Forced Expiratory Flow at 25% to 75% of forced vital capacity
FENO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
HBc Ab	Hepatitis B Core Antibody
HBs Ab	Hepatitis B Surface Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV Ab	Hepatitis C Virus Antibody
HFA	Hydrofluoroalkane
HLGT	High-Level Group Term
HLT	High Level Term
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
ICH	International Council for Harmonisation

ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee
IgE	Immunoglobulin E
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IRT	Interactive Response Technologies
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
K-M	Kaplan-Meier
LFT	Liver Function Test
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LLOQ	Lower Limit of Quantitation
LS	Least Squares
MCID	Minimal Clinically Important Difference
MDI	Metered Dose inhaler
MI	Multiple Imputation
MID	Minimal Important Difference
MMRM	Mixed-effect Model with Repeated Measures
NIMP	Noninvestigational Medicinal Product
NSAID	Nonsteroidal Anti-inflammatory Drug
PARC	Pulmonary and Activation-regulated Chemokine
PCSA	Potentially Clinically Significant Abnormalities
PD	Pharmacodynamics
PK	Pharmacokinetics
pre-BD	pre-bronchodilator
PROs	Patient-Reported Outcomes
PT	Preferred Term
q2w	Every 2 weeks
QoL	Quality of Life
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SABA	Short-Acting Beta-Agonist
SC	Subcutaneously
SD	Standard Deviation
SEM	Standard Error of the Mean
SGRQ	St. George’s Respiratory Questionnaire
SOC	System Organ Class
TE	Treatment-Emergent
TEAE	Treatment-Emergent Adverse Event
Th2	Type 2 T-helper cell
ULN	Upper Limit of Normal

US	United States
V	Visit
VAS	Visual Analogue Scale
WBC	White Blood Cell

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

Multinational, randomized, double-blind, placebo-controlled, parallel group (2 groups), 52-week Phase 3 study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-to-severe COPD with type 2 inflammation on an established background of triple therapy (LABA, LAMA and ICS unless ICS contraindicated). Study treatments are dupilumab 300 mg q2w or placebo q2w administered SC over a 52-week treatment period.

After a run-in period of 4 weeks ±1 week, patients will be centrally randomized using a permuted block randomization schedule via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 1:1 randomization ratio for dupilumab 300 mg q2w and a matching placebo q2w for sc administration. Randomization will be stratified by country and by ICS dose (high dose ICS [yes/no]) at baseline. Enrollment will be capped at 30% current smokers (as defined by smoking status at screening visit).

A total of approximately 924 patients with COPD will be randomized to two treatment arms (462 patients/arm).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate the efficacy of dupilumab 300 mg every 2 weeks compared to placebo in reducing annualized rate of acute moderate or severe COPD exacerbation (AECOPD) over the 52-week treatment period in patients with moderate or severe COPD.

1.2.2 Secondary objectives

To evaluate the effect of dupilumab 300 mg q2w on

- Pre-bronchodilator forced expiratory volume in 1 second (FEV1) over 12 weeks compared to placebo
- Health related quality of life, assessed by the change from baseline to Week 52 in the St. George's Respiratory Questionnaire (SGRQ)
- Pre-bronchodilator FEV1 over 52 weeks compared to placebo
- To evaluate the effects of dupilumab 300 mg q2w on lung function assessments
- To evaluate the effect of dupilumab on moderate and severe COPD exacerbations
- To evaluate safety and tolerability
- To evaluate dupilumab systemic exposure and incidence of antidrug antibodies (ADA)

1.2.3 Exploratory objectives

- To evaluate the drug concentration of dupilumab in serum over time
- To explore the association of biomarkers with treatment response
- To evaluate the effects of dupilumab compared with placebo on FEV1 and FVC
- To evaluate the effects of dupilumab compared to placebo on annualized rate of COPD exacerbation utilizing the Exacerbations of Chronic Pulmonary Disease Tool (EXACT)
- To evaluate the effects of dupilumab compared to placebo on treatment failure requiring background medication change

1.3 DETERMINATION OF SAMPLE SIZE

The sample size of the study is determined based on power calculations for the primary endpoint of annualized rate of acute moderate or severe COPD exacerbations over the 52-week treatment period. Assuming the number of exacerbations follows a negative binomial distribution with a dispersion parameter of 1, a placebo annualized rate of exacerbations of 1.5, an average treatment duration of 0.95 year (to account for an average of 5% of the planned treatment period with missing data), and a randomization ratio of 1:1 to the two treatment arms, with 924 randomized patients (462 for each treatment arm), the study will have 90% power to detect a 25% relative risk reduction (ie, annualized rate of 1.125 for the dupilumab group) in the annualized rate of moderate or severe COPD exacerbations at the 2-tailed significance level of α=0.049 (an administrative penalty of 0.001 will be taken from the significance level used at final analysis due to a planned interim analysis; details are provided in Section 3).

Patients will be randomized using a 1:1 randomization ratio to dupilumab 300 mg q2w or placebo. Randomization will be stratified by country and by ICS dose (high dose ICS [yes/no]) at baseline.

1.4 STUDY PLAN

The clinical trial consists of three periods:

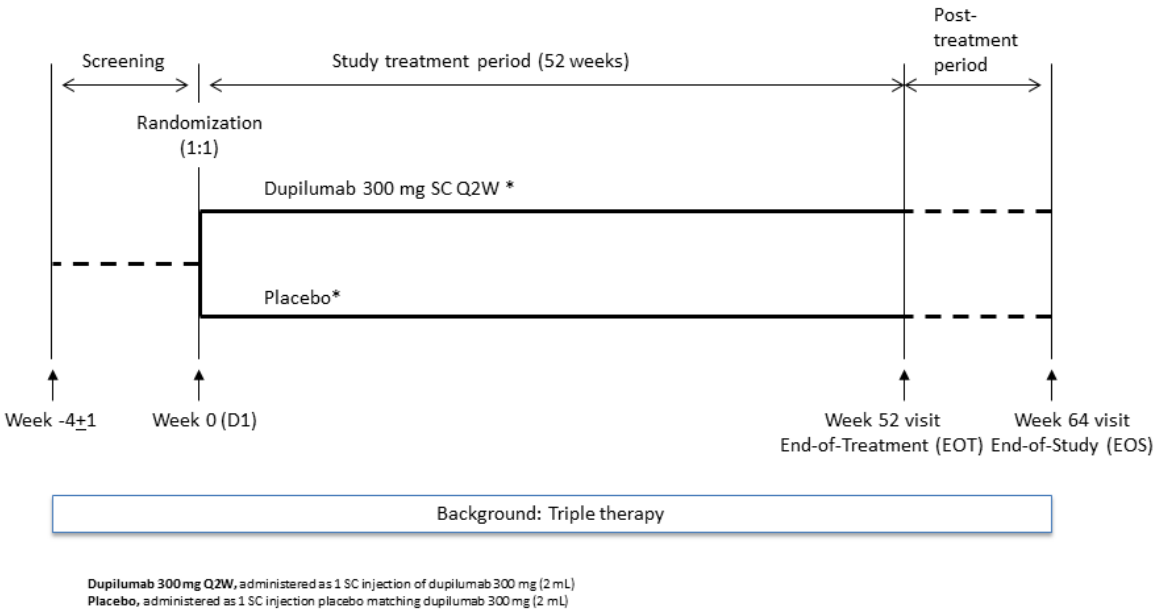
Screening period (4 weeks ±1 week): to determine a patient's eligibility and establish level of COPD control before randomization.

Randomized investigational medicinal product (IMP) treatment period (52 weeks +/- 3 days): to randomize the patient into a treatment arm and treat with dupilumab or placebo dose regimen.

Post IMP treatment period (12 weeks +/- 5 days): to continue to collect data for PK, immunogenicity, safety, and efficacy after the patient has completed the study drug treatment period.

1.4.1 Graphic study design

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



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled) and protocol amendment 7 (dated 06 December 2019). These changes are not based on any unblinded study data.

The modifications to the protocol statistical section in the SAP are listed below.

Table 1 - Modifications to the statistical section of the protocol in the SAP

	Text in the protocol	Text in the SAP	Rationale
1	The following description on the tertiary/exploratory endpoint in the protocol amendment 7 Table 1: To evaluate the effects of dupilumab compared to placebo on annualized rate of moderate to severe COPD exacerbation utilizing the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) • Evaluation of clinical respiratory symptoms of COPD using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) comprised in the EXACT tool • Annualized rate of moderate to severe COPD exacerbations assessed by the EXACT over 52 week	Is changed in the SAP version 1 to: To evaluate the effects of dupilumab compared to placebo on annualized rate of COPD exacerbation utilizing the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) • Evaluation of clinical respiratory symptoms of COPD using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) comprised in the EXACT tool • Annualized rate of COPD	To be aligned with reference manual for the EXACT tool

Text in the protocol	Text in the SAP	Rationale
	exacerbations assessed by the EXACT over 52 week	

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

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

The calculation of the baseline for daily ediary questionnare scores will be specified in Section 2.1.3.2.2.1.

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

Demographic characteristics

Demographic variables are

- Gender (Male, Female),
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Age in years (quantitative and qualitative variable: 40-64, 65–74, 75-80 years)
- Region (Asia: Japan, China, South Korea; Latin America: Argentina, Chile and Mexico; East Europe: Russia, Ukraine, Turkey, Hungary, Poland, Czech Republic, Romania, Bulgaria, Slovakia; Western Countries: Finland, Denmark, Spain, Israel, Sweden, Germany, Italy, Canada, USA)
- Territory (Canada and USA: Canada and USA; European Union: Hungary, Poland, Czech Republic, Romania, Bulgaria, Slovakia, Spain, Sweden, Germany, Italy, Finland, Denmark; Rest of World: Israel, Argentina, Chile, Japan, China, South Korea, Mexico, Russia, Ukraine, Turkey)
- Weight in kg (quantitative and qualitative variable : <50, 50-<100 and ≥100 kg)
- BMI in kg/m^2 (quantitative and qualitative variable: <30, ≥30 kg/m^2)

Medical or surgical history

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

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Comorbidity will be summarized separately. The following comorbid diseases will be summarized from eCRF pages which were filled in by investigators based on patient reporting.

Emphysema history (Yes, Ongoing condition)

Chronic bronchitis history (Yes, Ongoing condition)

Bronchiectasis history (Yes, Ongoing condition)

Nasal polyps history (Yes, Ongoing condition)

Chronic sinusitis history (Yes, Ongoing condition)

Atopic dermatitis history (Yes, Ongoing condition)

Allergic conjunctivitis history (Yes, Ongoing condition)

Allergic rhinitis history (Yes, Ongoing condition)

Food allergy history (Yes, Ongoing condition)

Hives history (Yes, Ongoing condition)

Eosinophilic esophagitis history (Yes, Ongoing condition)

Hypersensitivity to aspirin history (Yes, Ongoing condition)

Hypersensitivity to NSAID history (Yes, Ongoing condition)

Disease characteristics at baseline

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

- High ICS dose from medical history (Yes, No)
- High ICS dose from IVRS (Yes, No)
- Spirometry data including pre-bronchodilator FEV1 (L), post-bronchodilator FEV1 (L), forced expiratory flow (FEF) 25-75%, FEV1 reversibility (%)
    - FEV1 reversibility (%) is calculated as (Post-bronchodilator FEV1(L) - Pre-bronchodilator FEV1(L)) / Pre-bronchodilator FEV1(L) * 100
- SGRQ total score
- EQ-5D-5L (single index score and VAS)
- Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index (BODE Index) and its domain scores
- EXACT & E-RS: COPD total scores and sub-scores

- Time since first diagnosis of COPD (years) to be derived as
- (Year of randomization – Year of first diagnosis of COPD) + (month of randomization – month of first diagnosis of COPD)/12
- Age of onset of COPD (years)
- Smoking history (former, current), smoking duration (years) and smoking quantities in pack-years
- Cessation prior to screening (months) for former smokers to be derived as
  - (Year of randomization – Year of cessation)×12 + (month of randomization – month of cessation)
- Time since last COPD exacerbation (months) to be derived as
  - (Year of randomization – Year of last COPD exacerbation)×12 + (month of randomization– month of last COPD exacerbation)
- Number of moderate COPD exacerbations experienced within one year before Visit 1

  Among them, number of those required
  - systemic steroids and treatment days for systemic steroids
  - antibiotics and treatment days for antibiotics
- Number of severe COPD exacerbations experienced within one year before Visit 1

  Among them, number of those required
  - systemic steroids and treatment days for systemic steroids
  - antibiotics and treatment days for antibiotics
  - emergency medical care visit only
  - hospitalization without ICU
  - hospitalization in ICU
- Number of treatment days with systemic steroids use for moderate or severe COPD exacerbations experienced within one year before Visit 1
- FeNO at baseline
- Eosinophil counts at baseline

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

2.1.2 Prior or concomitant medications

All medications taken within 30 days prior to screening and until end of the study, including COPD controller medications, systemic corticosteroids, and all other medications are to be reported in the case report form (CRF) pages.

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

Prior medications are those the patient used prior to first IMP injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.

Concomitant medications are any treatments received by the patient concomitantly to the IMP, anytime from the first administration of IMP to the last administration of IMP + 98 days. A given medication can be classified as a prior medication, concomitant medication and posttreatment medication at the same time.

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

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

2.1.2.1 COPD controller medication

At Screening Visit 1, all patients must be on triple background therapy, for 3 months prior to Visit 2/Randomization and at a stable dose of medication for at least 1 month prior to the Screening/Visit 1, including triple therapy: LABA + LAMA +ICS (Double therapy: LABA + LAMA allowed if ICS is contraindicated).

Throughout the study, patients should continue their established background therapy for COPD, including dose and regimen.

Patients must be willing to stay on their established background medication for COPD throughout the duration of the treatment period. After successful management of an acute exacerbation of COPD (eg, with oral corticosteroids and/or antibiotics), all efforts should be made to resume the initial background COPD treatment regimen if in the investigator's opinion this is medically acceptable. Background medications should not be adjusted during Screening. After 1 severe or 2 moderate exacerbations of COPD, dose adjustments in background therapy will be permitted for symptom control and as needed for the remainder of the trial period.

Adjustment of background medication is allowed at the discretion of the investigator as clinically indicated during the post-treatment period

2.1.2.2 Reliever medication

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol or ipratropium or ipratropium/short-acting β agonists [SABA] combinations or terbutaline as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint

The primary endpoint for this study is the annualized rate of moderate or severe COPD exacerbation (as defined below) over the 52-week treatment period compared to placebo.

Moderate exacerbations are recorded by the Investigator and defined as AECOPD that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics.

Severe exacerbations are recorded by the Investigator and defined as AECOPD requiring hospitalization, or treatment for >24 hours in emergency department/urgent care facility or result in death.

For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days.

The number of moderate or severe exacerbation events during the 52-week treatment period is defined as the number of moderate or severe exacerbation events with onset during the 52-week treatment period per patient-year. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and their additional off-treatment moderate or severe exacerbation events up to Visit 16 (Week 52) will be included.

AECOPD recorded in eCRF will go through a confirmatory adjudication by experts independent of sponsor for the evaluation. Details of the adjudication process are described in the AC Charter/Manual of Operation. Only the adjudicated confirmed AECOPD will be used for analysis.

2.1.3.2 Secondary efficacy endpoint(s)

The key secondary endpoints of this study include:

- Change in pre-bronchodilator FEV1 from baseline to Week 12
- Change in pre-bronchodilator FEV1 from baseline to Week 52
- Change in pre-bronchodilator FEV1 from baseline to Week 12 in the subgroup of patients with baseline FeNO ≥ 20 ppb
- Change in pre-bronchodilator FEV1 from baseline to Week 52 in the subgroup of patients with baseline FeNO ≥ 20 ppb
- Change from baseline to Week 52 in SGRQ total score
- Proportion of patients with SGRQ improvement ≥4 points at Week 52
- Annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of patients with baseline FeNO ≥ 20 ppb

Other secondary efficacy endpoints include:

- Change in pre-bronchodilator FEV1 from baseline through weeks other than 12 and 52 (ie, Weeks 2, 4, 8, 16, 20, 24, 28, 36, 44 and 48)
- Change in post-bronchodilator FEV1 from baseline to Weeks 2, 4, 8, 12, 24, 36 and 52
- Change in forced expiratory flow (FEF) 25-75% from baseline to Weeks 2, 4, 8, 12, 16, 24, 28, 36, 44, and 52
- Annualized rate of severe COPD exacerbations compared to placebo over the 52-week treatment period
- Time to first moderate or severe COPD exacerbation compared with placebo during the 52-week treatment period

2.1.3.2.1 Key secondary endpoint

2.1.3.2.1.1 Spirometry

Spirometry at clinical site visits should be performed in accordance with the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (1) and prior to administration of investigational product.

For pre-bronchodilator measured parameters, including FEV1, FVC and forced expiratory flow (FEF) 25%-75%, spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 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), withholding the last dose of ipratropium for at least 8 hours and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.

Note: When both pre- and post-bronchodilator spirometry is assessed, the post-bronchodilator spirometry should be performed consistent with the mechanism of action of reliever (ie, 30 minutes for albuterol or another SABA).

At all visits, spirometry will be performed preferably in the morning; afternoon/evening is allowable in the exceptional circumstance when morning spirometry cannot be performed; spirometry should be done at approximately the same time at each visit throughout the study. Current smokers need to be reminded not to smoke for at least 1 hour before spirometry. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible.

2.1.3.2.1.2 St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire (SGRQ) (2, 3) is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation (see Appendix A).

Scores by dimension are calculated for three domains: Symptoms, Activity and Impacts (Psycho-social) as well as a total score. Global and domain scores range from 0 to 100, with 100 representing the worst possible health status and 0 indicating the best possible health status. See St. George's Respiratory Questionnaire manual Version 2.3 page 8-13 (Appendix C) for the scoring algorithm.

The first part ("Symptoms") evaluates symptomatology, including frequency and severity of cough, sputum production, wheeze, breathlessness and the duration and frequency of attacks of breathlessness or wheeze. The second part has two components: "Activity" and "Impacts". The "Activity" section addresses disturbances to patients' daily physical activities. The "Impacts" section covers a range of effects that chest troubles may have on patients' daily life and psycho-social functions (eg daily life activities and functioning, employment, physical functioning, emotional impact, stigmatization, and patients' perceptions when treated). The recall period of the questionnaire is over the past 4 weeks.

Psychometric testing has demonstrated its repeatability, reliability and validity. Sensitivity has been demonstrated in clinical trials. A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing (4, 5). The SGRQ has been used in a range of disease groups including asthma, COPD and bronchiectasis.

SGRQ is assessed at Visit 2 (Week 0), Visit 4 (Week 4), Visit 6 (Week 12), Visit 9 (Week 24), Visit 12 (Week 36), Visit 16 (Week 52) and Visit 19 (Week 64).

2.1.3.2.2 Exploratory/Tertiary efficacy endpoints

2.1.3.2.2.1 Exacerbations of chronic pulmonary disease tool (EXACT)

The EXACT tool quantifies and measures exacerbations of COPD and assesses the symptomatic manifestations of these COPD exacerbations (see Appendix D). The instrument is a daily diary composed of a total of 14 items representing the following domains:

- Breathlessness (5 items),
- Cough and sputum (2 items),
- Chest symptoms (3 items),
- Difficulty bringing up sputum (1 item),
- Tired or weak (1 item),
- Sleep disturbance (1 item), and
- Scared or worried (1 item).

The EXACT total score assesses COPD exacerbations. The higher the score, the more severe are the symptoms.

The EXACT questionnaire is assessed daily from screening to Visit 16 (Week 52). Baseline EXACT score as well as the post-baseline weekly scores will be calculated as the mean within-patient score over the prior 7 days, with data present for a minimum of 4 of the 7 days. If fewer

than 4 days of data are available in the 7-day window, the EXACT score cannot be calculated and will be considered as missing. For the exacerbation analysis, the baseline would be reset during the study. Additional information related to computing scores and frequency, severity, and duration of events can be found in the user manual (6).

The Evaluating Respiratory Symptoms (E-RS) in COPD (E-RS: COPD) scale is a part of the EXACT tool. It is a derivative instrument used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD. The E-RS utilizes the 11 respiratory symptom items contained in the 14-item EXACT.

The daily RS-Total score is computed by taking the sum of the 11 items comprising the instrument. It has a range of 0 to 40, with higher values indicating more severe respiratory symptoms.

The same summation procedure is used to derive the three daily domain scores:

- RS-Breathlessness (sum of items 7, 8, 9, 10, and 11; score range 0–17)
- RS-Cough and Sputum (sum of items 2, 3, 4; score range 0–11)
- RS-Chest Symptoms (sum of items 1, 5, 6; score range 0–12)

Like for EXACT, the baseline RS score as well as the post-baseline weekly domain and total scores are calculated as the mean within-patient score over the prior 7 days, with data present for a minimum of 4 of the 7 days. If fewer than 4 days of data are available in the 7-day window, the RS scores cannot be calculated and will be considered as missing.

2.1.4 Safety endpoints

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

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the time prior to first administration of the IMP.
- The **treatment** epoch is defined as the time from the first administration of the IMP to the last administration of the IMP + 14 days.
- The **residual treatment** epoch is defined as the time from the last administration of the IMP +15 days to the last administration of the IMP + 98 days.

The treatment-emergent adverse event period will include both **treatment** and **residual treatment** epochs.

- The **posttreatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the end of the study (defined as last

protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

- The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or lost to follow-up or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

Safety events adjudication

Adjudication will be performed by experts independent of sponsor for the evaluation of whether deaths, cardiovascular SAEs and respiratory SAEs meet criteria for cardiovascular assessment endpoints. A confirmatory adjudication will occur for AECOPD exacerbations. Adjudicators will adjudicate these events in a consistent and unbiased manner throughout the study.

The goal of the adjudication is to ensure that all events reported by the site are judged uniformly, using pre-specified criteria by a group independent of the Sponsor. Adjudication Committee members will be blinded to treatment allocation. Adjudication Committee members' responsibilities and the process for data review are described in the AC Charter/Manual of Operation.

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious during the screening epoch
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment epoch

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

The occurrence of adverse events (including serious adverse events and adverse events with prespecified monitoring) will be recorded from the time of signed informed consent until the end of the study.

Cardiovascular assessment

All events submitted for cardiovascular adjudication will be listed and summarized, including the final classification results. A swimmer plot including all events classified as cardiovascular, including cardiovascular death, will also be provided.

Furthermore, events classified as cardiovascular will be evaluated according to the following composite endpoints:

- **Major Cardiovascular Adverse Events (MACE)**: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke
- MACE + hospitalization for unstable angina
- Cardiovascular death: death resulting from myocardial infarction, stroke, pulmonary embolism, heart failure, procedure-related death or other cardiovascular cause.
- Hospitalization: for unstable angina, for atrial fibrillation/flutter, for other symptomatic arrhythmias, for transient ischemic attack.
- Other cardio/cerebrovascular events: non-fatal heart failure, peripheral arterial event, pulmonary embolism, non acute coronary syndrome/myocardial ischemia, others.

Adverse events of special interest (AESI) and other selected AE groupings will be searched based on the criteria in Table 2.

Table 2 - Criteria for adverse events of special interest and other selected AE groupings

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (*Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1*): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not.
Hypersensitivity (medically reviewed)	SMQ hypersensitivity (20000214) narrow search or PT in (Pruritus, Pruritus generalized) and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥ 24 hours or ongoing
Severe or serious infection	Primary SOC = 'Infections and infestations' and with severe or serious status
Parasitic infection	The Infection Type 'Parasitic' was checked on eCRF page "Infection Defined as AESI Complementary Form"
Opportunistic infection	The Infection Type 'Opportunistic' was checked on eCRF page "Infection Defined as AESI Complementary Form"
Drug-related hepatic disorder	Drug-related hepatic disorders-Comprehensive search narrow SMQ (20000006)
Pregnancy	Primary SOC = 'Pregnancy, puerperium and perinatal conditions' or PT in (Aborted pregnancy, False negative pregnancy test, Pregnancy test positive, Pregnancy test urine positive, Ectopic pregnancy termination)
Symptomatic overdose with IMP	Symptomatic Overdose is answered Yes, with Overdose of IMP answered Yes on AE eCRF.
Symptomatic overdose with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP answered Yes on AE eCRF.
Eosinophilia	HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased'
Other selected AE grouping	
Injection site reaction	HLT = 'Injection site reaction'
Malignancy	Sub-SMQ (20000091)– Malignant or unspecified tumors
Suicidal behavior	PT in (Completed suicide, Suicidal ideation, Depression suicidal, Suicidal behavior, Suicide attempt)

AE Grouping	Criteria
Partner pregnancy	PT in (Pregnancy of partner, Miscarriage of partner)
Conjunctivitis (narrow)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis)
Conjunctivitis (broad)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia)
Conjunctivitis (FDA)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye irritation, Eye inflammation, Giant papillary conjunctivitis)

2.1.4.2 Deaths

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

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

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis including cotinine. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 12), Visit 9 (Week 24), Visit 12 (Week 36), Visit 16 (Week 52), Visit 19 (Week 64) and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, red blood cell count, platelet count
  - **White blood cells:** white blood cell count, differential count
- Clinical chemistry
  - **Metabolism:** glucose, total cholesterol, total protein, creatine phosphokinase
  - **Electrolytes**: sodium, potassium, chloride, bicarbonate
  - **Renal function**: creatinine, blood urea nitrogen, uric acid

- **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), albumin
- **Pregnancy test**: Serum β-human chorionic gonadotropin (all female patients) will be performed at screening (V1) in women of childbearing potential, and a urine pregnancy test will be performed at V2 prior to randomization and every 4 weeks thereafter. A negative result must be obtained at V1 and V2 prior to randomization. In case of positive urinary test the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases.
- **Hepatitis screen:** hepatitis B surface antigen (HBs Ag), hepatitis B Surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab) will be tested at screening (V1). In case of results showing HBs Ag (negative), HBs Ab (negative) and HBc Ab (positive), an HBV DNA testing will be performed prior to randomization to rule out a false positivity if the investigator believes the patient is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the investigator believes the patient is a false positive.
- **HIV screen**: Anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1
- **Anti-nuclear antibody (ANA)** will be tested at Visit 1
- Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

- Urinalysis

  Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement. If positive for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs, including blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) will be measured at the screening (Visit 1), randomization (Visit 2) and every subsequent 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 EOT/EOS visits. Vital signs will be measured in the sitting position using the same arm (preferably) at each visit, and will be measured prior to receiving IMP at the clinic visits.

2.1.4.5 Electrocardiogram variables

A standard 12-lead electrocardiogram (ECG) will be performed centrally at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 6 (Week 12), Visit 9 (Week 24), Visit 12 (Week 36), Visit 16 (Week 52), and Visit 19 (Week 64). At the post randomization visits, ECGs will be performed prior to investigational product administration. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG. All ECG recordings will be centrally read by independent experts.

2.1.4.6 Physical Examination

Physical examinations will be performed at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 9 (Week 24), Visit 16 (Week 52), and Visit 19 (Week 64) including an assessment of skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. All deviations from normal will be recorded, including those attributable to the patient's disease.

2.1.5 Pharmacokinetic variables

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

Anti-dupilumab antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 12, Week 24, Week 52 and follow up at Week 64 will be provided. Patients who discontinue early from treatment may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall clinical presentation at that time.

ADA incidence will be classified as the following:

Pre-existing immunoreactivity are defined as:

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

Treatment-emergent anti-drug antibodies are defined as:

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

Treatment-emergent ADA responses are further classified as Persistent, Indeterminate or Transient

a) Persistent Response- defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days) ,with no ADA negative samples in between.

b) Indeterminate Response- defined as a treatment-emergent response with only the last collected sample positive in the ADA assay

c) Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

Treatment-boosted response is defined as:

An ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Titer values (Titer value category)

- Low (Titer <1000)
- Moderate (1000 ≤ Titer ≤10 000)
- High (Titer >10 000)

2.1.6 Pharmacodynamic/genomics endpoints

Whole blood biomarkers blood eosinophil and neutrophil counts will be measured as part of the standard 5-part WBC differential cell count on a hematology auto analyzer.

For plasma/serum biomarkers, Eotaxin-3 will be assayed at Visit 2 (Week 0), Visit 4 (Week 4), Visit 6 (Week 12), Visit 9 (Week 24), Visit 16 (Week 52) and Visit 19 (Week 64); total IgE will be assayed at Visit 2 (Week 0), Visit 6 (Week 12), Visit 16 (Week 52) and Visit 19 (Week 64); Pulmonary and Activation-Regulated Chemokine [PARC] will be assayed at Visit 2 (Week 0), Visit 16 (Week 52) and Visit 19 (Week 64); Fibrinogen will be assayed at Visit 2 (Week 0), Visit 9 (Week 24), Visit 16 (Week 52) and Visit 19 (Week 64).

Fractional exhaled nitric oxide (FeNO; postbronchodilator) will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden),or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour at Visit 2 (Week 0), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 12), Visit 9 (Week 24), Visit 12 (Week 36), Visit 16 (Week 52) and Visit 19 (Week 64).

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

2.1.7 Health Related Quality-of-life endpoints

2.1.7.1 Euro-QOL-5D

The European quality of life-5D scale (EQ-5D) (Appendix E) is a standardized HRQoL questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (7). EQ-5D is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ VAS. The EQ-5D comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. EQ-5D-5L health status will be converted into a single index value by using EQ-5D-5L value sets based on UK population. The EQ VAS records the respondent's self-rated health on a vertical VAS. The EQ VAS 'thermometer' has endpoints of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. EQ-5D self-reported VAS data generates information on the self-perceived overall health-related quality of life.

EQ-5D will be assessed at Visit 2 (Week 0).

2.1.7.2 Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index (BODE Index)

The BODE Index is a composite measure composed of a Performance Outcome Measure, a Patient-Reported Outcome Measure and a Biomarker. The BODE Index is a multidimensional grading system to assess the respiratory and systemic expressions of COPD (8). It comprises 4 domains: 1) Degree of pulmonary impairment (FEV1 percent predicted); 2) Patient's perception of symptoms (mMRC); and 2 independent domains: the 6 Minute Walking Distance (6MWD) and the Body-Mass Index (BMI). Each domain can be scored independently; the global score ranges from 0 to 10, with a higher score indicating a higher risk of death (see Appendix F for scoring algorithm details)

The BODE index is assess at Visit 2 (Week 0) only.

2.1.8 Health economic endpoints

A questionnaire of health care resource utilization (collection of sick days, lost usual activities, and additional physician visits or other health care utilization) will be administered at Visit 2 (Week 0), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 12), Visit 7 (Week 16), Visit 8 (Week 20), Visit 9 (Week 24), Visit 10 (Week 28), Visit 11 (Week 32), Visit 12 (Week 36), Visit 13 (Week 40), Visit 14 (Week 44), Visit 15 (Week 48), Visit 16 (Week 52) and Visit 19 (Week 64).

2.2 DISPOSITION OF PATIENTS

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

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

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

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

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

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

All critical or major deviations related to randomization procedures will be summarized in tables giving numbers and percentages of deviations by treatment group.

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

- Efficacy population: intent-to-treat (ITT) population defined in Section 2.3

The analysis populations for safety defined in Section 2.3 pharmacokinetics/pharmacodynamics (PK/PD) will be summarized by number of patents on the safety population.

- Safety population
- PK population
- ADA population

2.2.1 Protocol deviations

The number and percentage of patients with a critical or major protocol deviation will be summarized by deviation and overall within treatment group. Specific deviations related to randomization may be summarized separately. A listing of patients with at least one critical or major deviation will be provided.

2.3 ANALYSIS POPULATIONS

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

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

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

2.3.1 Efficacy populations

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

2.3.1.1 Intent–to-treat population

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

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

2.3.2 Safety population

The safety population is defined as: All patients who actually received at least 1 dose or partial of a dose of the IMP, analyzed according to the treatment patients actually received.

In addition:

- Nonrandomized but treated patients will be part of the safety population

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

2.3.3 Pharmacokinetics (PK) population

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

2.3.4 Anti-drug antibody population

The anti-drug antibody (ADA) population will consist of all patients in the safety population with at least one reportable ADA results (either 'ADA negative' or 'ADA positive') after first dose of the study treatment. Patients will be analyzed according to the treatment actually received.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

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

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

Medical and surgical history will be summarized by treatment group and by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC based on the overall incidence across treatment groups. Atopic medical history will be summarized separately.

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

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the randomized population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medication received during first IMP to last IMP +14 days and concomitant medication received during first IMP to last IMP +98 days will be summarized separately. The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the dupilumab 300 q2w group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Medications will also be summarized by generic name sorted by decreasing frequency based on the incidence in the dupilumab group.

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

2.4.2.1 ICS in combination with other controllers

ICS and other COPD controller medications will be identified as the medications reported on the "Prescribed COPD Controller Medications" eCRF page.

Prior COPD controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the overall treatment group.

Concomitant COPD controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the dupilumab group.

The total daily dose of ICS in COPD controller medication at randomization will be classified as high dose or lower dose according to Appendix G. If a patient takes more than one medication containing ICS, the ICS dose of different products will be standardized according to equivalent dose specified in Table 3 and Table 4. After conversion, the total daily dose for inhaled corticosteroid will be calculated and classified as high dose or lower dose.

Table 3 – Equivalent dose for inhaled corticosteroids for adults

Inhaled corticosteroid	Equivalent dose (mcg) to 500 mcg Fluticasone propionate (DPI or HFA)
FLUTICASONE FUROATE	200-*
BECLOMETASONE DIPROPIONATE (CFC)	1000
BECLOMETASONE DIPROPIONATE (HFA)	400
BUDESONIDE (DPI)	800
CICLESONIDE (HFA)	320
MOMETASONE FUROATE	440
TRIAMCINOLONE ACETONIDE	2000

ADAPTED FROM GINA 2016 GUIDELINES
HFA=hydrofluoroalkane, DPI= Dry Powder Inhaler
* Fluticason furoate (FF) dose >=200 mcg is converted to equivalent fluticasone propionate(DPI or HFA) dose of (FF dose +1) × 2.5; FF dose <200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of FF dose × 2.5.
Example: A patient received 400 mcg budesonide (DPI) and 440 mcg mometasone furoate. They are equivalent to 250 mcg and 500 mcg fluticasone propionate correspondingly. The combined total daily dose is equivalent to 750 mcg fluticasone propionate and classified as high dose.

Table 4 – Equivalent dose of inhaled corticosteroid for adults (Japan)

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

Adapted from Japanese Guideline for Adult Asthma 2014
Example: A patient received 400 mcg Beclomethasone dipropionate -HFA and 400 mcg Ciclesonide-HFA. They are both equivalent to 400 fluticasone propionate. The combined total daily dose is equivalent to 800 fluticasone propionate.

Number and percentage of patients on ICS, ICS/LABA, LABA, LAMA, LTRA, Anti-Leukotriene, Methylxanthine and other controller medications at baseline will also be summarized.

2.4.2.1.1 Compliance

During the study, the daily intake of each prescribed COPD controller medication will be recorded on the electronic diary every evening. Compliance for the controller medications with ICS component and overall compliance to all prescribed controller medications will be calculated for each patient. For each day, a patient is considered as compliant with the prescribed controller medication with ICS component if the actual dose of each controller medication with ICS

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

Compliance for controller medication(s) with ICS component is defined as the number of days when the patient is compliant with the prescribed controller medication(s) with ICS component divided by the number of days the patient stays in the treatment period (from first dose to last dose + 14 days).

Overall controller medication(s) compliance is defined as the number of days when the patient is compliant with all prescribed controller medication divided by the number of days the patient stays in the treatment period.

2.4.3 Extent of investigational medicinal product exposure and compliance

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

2.4.3.1 Extent of investigational medicinal product exposure

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

Duration of IMP exposure is defined as last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data). Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- >0 and ≤2 weeks
- >2 and ≤4 weeks
- >4 and ≤8 weeks
- >8 and ≤12 weeks
- >12 and ≤16 weeks
- …
- …
- >48 and ≤52 weeks
- >52 weeks and ≤ 52 weeks + 3 days
- > 52 weeks + 3 days

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

2.4.3.2 Compliance

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

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations that the patient was planned to take during the treatment epoch defined in Section 2.1.3.2.2.1.

Treatment compliance percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized in Section 2.4.4.5.

Cases of overdose (defined as at least twice the intended dose during an interval of less than 11 days) will constitute serious adverse events and will be listed as such.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

Primary efficacy variable

The primary efficacy variable is annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period compared to placebo.

The following null hypothesis and alternative will be tested for dupilumab arm against placebo:

- H0: No treatment difference between the dupilumab dose regimen and placebo in annualized rate of COPD exacerbation.
- H1: There is a treatment difference between the dupilumab dose regimen and placebo in annualized rate of COPD exacerbation.

Primary statistical model (ITT analysis)

The primary analysis of the annualized rate of moderate or severe exacerbation events during the 52-week placebo-controlled treatment period is to assess the efficacy of dupilumab in an intention-to-treat setting. Adjudicated COPD exacerbation events data will be used. Patients who permanently discontinue the study medication will be encouraged to return to the clinic for all remaining study visits. If a patient stays in study until the end of 52-week treatment period, all moderate or severe exacerbation events that happen up to Visit 16 will be included in the primary analysis, regardless if the patient is on treatment or not. And the observation duration is defined as from randomization to Visit 16 (Week 52). If a patient withdraws from study prior to the end of 52-week treatment period, all observed moderate or severe exacerbation events up to the last contact date or the end date of the planned 52-week treatment period (whichever is earlier) will be included in the analysis, and the observation duration is defined as from randomization to the last contact date or the end date of the planned 52-week treatment period whichever is earlier. No

imputation will be performed for the unobserved events that may happen after study discontinuation and up to Week 52. This estimand compares the rates of moderate or severe exacerbation for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo (6).

The annualized rate of moderate or severe COPD exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurred during the 52-week planned treatment period as the response variable, with the treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4) as covariates. Log-transformed observation duration will be used as offset variable. The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals will be derived. The event rate ratio of the dupilumab group against placebo, its two-sided 95% confidence interval and p-value will be provided.

The rate difference between dupilumab and placebo, two-sided 95% confidence intervals of the rate difference and its p-value derived using delta method will also be provided as supportive information.

The analysis model will be built with the following sample SAS code:

```
proc glimmix data=event;
class  ics trt01pn cntygr1n smoking copdnum;
model   numevents=tr    t01pn cn    tygr1n ics smoking fev1bl copdnum
/offset=logdu       r dist=negbin link=log solution;
run;
```

If the model fails to achieve convergence, different estimation algorithms will be applied following the order: default→LAPLACE→QUAD (7). If the issue still exists, other handling may be considered. The adjustment will be added to the footnote of the corresponding outputs.

The gross estimated annualized event rate will also be presented by treatment group.

Mean cumulative function plot will be provided for descriptive purpose.

Sensitivity analysis

If patients withdraw from the study before Visit 16 (Week 52), moderate or severe exacerbation events that may occur after study discontinuation will not be observed. These patients are considered as patients with missing data on moderate or severe exacerbation. Number of patients with missing data, reasons and timing for patient withdrawals will be summarized by treatment groups. Summary statistics of selected demographic and baseline disease characteristics will be provided for patients with missing data and patients with complete data separately. In addition, the

following sensitivity analyses will be conducted to assess the robustness of the conclusion based on the primary analysis.

Pattern mixture model - multiple imputation (PMM-MI)

For each patient with missing data of moderate or severe exacerbation events, individual bi-weekly event probability will be estimated using observed data with adjustment of the planned treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4). The total number of AECOPD moderate or severe events (on bi-weekly basis) will be calculated based on data imputed using multiple imputation.

Control-based PMM-MI

For each patient with missing data of moderate or severe exacerbation events, individual bi-weekly event probability will be estimated using observation in the placebo arms only, with adjustment of region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4). The total number of AECOPD moderate or severe events (on bi-weekly basis) will be calculated based on data imputed using multiple imputation.

Tipping point analysis

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

For each of the above methods, a negative binomial model will be fitted using each of the complete datasets composed of observed and imputed data, including the total number of observed and imputed events during the 52 weeks as the response variable, with the treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4) as covariates. Log transformed observation duration will be the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 16 (Week 52). SAS MIANALYZE procedure will be used to generate statistical

inferences by combining results from the analysis with each dataset using Rubin's formula.

More details of the imputation and analyses methods are provided in Appendix J:

Subgroup analyses

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

- Age group (<65, ≥65 years)
- Gender (Male, Female)
- Region
- Territory
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, Others)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline weight (<70, ≥70- < 90, ≥ 90 kg; <60, ≥ 60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m^2)
- ICS high dose level at baseline (Yes, No)
- Smoking status at screening (current smokers, former smokers)
- Number of moderate-or-severe COPD exacerbation events within one year prior to V1 (≤2, 3, or ≥4)
- Number of severe COPD exacerbation events within one year prior to V1 (0, 1, ≥ 2)
- Baseline predicted post-bronchodilator FEV1% (<50%, ≥50%)
- Baseline pre-bronchodilator FEV1 (< median, ≥ median)
- Baseline FEV1 reversibility (<12%, ≥ 12%; < median, ≥ median)
- Baseline fractional exhaled nitric oxide (FeNO) (<20, ≥ 20 ppb)
- Baseline eotaxin-3 (< median, ≥ median)
- Baseline IgE (< 100 , ≥ 100 IU/ml)
- Baseline PARC (< median, ≥ median)
- Baseline Fibrinogen (< 350, ≥ 350 mg/dL)
- Baseline mMRC (< median, ≥median)
- Maximum eosinophils counts during screening (≥ 0.3-<0.5, ≥0.5 Giga/L)

Treatment by subgroup interaction and its p-value will be derived from a negative binomial model. This model will include the total number of events occurring during the observation period as the response variable, with the two treatment groups, region (pooled country), ICS dose at baseline

(high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4), subgroup (if different than the aforementioned covariates) and treatment by subgroup interaction as covariates. Log transformed observation duration will be the offset variable. If quantitative treatment by subgroup interaction is detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test will be performed to evaluate possible qualitative interaction. Summary statistics of moderate or severe exacerbations will be provided within each subgroup. Forest plot of relative risks and corresponding CIs and forest plot of risk differences and corresponding CIs comparing dupilumab dose group vs. placebo for the subgroups will be provided.

2.4.4.2 Analyses of key secondary efficacy endpoints

2.4.4.2.1 Analysis of the change from baseline in pre-bronchodilator(pre-BD) FEV1 at Week 12 for dupilumab versus placebo

The change from baseline in pre-bronchodilator FEV1 at Week 12 will be analyzed using mixed-effect model with repeated measures (MMRM). The analysis will be performed in the full ITT population and also in the baseline FENO ≥ 20 ppb subgroup. The model will include change from baseline in FEV1 values up to Week 12 as response variables, and factors for treatment group, age, sex, height, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV1, and FEV1 baseline-by-visit interaction as covariates. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method using the Newton-Raphson algorithm. The least square (LS) mean of the change in pre-bronchodilator FEV1 of each treatment group, difference in the LS mean changes between the dupilumab group and placebo, the corresponding 95% CI of the differences and p-values will be provided. For patients who discontinued the study treatment, off-treatment FEV1 values will be included in the analysis.

Subgroup analyses

To assess the consistency treatment effects across the subgroup levels, subgroup analyses will be conducted for the change from baseline in pre-BD FEV1 at Week 12 with the same set of subgroups as defined for the annualized rate of moderate or severe AECOPD events in Section 2.4.4.1.

Treatment-by-subgroup interaction at Week 12 and its p-value will be derived from a MMRM model. The model will include change from baseline in pre-BD FEV1 values up to Week 12 as response variables, and treatment, age, sex, height, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV1, and FEV1 baseline-by-visit interaction, subgroup (if different than the aforementioned covariates), subgroup-by-treatment interaction and subgroup-by-treatment-by-visit interaction as covariates. If quantitative treatment by subgroup interaction at Week 12 is detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test will be used to test the qualitative interaction. Summary statistics of change from baseline in pre-bronchodilator FEV1 will be provided within each subgroup. Forest plot of LS mean difference and corresponding CIs for the subgroups will be provided.

Sensitivity analysis

Patients who discontinue the treatment are encouraged to follow the planned clinical visits, and all data collected after treatment discontinuation will be used in the analysis. Descriptive statistics of pre-BD FEV1 by visit up to Week 12 will be summarized for patients with some missing data and patients with complete data up to Week 12 separately. Number of patients with missing pre-BD FEV1, reasons and timing for missing pre-BD FEV1 will be summarized by treatment groups. In addition, following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model using the full ITT population:

Pattern mixture model-multiple imputation (PMM-MI)

Missing pre-BD FEV1 values will be imputed multiple times with adjustment for covariates including treatment groups, age, sex, height, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), and baseline pre-BD FEV1. Each of the complete datasets will be analyzed using the ANCOVA model with change from baseline in pre-BD FEV1 at Week 12 as the response variable, treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline pre-BD FEV1 value as covariates. Then the SAS MIANALYZE procedure will be used to generate statistical inference by combining results using Rubin's formula.

Tipping point analysis

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

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

2.4.4.2.2 Analysis of the change from baseline in pre-bronchodilator FEV1 and SGRQ total score at Week 52 for dupilumab versus placebo

The change from baseline in pre-bronchodilator FEV1 at Week 52 will be analyzed in a similar way as change from baseline in pre-bronchodilator FEV1 at Week 12 and the model will include values up to Week 52 as response variables. The analysis will be performed in the full ITT population and also in the baseline FENO ≥ 20 ppb subgroup.

The change from baseline in SGRQ total score at Week 52 will be analyzed in a similar way as change in pre-bronchodilator FEV1 at Week 52 except that the MMRM model will include the following covariates: treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), visit, treatment-by-visit interaction, baseline SGRQ total score, and SGRQ baseline-by-visit interaction.

Descriptive statistics including number of patients, mean, standard error, and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

2.4.4.2.3 Analysis of proportion of patients with SGRQ improvement ≥4 points at Week 52 dupilumab versus placebo

The proportion of patients with SGRQ improvement ≥4 points at Week 52 will be analyzed using a logistic regression model. The model will include treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), and baseline SGRQ total score as covariates. For patients who discontinue treatment early, data collected during the off- treatment period will be used to determine the responder/non- responder status. Patients with missing SGRQ total score at Week 52 will be considered as non-responders.

Odds ratio of being a responder comparing dupilumab to placebo will be provided along with the corresponding 95% CI and p-value. Descriptive statistics including number and percentage of responders will also be provided.

Cumulative distribution function (CDF) of change from baseline in SGRQ at Week 52 will be presented by treatment group.

2.4.4.2.4 Analysis of annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of patients with baseline FENO ≥ 20 ppb

The annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of patients with baseline FENO ≥ 20 ppb will be performed in the same approach as that for the primary efficacy endpoint except that the analyzed population is not the full ITT population but the subgroup of patients with baseline FENO ≥ 20 ppb.

The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals will be derived. The event rate ratio of the dupilumab group against placebo, its two-sided 95% confidence interval and p-value will be provided.

The rate difference between dupilumab and placebo, two-sided 95% confidence intervals of the rate difference and its p-value derived using delta method will also be provided as supportive information.

Mean cumulative function plot will be provided for descriptive purpose.

2.4.4.3 Multiplicity issues

The multiplicity procedure is proposed to control the overall type-I error rate for testing the primary and selected secondary endpoints listed below. The overall alpha is 0.05.

A non-binding futility interim analysis (IA) is planned in this study (details are provided in Section 3), and an administrative penalty of 0.001 will be taken from the significance level used at final analysis and thus two-sided 0.049 will be used. No further multiplicity adjustment will be performed for the IA.

At the final analysis, the comparisons with placebo will be tested based on the hierarchical order below at 2-sided alpha=0.049.

1) Primary efficacy endpoints:
   - Annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period compared to placebo.

2) Secondary/exploratory efficacy endpoints:
   - Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo
   - Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo
   - Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo in the subgroup of patients with baseline FENO ≥ 20 ppb
   - Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo in the subgroup of patients with baseline FENO ≥ 20 ppb
   - Change from baseline to Week 52 in SGRQ total score compared to placebo
   - Proportion of patients with SGRQ improvement ≥4 points at Week 52 compared to placebo
   - Change in E-RS COPD scores from baseline to Week 52 compared to placebo
   - Annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of patients with baseline FENO ≥ 20 ppb

The study is considered positive when the primary endpoint achieves statistical significance.

2.4.4.4 Additional efficacy analyses

2.4.4.4.1 Comparisons for other secondary efficacy endpoints

- Change in pre-bronchodilator FEV1 from baseline to Weeks other than 12 and 52
- Change in post-bronchodilator FEV1, forced expiratory flow (FEF) 25-75%, FEV1/FVC from baseline to Weeks up to Week 52
- Time to first moderate or severe COPD exacerbation compared to placebo during the 52-week treatment period
- Annualized rate of severe COPD exacerbations over the 52-week treatment period

2.4.4.4.2 Analyses of other efficacy endpoints for dupilumab versus placebo up to Week 52

Change from baseline in continuous endpoint (pre-bronchodilator FEV1, post-bronchodilator FEV1, FEF25-75%, SGRQ total scores) at all time-points will be analyzed in a similar way as change from baseline in pre-bronchodilator FEV1 at Week 52. Age, sex and height will be included as covariates only in the models for spirometry parameters. Descriptive statistics including number of patients, mean, standard error, and least squares (LS) means will be provided for all visits. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

Proportion type efficacy endpoints (SGRQ improvement from baseline ≥4 points) during the treatment period will be analyzed in a similar way as proportion of patients with SGRQ improvement ≥4 points at Week 52, except that the response variable will be the responder status at the corresponding visit instead of at Week 52. Odds ratio of being a responder comparing dupilumab to placebo will be provided along with the corresponding 95% CI and p-value at each visit. Descriptive statistics including number and percentage of responders will also be provided.

2.4.4.4.3 Analyses of time to first moderate or severe COPD exacerbation compared to placebo during the 52-week treatment period

The time to first moderate or severe COPD exacerbation will be analyzed using a Cox regression model. The model will include the time to the first event as the dependent variable, and treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤ 2, 3, or ≥ 4) as covariates. Hazard ratio and corresponding 95% CI and p values will be estimated for dupilumab versus placebo. The

Kaplan-Meier method will be used to derive the probabilities that a patient would experience an event up to specific timepoints for each treatment group. Kaplan-Meier curves will be generated; point probabilities will be calculated. Interval estimates will be calculated using 95% point wise confidence intervals.

2.4.4.4.4 Analyses of annualized rate of severe COPD exacerbations over the 52-week treatment period

The annualized event rate of severe COPD exacerbations will be analyzed in the same way as the primary analysis for the annualized rate of moderate or severe COPD exacerbation events. The estimated event rate for each treatment group and its two-sided 95% confidence intervals will be provided. The event rate ratio of dupilumab against placebo, two-sided 95% confidence intervals of the rate ratio and the corresponding p-value will also be provided.

2.4.4.4.5 Additional subgroup analyses

- Smoking status at screening (current smokers, former smokers)

For the annualized rate of COPD exacerbation endpoints, treatment by subgroup interaction and its p-value will be derived from a negative binomial model respectively, same as the approach in subgroup analysis specified in Section 2.4.4.1. Summary statistics of exacerbations will be provided within each subgroup. Forest plot of relative risks and corresponding CIs and forest plot of risk differences and corresponding CIs comparing dupilumab dose group vs. placebo for the subgroups will be provided.

For other efficacy endpoints specified in Section 2.4.4.3 and Section 2.4.4.4.1, treatment by subgroup interaction and its p-value will be derived from MMRM models (for continuous endpoints), logistic regression models (for proportion type endpoints) or Cox regression models (for time to event endpoints) respectively. The model will include all the covariates in the main statistical model for the corresponding endpoints plus the subgroup variable (if not one of the covariates adjusted in the main model already) and the subgroup-by-treatment interaction. A p-value for the test of interaction will be provided.

In each subgroup, the endpoints will be analyzed using the same primary analysis approach for their corresponding endpoints in the total population.

- For continuous endpoints, descriptive statistics including number of patients, mean, standard error, and least squares (LS) means for each subgroup will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided for each subgroup.
- For proportion type endpoints, odds ratio of being a responder comparing dupilumab to placebo will be provided for each subgroup along with the corresponding 95% CI and

p-value. Descriptive statistics including number and percentage of responders will also be provided for each subgroup.

- For time to event endpoints, hazard ratio and corresponding 95% CI and p values will be estimated for dupilumab versus placebo for each subgroup. The Kaplan-Meier method will be used to derive the probabilities that a patient would experience an event up to specific timepoints for each treatment group within the subgroup. Kaplan-Meier curves will be generated; point probabilities will be calculated. Interval estimates will be calculated using 95% point wise confidence intervals.

In addition, for each subgroup analysis, the forest plot will be provided.

2.4.4.5 Analyses of exploratory efficacy endpoints

2.4.4.5.1 Analyses of other continuous endpoints

For post-bronchodilator FEV1, the rate of change in FEV1 (termed as FEV1 slope) will be compared between dupilumab against placebo. Repeated post-bronchodilator FEV1 after Week 4 and after Week 8 up to Week 52 will be analyzed correspondingly using linear mixed-effects model with treatment, age, sex, height, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), time since randomization, and treatment-by-time interaction and baseline post-bronchodilator FEV1 as covariates. Intercept and time since randomization are random effects. Individual post-BD FEV1 slope will be calculated as the slope of a linear regression model with the post-BD FEV1 (L) at each visit as the response variable and the time since randomization as the independent variable. Descriptive statistics including number of patients, mean, standard error of the individual post BD FEV1 slopes will be provided. Estimated from the linear mixed-effects model, least squares (LS) means, difference in LS means and the corresponding 95% confidence intervals (CI) will also be provided.

Change from baseline in FVC (percent predicted and absolute change in ml), weekly E-RS symptom scores at all time-points will be analyzed in a similar way as change from baseline in pre-bronchodilator FEV1 at Week 52. Age, sex and height will be included as covariates only in the models for spirometry parameters. Descriptive statistics including number of patients, mean, standard error, and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided.

2.4.4.5.2 Analyses of time to first severe COPD exacerbation compared to placebo during the 52-week treatment period

The time to first severe COPD exacerbation will be analyzed using the same approach as that for the analyses of time to first moderate or severe COPD

exacerbation compared to placebo during the 52-week treatment period. Hazard ratio and corresponding 95% CI and p values will be estimated for dupilumab versus placebo. The Kaplan-Meier method will be used to derive the probabilities that a patient would experience an event up to specific timepoints for each treatment group. Kaplan-Meier curves will be generated; point probabilities will be calculated. Interval estimates will be calculated using 95% point wise confidence intervals.

2.4.4.5.3 Analyses of COPD exacerbation utilizing the Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

COPD exacerbation will be derived using EXACT method as specified in the *The Exacerbations of* Chronic *Pulmonary Disease Tool (EXACT) Patient-Reported Outcome (PRO) User Manual- Scoring guide* (Version 8.0), March 2016.

The annualized event rate of COPD exacerbations assessed by the EXACT over 52 week (a tertiary/exploratory endpoint) will be analyzed in the same way as the primary analysis for the annualized rate of moderate or severe COPD exacerbation events but based on exacerbation defined by EXACT method instead of the adjudicated data of AECOPD page in eCRF. The estimated event rate for each treatment group and its two-sided 95% confidence intervals will be provided. The event rate ratio of dupilumab against placebo, two-sided 95% confidence intervals of the rate ratio will also be provided.

2.4.4.5.4 Analyses of controller medication change after exacerbation

Increase in number of controller medication and/or total daily dose after adjudicated exacerbation during the treatment period will respectively be summarized by treatment group in terms of number of exacerbation events. For patients who discontinue treatment, data collected during the off- treatment period will also be used. Descriptive statistics including number, mean, median, standard deviation, min, and max will be provided, and no statistical testing will be conducted.

2.4.4.6 Missing data handling

For all continuous efficacy endpoints, the details of missing data handling are described in Section 2.4.4.1.

For responder type endpoints, the details of missing data handling are described in Section 2.4.4.4.2.

In addition, the reason and pattern of missing data will be carefully examined and pattern mixture modeling approach and other sensitivity analyses will also be performed as specified in Section 2.4.4.1.

2.4.5 Analyses of safety data

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

General common rules

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

- The baseline value is defined as the last available value before the first dose of IMP.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs and ECG [Appendix A]
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the endpoint value and/or the worst on-treatment value. The endpoint value is commonly defined as the value collected at the end of treatment. If this value is missing, this endpoint value will be the closest value prior to the end of treatment epoch. The worst value is defined as the nadir and /or the peak post-baseline (up to the end of treatment epoch or EOT) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus placebo and their 95% confidence intervals may be provided, if relevant
- All safety values including unscheduled measurements will be assigned to the appropriate safety analysis visit window defined in Section 2.5.3.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment and posttreatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-

emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.2.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the dupilumab 300 mg q2w group.

Analysis of all treatment-emergent adverse events

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

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC in the 300 q2w treatment group
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC in the 300 q2w treatment group
- Number (%) of patients experiencing treatment-emergent adverse event(s) presented by primary and secondary SOC, HLGT, HLT, and PT sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

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

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC in the 300 q2w treatment group.

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

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC and PT, showing number (%) of patients with at least one TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC in the 300 q2w treatment group.

Analysis of Major Cardiovascular Adverse Events (MACE)

- The number and percentage (%) of patients with any treatment-emergent event selected for adjudication will be summarized by primary SOC and PT.
- All events submitted for adjudication will be listed, including the final adjudicated result.
- The number and percentage (%) of patients experiencing a treatment-emergent adjudicated event will be summarized within each treatment group.

- The risk difference (asymptotic 95% CI with continuity correction) will be computed for the dupilumab dose versus placebo. Kaplan-Meier plots to depict the course of onset over time will also be provided.

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

- All treatment-emergent adverse events, by selected standardized MedDRA query (SMQ) and PT or by laboratory values (as in ALT elevation), showing the number (%) of patients with at least 1 PT, sorted by decreasing incidence of PTs within each SMQ in the 300 q2w treatment group.
- For each AESI and other selected AE groupings,
  - Number (%) of patients with any specific TEAE
  - Number (%) of patients with any specific serious AE (regardless of treatment emergent status)
  - Number (%) of patients with any specific treatment emergent serious AE
  - Number (%) of patients with any specific AE leading to death
  - Number (%) of patients with any specific TEAE leading to permanent study drug discontinuation
  - Number (%) of patients with any specific TEAE related to IMP reported by investigator
  - Number (%) of patients with any specific TEAE by maximum intensity, corrective treatment, and final outcome
  - Number of any specific TEAE adjusted by the exposure duration
  - Number of patients with any specific TEAE adjusted by the exposure duration at risk. For each specific TEAE, Kaplan-Meier estimates of cumulative incidence at Week 12, 24, 36 and 52 and K-M plot may be provided to depict the course of onset over time if the number of events is large enough.
  - Number (%) of patients with injection site reactions by the related injection.
  - Number (%) of patients with different number of injection site reactions.
- In addition, AESIs reported by the investigator in CRF will be summarized separately.

Analysis of pretreatment adverse events

- All pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC in the 300 q2w treatment group.
- All serious pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

- All pretreatment adverse events leading to permanent treatment discontinuation by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- If only a few patients have pretreatment adverse events leading to permanent treatment discontinuation, a listing will be presented instead of the summary table above.

2.4.5.2 Deaths

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

- Number (%) of patients who died by study period (TEAE, on-study, on-treatment, poststudy)
- Deaths in nonrandomized patients or randomized but not treated patients
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC.
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

A listing of deaths will be provided.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For each continuous parameters listed in Section 2.1.4.3, mean changes from baseline with the corresponding standard error will be plotted over time in each treatment group. This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

For PCSA analyses, the laboratory measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local test results should be used, as long as their available dates/time is different from each other's. Centralized data will be used preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time for a given laboratory test.

Possible Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group.

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

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin and creatine phosphokinase, serum creatinine, complete blood count, HCV RNA.

Summarize the normalization by parameter (to ≤1 x ULN or return to baseline) of elevated liver function tests by categories of elevation (3 x, 5 x, 10 x, 20 x ULN for ALT and AST, 1.5 x ULN for alkaline phosphatase, and 1.5 x and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized despite treatment continuation of IMP, or normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category.

2.4.5.4 Analyses of vital sign variables

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

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.5.5 Analyses of electrocardiogram variables

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

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.6 Abnormal Analyses of pharmacokinetic and pharmacodynamic variables

2.4.6.1 Pharmacokinetic analyses

2.4.6.1.1 Analyses of serum concentrations of SAR231893 (REGN668)

Serum concentrations of SAR231893 (REGN668) will be summarized in the PK population using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time. If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. For drug-treated patients, where concentration values are below the lower limit of quantification (LLOQ), one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three significant figures. For patients in the placebo group, concentration values are below the LLOQ will be taken into account with a plasma concentration considered equal to 0.

2.4.6.1.2 Analyses of ADA variables

The following summary will be provided based on ADA population:

- Number (%) of patients with pre-existing immunoreactivity
- Number (%) of patients with treatment-emergent ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent ADA, and patients with persistent, indeterminate and transient ADA response
- Number (%) of patient with transient treatment-emergent ADA

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

Kinetics of treatment-emergent ADA response

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

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

Impact of ADA on PK

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

Association of ADA with clinical efficacy endpoints

Associations between the ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and the primary efficacy endpoint may be explored for the dupilumab dosed group.

Association of ADA with clinical safety endpoints

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

Severe injection site reactions last longer than 24 hours or serious injection site reactions

- Hypersensitivity reactions (SMQ (20000214) hypersensitivity narrow search confirmed by medical review)
- Anaphylactic reactions (SMQ (20000021) anaphylactic reaction narrow search)

- In response to AESI like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgment of the medical investigator and/or medical monitor.
- Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent and treatment-boosted) and safety may be explored.

2.4.6.2 Pharmacodynamics/genomics analyses

All biomarkers listed in Section 2.1.6 will be summarized in the Safety population defined as patients who actually received at least 1 dose or part of a dose of the IMP. Baseline values will be the last value collected prior to the first IMP. Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) of biomarkers at baseline will be summarized.

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

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

2.4.7 Analyses of health economics variables

Analyses of healthcare resource utilization will be performed outside of CSR under the responsibility of the Health Economics Outcomes Research (HEOR) department of Sanofi.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age is calculated as:

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

Age of onset of COPD is calculated as:

Integer part of (COPD diagnosis date - birth date)/365.25

BMI is calculated as:

Weight in kg / (height^2 in meters)

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

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

Renal function formulas

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

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

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

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

2.5.2 Data handling conventions for secondary efficacy variables

Periodical average of daily efficacy endpoints at designated study days

For the daily efficacy endpoints, the time period used to calculate the periodical average at each designated study day is summarized in Table 5.

Randomization day is used as the reference day (Day 1).

Table 5 - Periodical average of daily efficacy assessment

Time point	EXACT, E-RS:COPD
Day 8 (Week 1)	2-8
Day 15 (Week 2)	9-15
Day 22 (Week 3)	16-22
Day 29 (Week 4)	23-29
Day 36 (Week 5)	30-36
Day 43 (Week 6)	37-43
…	…
Day 365 (Week 52)	359-365
…	…
Day 449 (Week 64)	443-449

2.5.3 Missing data

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

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and posttreatment medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

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

2.5.4 Windows for time points

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP administration. Selected safety variables will be summarized by the analysis window define in Table 6 for the by visit descriptive analysis. All available values from central lab will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 6 – Time window for safety endpoints

		Time windows for						
Visit	**Target Day**	**Vital signs**	**Hema-tology, biochem-istry, urinalysis**	**Serum Pregnancy test, Hepatitis and HIV serology tests, height**	**Urine Pregnancy test**	**Physical examination**	**Body weight**	**ECG**
Visit 1 (Week -4±1)	-28±7	<-14	<-14	1-		<-14	1-	<-14
Visit 2 (Week 0)	1	-14-1-	-14-1-		1-	-14-1-		-14-1-
Visit 3 (Week 2)	15	1+-21						
Visit 4 (Week 4)	29	22-42	1+-42		1+-42			

		Time windows for						
Visit	**Target Day**	**Vital signs**	**Hema-tology, biochem-istry, urinalysis**	**Serum Pregnancy test, Hepatitis and HIV serology tests, height**	**Urine Pregnancy test**	**Physical examination**	**Body weight**	**ECG**
Visit 5 (Week 8)	57	43-70	43-70		43-70			
Visit 6 (Week 12)	85	71-98	71-126		71-98			1+-126
Visit 7 (Week 16)	113	99-126			99-126			
Visit 8 (Week 20)	141	127-154			127-154			
Visit 9 (Week 24)	169	155-182	127-210		155-182	1+-266		127-210
Visit 10 (Week 28)	197	183-210			183-210			
Visit 11 (Week 32)	225	211-238			211-238			
Visit 12 (Week 36)	253	239-266	211-308		239-266			211-308
Visit 13 (Week 40)	281	267-294			267-294			
Visit 14 (Week 44)	309	295-322			295-322			
Visit 15 (Week 48)	337	323-350			323-350			
Visit 16 (Week 52)	365	351-378	309-406		351-406	267-406	1+-406	309-406
Visit 17 (Week 56)	393	379-406						

		Time windows for						
Visit	**Target Day**	**Vital signs**	**Hema-tology, biochem-istry, urinalysis**	**Serum Pregnancy test, Hepatitis and HIV serology tests, height**	**Urine Pregnancy test**	**Physical examination**	**Body weight**	**ECG**
Visit 18 (Week 60)	421	407-434						
Visit 19 (Week 64)	449	>434	>406		>406	>406	>406	>406
		1⁻: up to 1st dose date/time; 1⁺: after 1st dose date/time;						

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the randomization day. If a patient receives IMP prior to the randomization by mistake, the reference date of efficacy assessment will be the date of the first IMP administration for that patient. For the primary analyses, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 7. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used.

Table 7 – Time window for efficacy variables

Visit	Target Day	Time windows for		
		Pre-bronchodilator Spirometry	**Post-bronchodilator Spirometry**	**SGRQ**
Visit 1 (Week -4±1)	-28±7	<-14	<-14	
Visit 2 (Week 0)	1	-14-1-	-14-1-	1-
Visit 3 (Week 2)	15	1+-21	1+-21	
Visit 4 (Week 4)	29	22-42	22-42	1+-56
Visit 5 (Week 8)	57	43-70	43-70	
Visit 6 (Week 12)	85	71-98	71-126	57-126
Visit 7 (Week 16)	113	99-126		
Visit 8 (Week 20)	141	127-154		
Visit 9 (Week 24)	169	155-182	127-210	127-210
Visit 10 (Week 28)	197	183-224		
Visit 11 (Week 32)	225			
Visit 12 (Week 36)	253	225-280	211-308	211-308

Visit	Target Day	Time windows for		
		Pre-bronchodilator Spirometry	**Post-bronchodilator Spirometry**	**SGRQ**
Visit 13 (Week 40)	281			
Visit 14 (Week 44)	309	281-322		
Visit 15 (Week 48)	337	323-350		
Visit 16 (Week 52)	365	351-378	309-406	309-406
Visit 17 (Week 56)	393	379-406		
Visit 18 (Week 60)	421	407-434		
Visit 19 (Week 64)	449	>434	>406	>406

1⁻: up to randomization and before 1st dose date/time; 1⁺: after randomization or 1st dose date/time

For the pharmacokinetics/pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP administration if the patient is treated with study treatment, or the randomization date if the patient is not treated. Pharmacokinetics /pharmacodynamics variables will be summarized by the analysis window defined in Table 8 for the by visit descriptive analyses. All available values of measurements will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 8 – Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target day	Time windows for						
		FENO post-Bronchodilator	Serum dupilumab concentration	Anti-drug antibodies	Total IgE	PARC	Eotaxin-3	Fibrinogen
Visit 1 (Week -4±1)	-28±7							
Visit 2 (Week 0)	1	1-	1-	1-	1-	1-	1-	1-
Visit 3 (Week 2)	15		1+-21					
Visit 4 (Week 4)	29	1+-42	22-42				1+-56	
Visit 5 (Week 8)	57	43-70	43-70					
Visit 6 (Week 12)	85	71-126	71-98	1+-126	1+-224		57-126	
Visit 7 (Week 16)	113		99-140					
Visit 8 (Week 20)	141							
Visit 9 (Week 24)	169	127-210	141-210	127-266			127-266	1+-266
Visit 10 (Week 28)	197							
Visit 11 (Week 32)	225							
Visit 12 (Week 36)	253	211-308	211-308					

Visit	Target day	Time windows for						
		FENO post-Bronchodilator	Serum dupilumab concentration	Anti-drug antibodies	Total IgE	PARC	Eotaxin-3	Fibrinogen
Visit 13 (Week 40)	281							
Visit 14 (Week 44)	309							
Visit 15 (Week 48)	337							
Visit 16 (Week 52)	365	309-406	309-378	267-406	225-406	1^{+}-406	267-406	267-406
Visit 17 (Week 56)	393		379-406					
Visit 18 (Week 60)	421		407-434					
Visit 19 (Week 64)	449	>406	>434	>406	>406	>406	>406	>406

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

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

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

- Asia: Japan, China, South Korea;
- Latin America: Argentina, Chile and Mexico;
- East Europe: Russia, Ukraine, Turkey, Hungary, Poland, Czech Republic, Romania, Bulgaria, Slovakia;
- Western Countries: Finland, Denmark, Spain, Israel, Sweden, Germany, Italy, Canada, USA.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

A nonbinding futility IA in the study is planned to be performed when approximately 408 patients would have completed Week 12 visit. Guideline for the futility decision will be provided in the DMC charter. The purpose of the IA is to obtain an understanding of the possible drug effect in this population. The IA will be performed by independent statisticians that support the DMC and are separated from personnel involved in the trial conduct. DMC will review the unblinded IA results and recommend action based on the non-binding futility criterion that is specified in the DMC charter and DMC SAP. The DMC will inform a group of senior sponsor individuals whether the criterion is met. If the criterion is met, and only if the criterion is met, the unblinded futility analysis results as well as select additional analyses will be provided to the senior sponsor group. The senior sponsor group will make a decision regarding stopping or continuing the study. The senior sponsor group are the only sponsor individuals that are planned to view this data. A detailed plan will be defined in the DMC charter and DMC SAP, including a plan to describe the processes intended to control access to comparative interim results to preserve trial integrity. People involved in the conduct of the study (patients, Investigators, Study Team, and Project Team) will not have access to the IA results.

At the IA, the efficacy endpoints will be analyzed using the same methods described in the efficacy analyses section (Section 2.4.4). The analysis population for the IA will be the first 408 patients randomized. The analysis of the endpoints will use all the data collected for the analysis population up to the IA cutoff time. An administrative penalty of 0.001 will be taken from the significance level used at final analysis (ie, two-sided 0.049 will be used for the final analysis).

4 DATABASE LOCK

The database lock for final analysis is planned based on the date when the last patient completes the Week 52 visit or discontinues from the study before Week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analysis in the CSR. Additional data between this database lock and last patient completing last visit will be summarized in a CSR addendum.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A:	Potentially clinically significant abnormalities (PCSA) criteria
Appendix B:	St. George's respiratory questionnaire
Appendix C:	SGRQ scoring algorithm
Appendix D:	EXACT questionnaire
Appendix E:	EQ-5D
Appendix F:	BODE
Appendix G :	High dose of inhaled corticosteroids : adults
Appendix H:	Definition of anaphylaxis
Appendix I	List of opportunistic infections
Appendix J:	Handling of missing data

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies
(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	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 and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies
(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
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	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies
(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
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.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than 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 (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	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	
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.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
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.

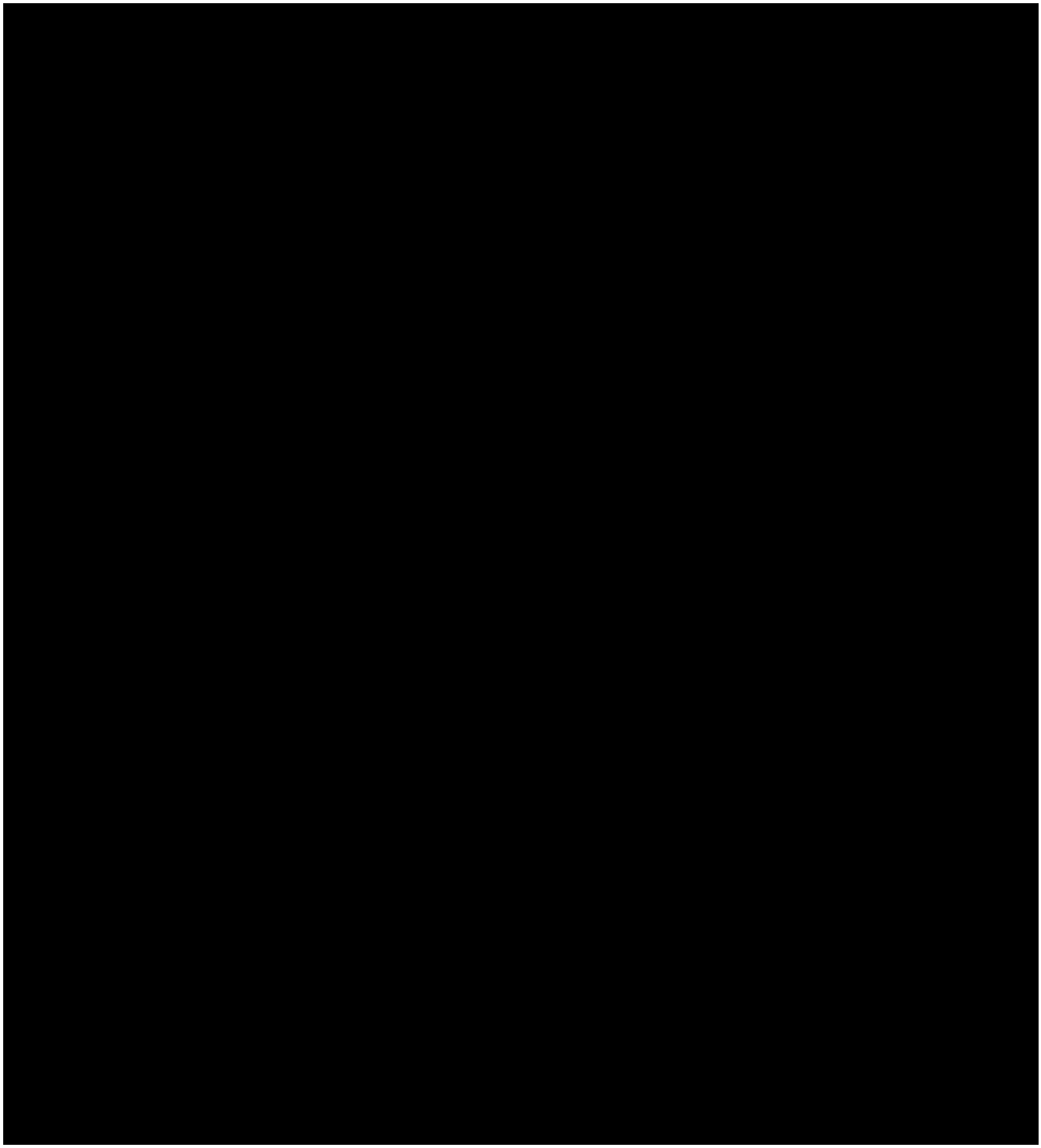
CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies
(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
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 <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

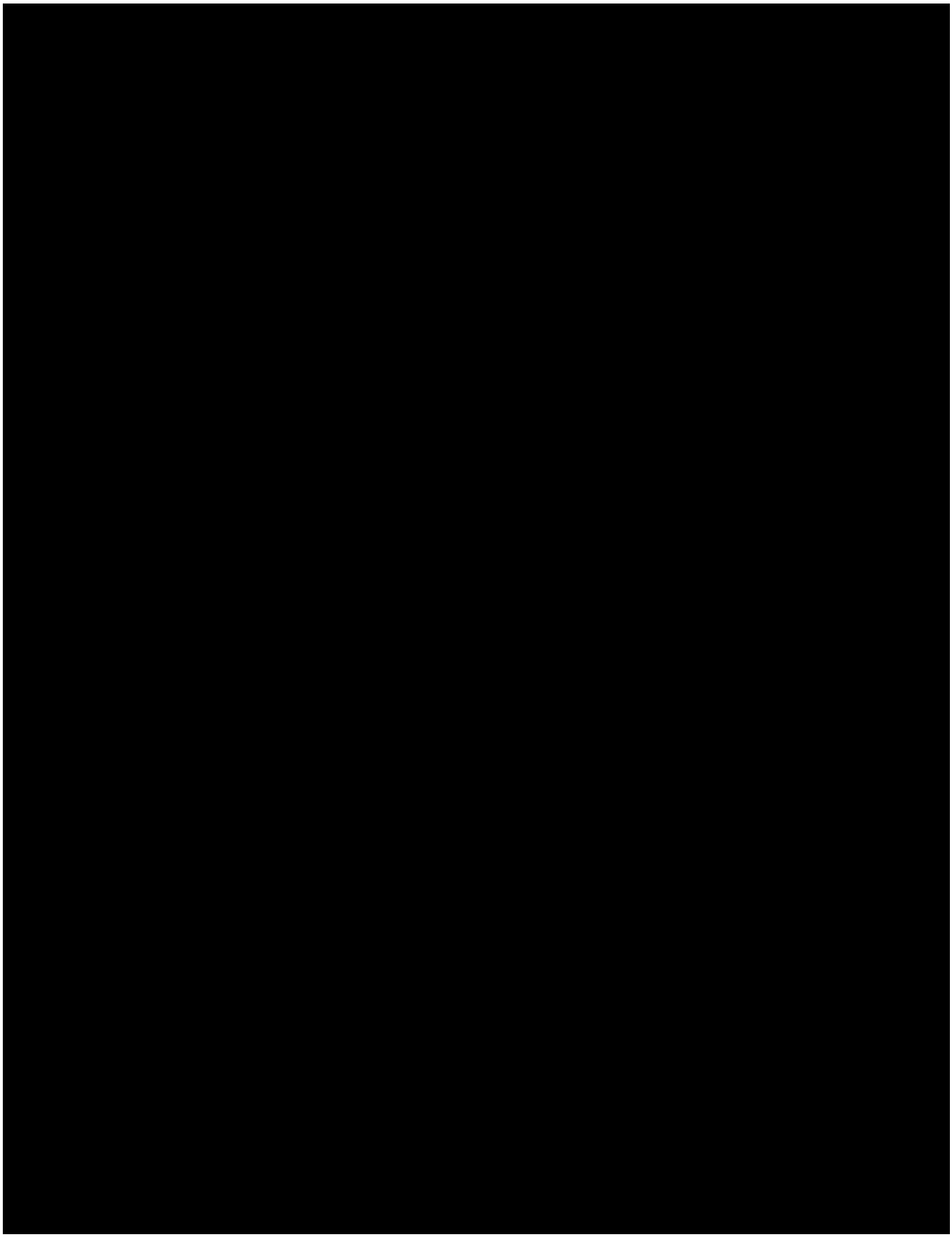
CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies
(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

Appendix B St. George's respiratory questionnaire



[redacted]



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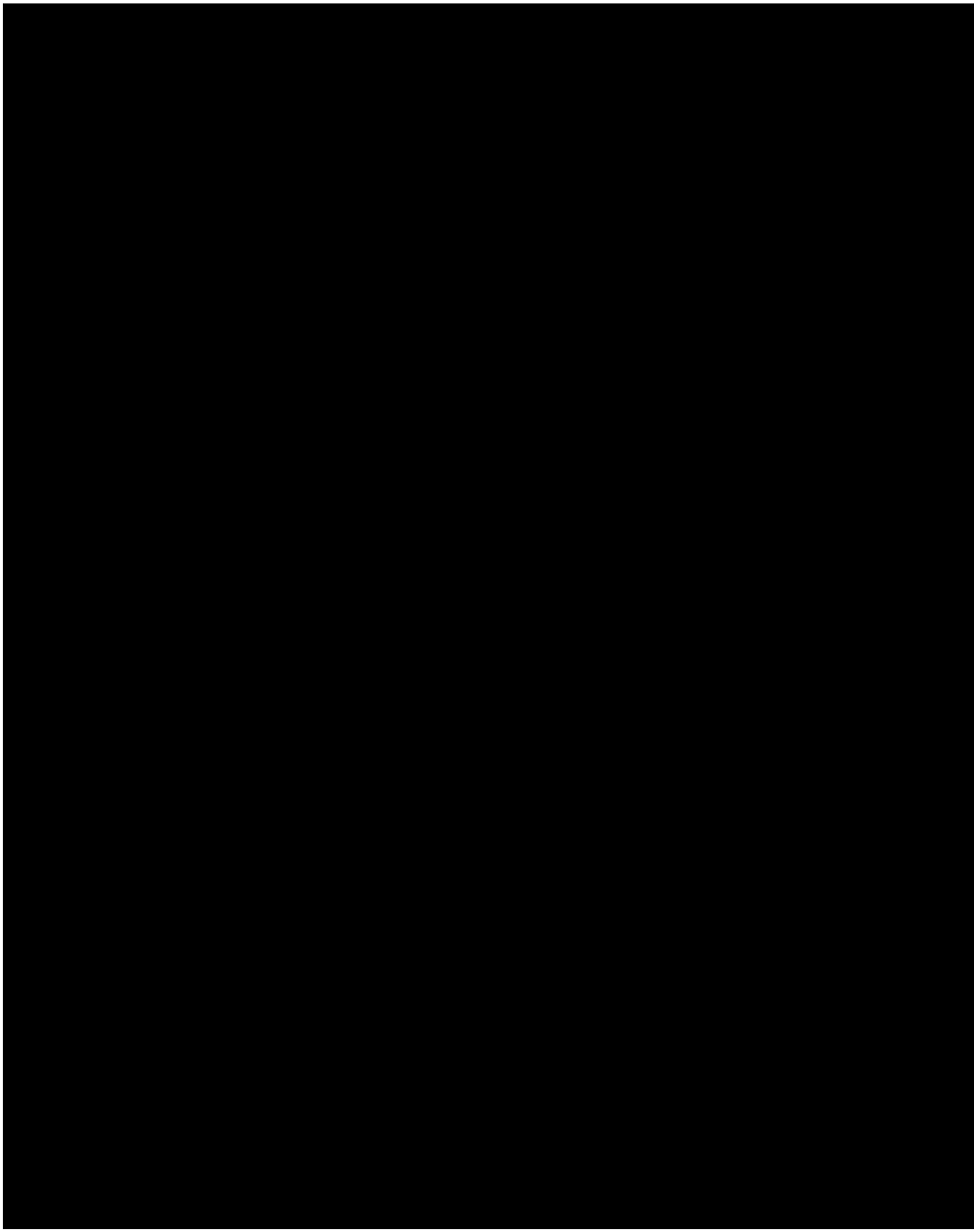
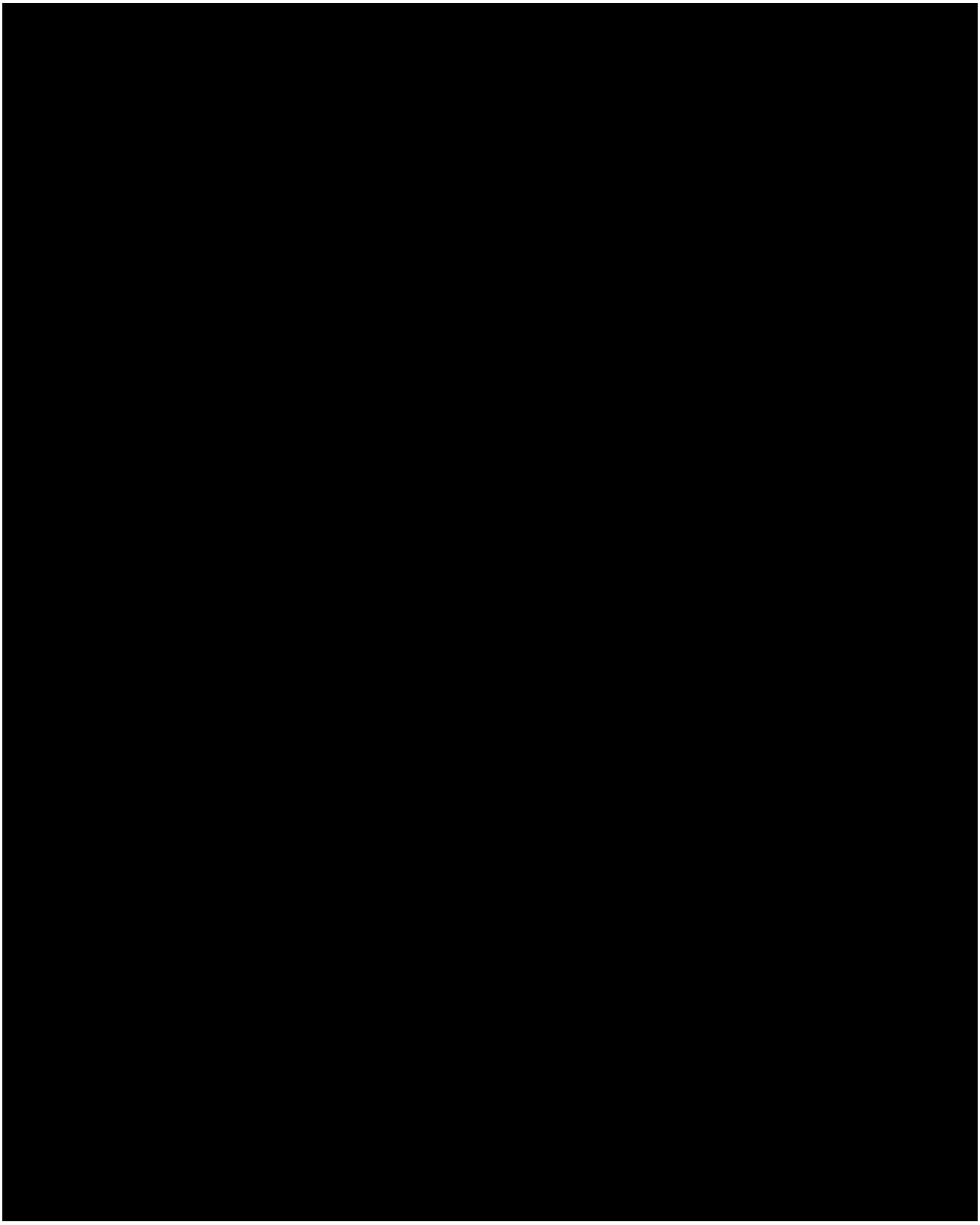
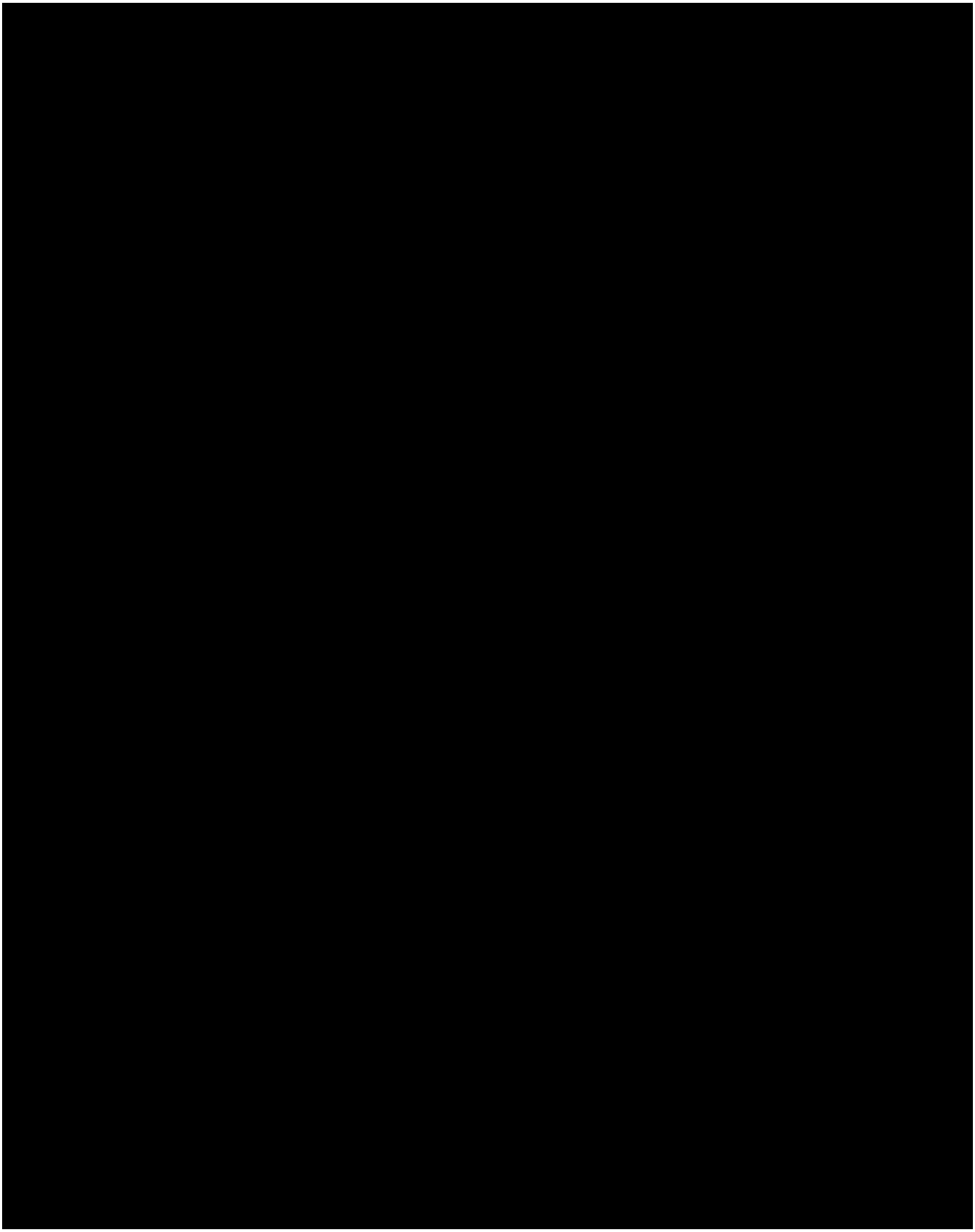


[redacted]

Appendix C SGRQ scoring algorithm





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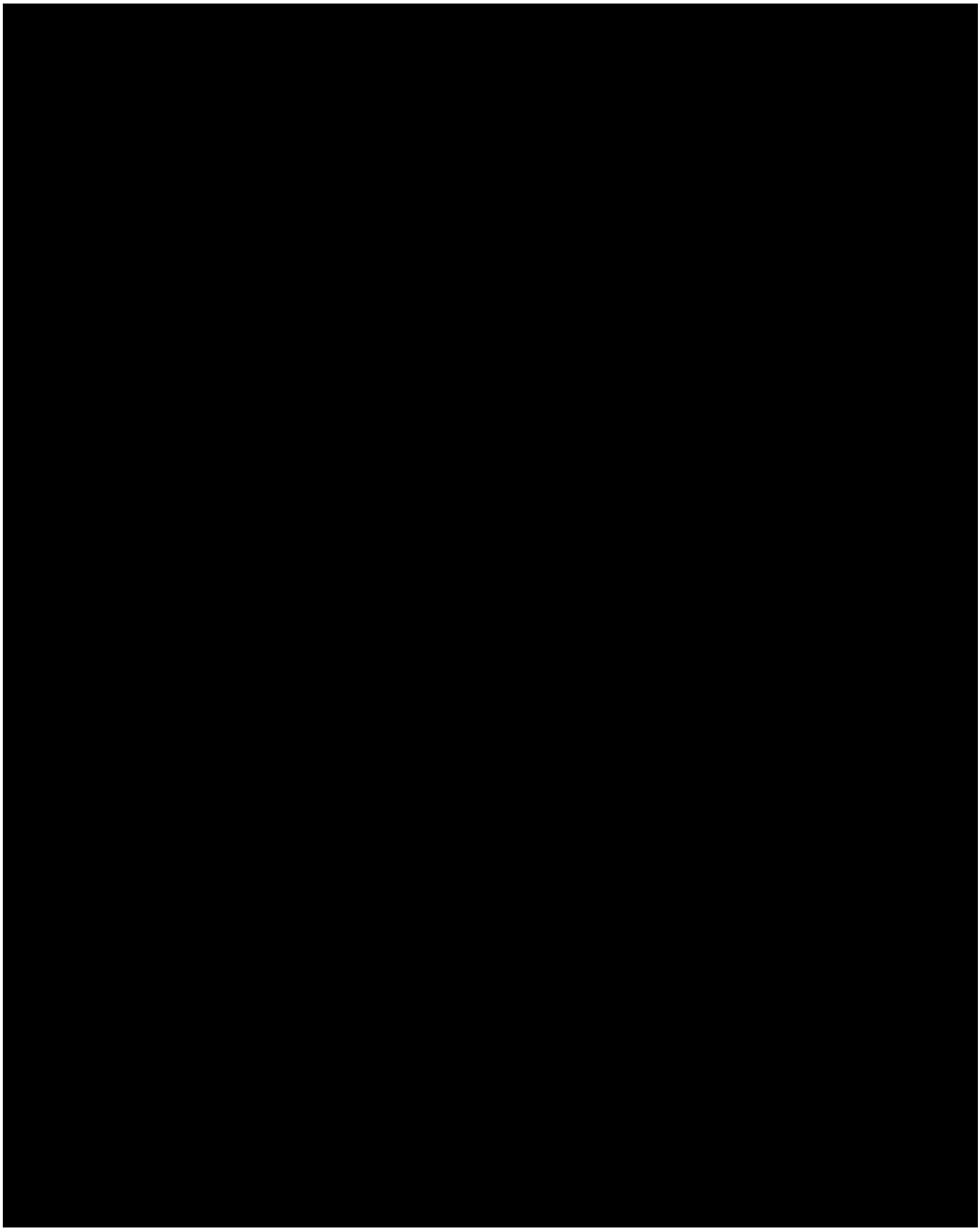
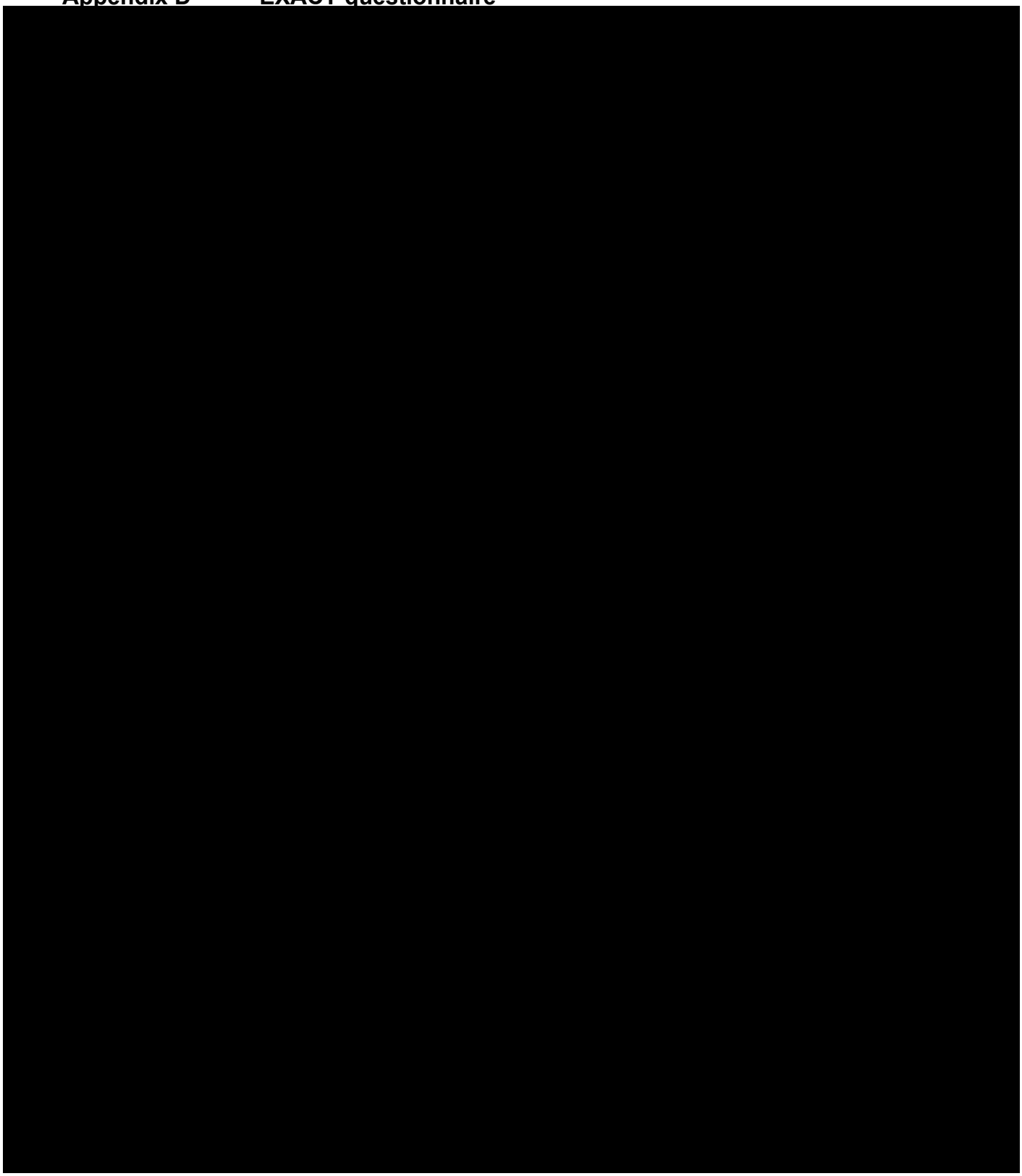
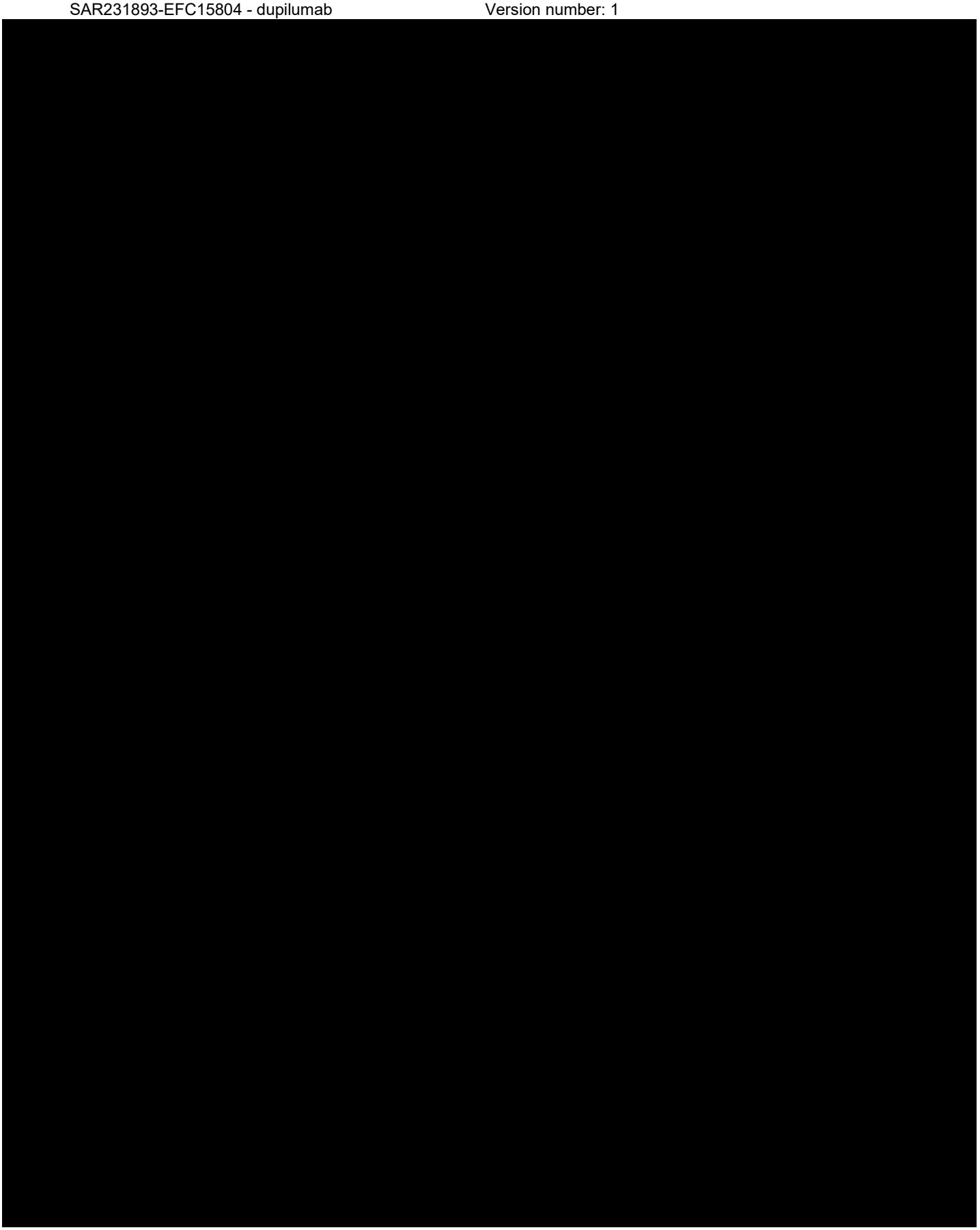


Appendix D EXACT questionnaire





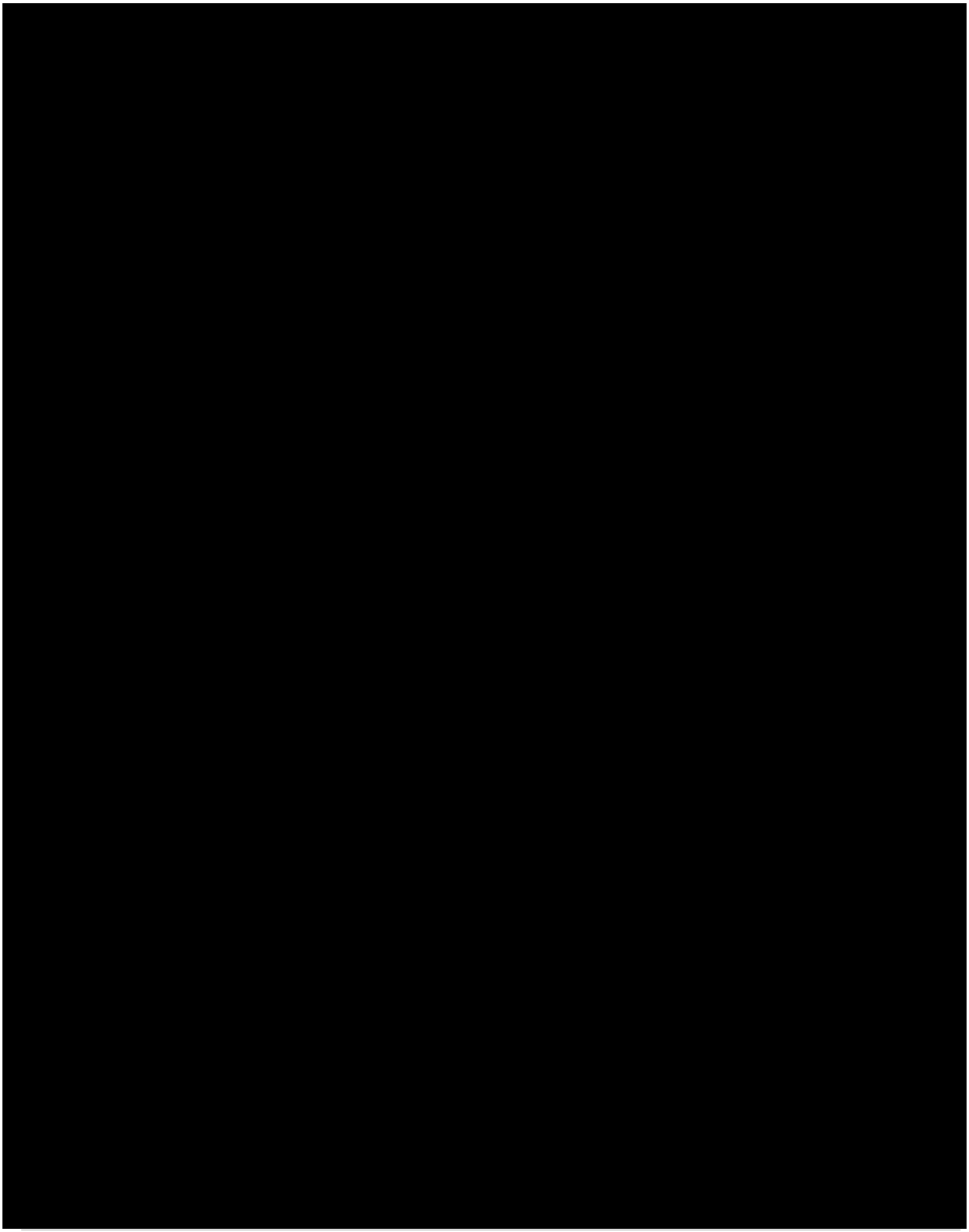
[redacted]

[redacted]

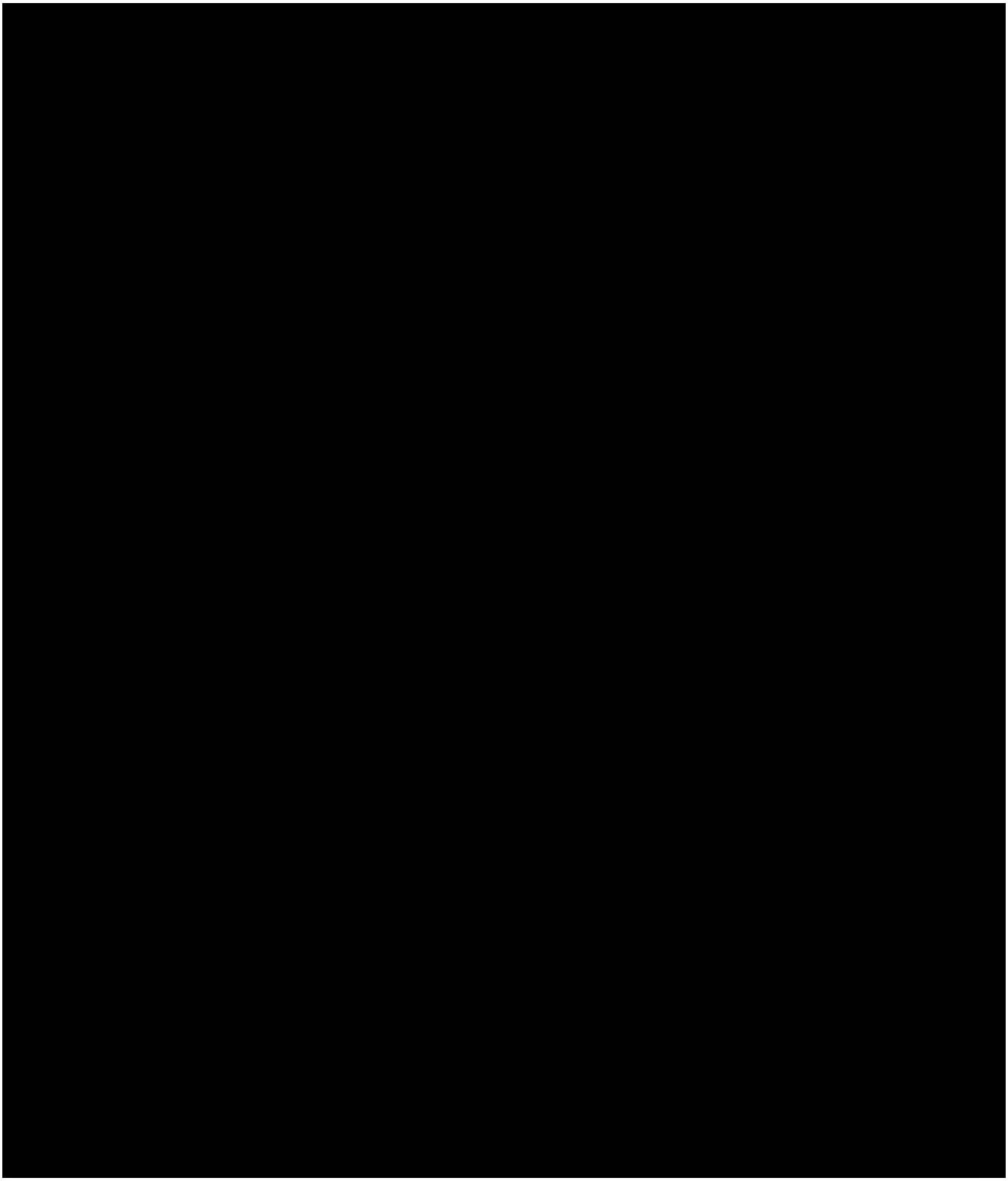
[redacted]

[redacted]

Appendix E EQ-5D



UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group



UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Appendix F BODE

BODE Index for COPD

The BODE Index is a composite marker of disease taking into consideration the systemic nature of COPD (Celli et al., 2004).

Scoring the BODE Index

	0	1	2	3
FEV_1% pred	≥65	50-64	36-49	≤35
6MWD (m)	≥350	250-349	150-249	≤149
MMRC	0-1	2	3	4
BMI ($kg.m^{-2}$)	>21	≤21		

Total BODE Index score = 0 to 10 units

(FEV1% pred = predicted amount as a percentage of the forced expiratory lung volume in one second; 6MWD = six minute walking distance; MMRC = modified medical research council dyspnea scale; BMI = body mass index)

Modified MRC Dyspnoea Scale	
0	Breathless only with strenuous exercise
1	Short of breath when hurrying on the level or walking up a slight hill
2	Slower than most people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
3	Stop for breath after walking about 100 meters or after a few minutes at my own pace on the level
4	Too breathless to leave the house or I am breathless when dressing

Appendix G High dose of inhaled corticosteroids : Adults

The following list of high dose of ICS is not a comprehensive list; the ICS that are not part of the list should be discussed with the Sponsor to confirm high vs. lower dose prior to randomization.

Inhaled corticosteroid	Daily dose (mcg)	
	High	Lower doses
Beclometasone dipropionate (CFC)	>1000	</=1000
Beclometasone dipropionate (HFA)	>400	</=400
Budesonide (DPI)	>800	</=800
Ciclesonide (HFA)	>320	</=320
Fluticasone propionate (DPI or HFA)	>500	</=500
Mometasone furoate	>440	</=440
Triamcinolone acetonide	>2000	</=2000

(Adapted from GINA 2014 Guidance)

High dose of inhaled corticosteroids: Adults (Japan)

Inhaled corticosteroid	Daily dose (mcg)	
	High dose	lower doses
Beclometasone dipropionate (HFA)	401-800	</= 400
Fluticasone propionate (HFA)	401-800	</=400
Ciclesonide (HFA)	401-800	</=400

Fluticasone propionate (DPI)	401-800	</=400
Budesonide (DPI)	801-1600	</=800
Budesonide inhalation suspension	1<x<=2	</=1.0

(Adapted from Japanese Asthma Prevention and Management Guideline 2018)

CFC – chlorofluorocarbon; HFA – hydrofluoroalkane; DPI – dry powder inhaler;

Appendix H Definition of anaphylaxis

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."

(Adapted from *Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA , Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117: 391-397)*

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Appendix I List of opportunistic infections

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis – Note that all cases should be collected as AEs.. only systemic or extensive mucosal or cutaneous candidiasis is considered opportunistic infections
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (disseminated)
- Herpes Zoster (disseminated; ophthalmic ; involvement of 2 or more dermatomes)
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)

This list is indicative and not exhaustive

Appendix J Handling of missing data

Annualized rate of moderate or severe exacerbation events during the 52-Week period

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

Step 1. The 52-week observation period is partitioned into bi-weekly (2-week) segments.

By clinical definition, a patient can have at maximum 1 moderate or severe exacerbation event per two weeks. For each patient, his/her event count over 52 weeks is broken down into a series of binary outcomes across each of the 26 bi-weekly segments (52 weeks). In the analysis, for each patient, in each bi-weekly segment, an imputation flag (imputefl) will indicate whether the patient needs imputation in that segment.

Step 2. Estimation for the bi-weekly binary event probability using observed data

Within each bi-weekly segment, the logistic regression model will be fitted to the observed data to model coefficient estimates and the estimated variance-covariance matrix, with adjusting for the planned treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study ($\leq$2, 3, or $\geq$4). From the posterior distribution of the model coefficients, we randomly draw 40 sets of iid samples. As a result, for each patient and in each bi-weekly segment, 40 estimated probabilities can be obtained by using the 40 samples of coefficients and the patient's covariate values.

Step 3. Multiple Imputation of binary event by bi-weekly segment after study withdrawal

If a patient withdraws from the study at the kth ($1 \leq k < 14$) day of Segment i prior to Week 52, and experienced a moderate or severe exacerbation within the first k days, this patient will be considered as "observed" (imputefl=0) up to Segment i and will need imputations (imputefl=1) from Segment i+1 to Segment 26 (Week 52).

If a patient withdraws from the study at the kth ($1 \leq k < 14$) day of Segment i prior to Week 52, and has no moderate nor severe exacerbation in Segment i, this patient will be considered as "observed" (imputefl=0) up to Segment i-1 and will need imputations (imputefl=1) from Segment i to Segment 26 (Week 52).

For a patient who needs imputation from Segment i+1 to Segment 26, in each bi-weekly segment, 40 independent random samples will be respectively drawn from 40 estimated Bernoulli distributions, whose probabilities are obtained in Step 2.

For each patient who early withdraws from the study, 40 sets of complete event count data can be obtained by summing the observed event count prior to withdrawal and each series of imputed binary events after withdrawal up to Week 52.

Step 2 and 3 can be realized by using PROC MI in SAS. Sample code can be found below:

```
proc mi    data =dd  seed =9816388  nimpute  =40  out =outdata;
by  month;
class    outcome trt01pn  cnt        ygr1 ics copdnum;
monotone re   g  (fev1bl/details)        ;
logistic      (outcome=trt01pn cntygr1 ics smokin             g  fev1bl copdnum    /details
DESCENDING);
var     cntygr1 ics smoking fev1bl trt01pn copdnum outcome;
run ;
```

Step 4. Combining MI results by Rubin's formula

A negative binomial model with the same set of covariates as in the primary analysis will be fitted with 40 sets of complete datasets obtained in Step 3, so as to obtain 40 sets of treatment effect estimates (in log-scale) and p-values accordingly. Log transformed observation duration will be the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 16 (Week 52). At last, the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results (in log-scale) from the 40 analyses using Rubin's formula. These and their confidence interval limits are then exponentiated to derive relative rates. Of note, the rule will be applied on the log risks and log risk ratio.

Step 4 can be realized by using PROC MIANALYZE in SAS. Sample code can be found below

```
proc mianalyze      data=rr_conv;
by Label;
modeleffects Estimate;
stderr StdErr;
ods output ParameterEstimates=rr_pooled;
run ;
proc mianalyze      data=aer_conv;
by TRT01PN;
modeleffects Estimate;
stderr StdErr;
ods output ParameterEstimates=aer_pooled;

run ;
/* estimated RR and corresponding 95% CI */
data pouttx;
set rr_pooled;
if Parameter="txval";

rr = exp(estimate);
```

run ;

- ***Control-based PMM-MI***

All steps are the same as the aforementioned approach except in **Step 2**: the individual bi-weekly mean probability will be calculated based on observations in matching placebo arms only, with adjustment of missing observation duration.

- ***Tipping point analysis***

The tipping point analysis for severe exacerbation events will use the similar approach as
PMM-MI with tipping values for the odds.

Step 1. Estimation for the bi-weekly binary event probability using observed data

Within each bi-weekly segment up to Week 52, the logistic regression model will be fitted to the observed data to obtain the model coefficient estimates and the estimated variance covariance matrix, with adjusting for the planned treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study ($\leq$2, 3, or $\geq$4). From the posterior distribution for the model coefficients, we randomly draw 40 sets of iid samples. As a result, for each patient and in each segment, 40 estimated binary event probabilities can be obtained by using the 40 samples of coefficients and the patient's covariate values.

Step 2. Tip on the bi-weekly binary odds (the probability of having an event in the segment over the probability of being event-free in the segment)

Within each segment, for the patients from the placebo group and need imputation in that segment, the estimated odds for binary event will be deflated by decreasing a positive amount; for the patients from the treatment group and need imputation in that segment, the estimated odds for binary event will be inflated by increasing a positive amount. After the deflation/inflation, 40 sets of binary event probabilities can be obtained for the placebo and treatment groups, respectively.

Step 3. Multiple Imputation of binary event by bi-weekly segment after study withdrawal

For a patient who needs imputation from Segment i+1 to Segment 26, in each segment, 40 independent random samples will be respectively drawn from 40 estimated Bernoulli distributions, whose probabilities are obtained in Step 2.

For each patient who early withdraws from the study, 40 sets of complete event count data can be obtained by summing the observed event count prior to withdrawal and each series of imputed binary events after withdrawal up to Week 52.

Step 4. A negative binomial model with the same set of covariates as in the primary analysis will be fitted to the 40 sets of complete datasets obtained in Step 3, so as to obtain 40 sets of treatment effect estimates and p-values accordingly. Log transformed observation duration will be the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 16 (Week 52). Then, the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 2, 3 and 4 will be repeated iteratively until the p-value for combined treatment effect of dupilumab compared to placebo estimated in Step 4 is > 0.05 or the maximum applicable treatment effect has been reached.

Change from baseline in pre-BD FEV1 at Week 12

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

Step 1. Monotone missing pattern was induced by Markov Chain Monte Carlo (MCMC) method using PROC MI: for patients who have missing values at intermediate visits, but have value at subsequent visits, the intermediate missing values were imputed assuming a multivariate normal distribution over observations from all visits. 40 datasets with a monotone missing pattern will be obtained using this method.

Step 2. For each of the imputed dataset with monotone missing pattern obtained in Step 1, the remaining missing data will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, age, sex, height, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), and baseline pre-BD FEV1. All available data in the monotone missing pattern data will be used. 40 fully imputed datasets are obtained.

Step 3. Each of the 40 complete datasets will be analyzed using an ANCOVA model with change from baseline in pre-BD FEV1 at Week 12 as the response variable, treatment, age, sex, height, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), and baseline pre-BD FEV1 value as covariates. Then the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

- ***Tipping point analysis***

Step 1. 40 imputations will be performed to generate 40 completed data sets following Step 1 and 2 for PMM-MI.

Step 2. The imputed FEV_1 values in Dupilumab group are subtracted by a positive amount d for each imputed data sets.

Step 3. The imputed FEV_1 values in placebo group are added by a positive amount p for each imputed data sets.

Step 4. Change from baseline in pre-BD FEV1 will be analyzed using the ANCOVA model as described in the PMM-MI for each of the 40 complete datasets. Then the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 2 and Step 3 will be repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated in Step 4 is >0.05 or the maximum applicable treatment effect has been reached.