AMENDED CLINICAL TRIAL PROTOCOL 03

Protocol title:	**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**
Protocol number:	**EFC15805 (NOTUS)**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR231893/REGN668 (dupilumab)**
Study phase:	**Phase 3**
Short title:	**Pivotal study to assess the efficacy, safety and tolerability of dupilumab in patients with moderate-to-severe COPD with Type 2 inflammation (NOTUS)**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette 91380 Chilly-Mazarin FRANCE**
Monitoring Team's Representative Name and Contact Information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	28-Oct-2023, Version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	All	16-Dec-2021, Version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	29-Sep-2020, Version 1 (electronic 1.0)
Original Protocol		06-Dec-2019, Version 1 (electronic 1.0)

Amended protocol 03 (28-October-2023)

This amended protocol 03 (amendment 3) is considered to be non substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The overall rationale for the changes implemented in the protocol amendment is to add an interim analysis to determine if efficacy in the primary endpoint of annualized rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations is met at the time of the interim analysis, as COPD is a disease with a high unmet medical need. The interim analysis will be performed when ≥92% of the information fraction for the primary endpoint is available, but prior to all patients completing the 52-week treatment period.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Added a bullet on an interim analysis.	Interim analysis is planned for efficacy as COPD is a disease with high unmet medical need.
	Update of the data monitoring committee activities.	Update
Section 8.3.8 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs	Deletion of “and thus will not be considered unexpected condition” and “Any other AE not listed as an expected event in the IB or in this protocol will be considered unexpected”.	For accuracy and to clarify the current process.
Section 9.2 Sample Size Determination	Added details on alpha value at final analysis.	Interim analysis is planned for efficacy.

Section # and Name	Description of Change	Brief Rationale
Section 9.4 Statistical Analyses	Clarified the statistical analysis plan (SAP) will be finalized before the interim analysis.	Interim analysis is planned for efficacy.
Section 9.4.1 Efficacy analysis	Added details that if the primary endpoint is positive at the interim analysis, Week 52 endpoints will be analyzed using participants who had the opportunity to reach Week 52 at the time of the IA cut-off date.	Interim analysis is planned for efficacy.
	Update of the Statistical Analysis Methods wording for exploratory endpoints.	Clarification
Section 9.4.1.1 Multiplicity Considerations	Added details on the Kim-DeMets spending function for the interim analysis and hierarchical procedure for multiple endpoints.	Interim analysis is planned for efficacy.
Section 9.5 Interim Analyses	Updated text from “No interim analysis is planned” to add details of an interim analysis.	Interim analysis is planned for efficacy.
Section 10.1.4 Committees structure	Update of the data monitoring committee activities.	Update
Section 10.1.5 Dissemination of clinical study data	Update of the web address for the clinical study data sharing “vivli.org”” replaces “clinicalstudydatarequest.com”.	Update
Throughout	Minor editorial and document formatting revisions are made.	Correction

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

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

Short title:

Pivotal study to assess the efficacy, safety and tolerability of dupilumab in patients with moderate-to-severe COPD with Type 2 inflammation (NOTUS)

Rationale:

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease worldwide, associated with significant economic burden, and for which available standard-of-care therapy shows insufficient treatment effect on symptoms, lung function, exacerbations and long-term evolution of the disease. Though the inflammatory component in COPD is typically thought to be neutrophilic, there has been an identified subgroup of COPD which is characterized by a concomitant elevation in blood eosinophils which suggests a Type 2 inflammatory component of the disease in these patients. This study is designed to investigate the efficacy and safety of dupilumab over one year in patients with COPD with Type 2 inflammation who are in need of an additional treatment added to their current management. The presence of a placebo arm is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab. All patients will receive standard of care background medication throughout the study. The proposed study design provides the opportunity to assess the efficacy of dupilumab on multiple COPD domains including lung function, prevention of moderate and severe exacerbations, and symptom control. The effect on lung function and symptom control will be evaluated over both the short and long term.

Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of dupilumab 300 mg q2w in patients with moderate or severe COPD as measured by • Annualized rate of acute moderate or severe COPD exacerbation (AECOPD).	• Annualized rate of moderate* or severe** COPD exacerbations 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 observation for >24 hours in an emergency department/urgent care facility or resulting in death. For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days.

Objectives	Endpoints
Key secondary	
To evaluate the effect of dupilumab 300 mg q2w on • Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) 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 FEV_1 over 52 weeks compared to placebo.	• Change in pre-bronchodilator FEV_1 from baseline to Week 12 compared to placebo. • Change from baseline to Week 52 in SGRQ total score compared to placebo. • Proportion of patients with SGRQ improvement ≥4 points at Week 52. • Change in pre-bronchodilator FEV_1 from baseline to Week 52 compared to placebo.

Overall design:

Multinational, randomized, double-blind, placebo-controlled, parallel group (2 groups), 52-week, pivotal Phase 3 study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-or-severe COPD with Type 2 inflammation such as that driven by activation of IL-4, IL-5, and IL-13 on an established long acting beta-agonist (LABA), long acting muscarinic antagonist (LAMA) and/or inhaled corticosteroid (ICS) background therapy (triple therapy unless ICS contraindicated). Study treatments are dupilumab 300 mg q2w or placebo q2w administered during the 52-week randomized treatment period. The study includes 3 study periods.

- Screening (4 weeks ±1 week).
- Randomized investigational medicinal product (IMP) treatment period (52 weeks ±3 days).
- Post IMP treatment period (12 weeks ±5 days).

Patients who satisfy the inclusion and exclusion criteria will be randomized (1:1) to one of the following IMP treatment groups to be administered for 52 weeks.

- Dupilumab 300 mg, administered as 1 subcutaneous (SC) injection q2w.
- Placebo, administered as 1 SC injection of placebo matching dupilumab.

Randomization will be stratified by country, ICS dose (high dose ICS [yes/no]) at baseline, and smoking status at screening (current smokers or not). Enrollment will be capped at 30% current smokers (as defined by smoking status at screening visit).

Treatment discontinuation follow-up:

Patients who discontinue the study treatment prematurely (prior to completing the 52-week treatment period) will perform, as soon as possible, the early treatment discontinuation (ETD) visit with all assessments normally planned for the end of treatment (EOT) visit, to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment is available. In addition, to allow assessment of patient outcomes over the stipulated

study period, patients will be asked and encouraged to complete all remaining study visits, and participate in all safety follow-up assessments according to the visit schedule. For these patients the assessment schedule will be reduced (see Section 1.3.2) and visits during the planned treatment period may be conducted by phone (except for planned EOT) if patient is unable to come in for a site visit. Assessments not completed via phone should be performed at the next scheduled visit. For further details please see Section 7.1.1.

Post-IMP treatment follow-up

Upon completing the 52-weeks randomized IMP treatment period, patients will continue their background ICS/LABA/LAMA therapy and enter the 12-week safety follow-up period. Adjustment of background medication is allowed at the discretion of the Investigator as clinically indicated during the post-treatment period (see Section 6.1.2 for further details).

Disclosure Statement: This is a Parallel Treatment study with 2 arms that is blinded for patients and the Investigator.

Number of participants:

Approximately 924 patients are planned to be randomly assigned to study intervention for an estimated total of 462 evaluable patients per intervention group (see Section 9.2).

Intervention groups and duration:

Study participation for each patient will be a total of approximately 69 weeks including up to 5 weeks for screening, 52 weeks of IMP treatment period and 12 weeks of follow-up.

Study intervention(s)

Investigational medicinal products.

- *Dupilumab 300 mg.*
  - Formulation: Dupilumab 300 mg for SC administration is supplied as 150 mg/mL solution in 2.25 mL prefilled glass syringes to deliver 300 mg in 2 mL.
  - Route of administration: subcutaneous injection. All IMP applications will be done as separate injections into different injection sites.
  - Dose regimen: dupilumab 300 mg q2w administered as 1 SC injection.
- *Matching Placebo for dupilumab.*
  - Formulation: Placebo matching dupilumab will be supplied as an identical formulation to the active formulation but without dupilumab.
  - Route of administration: subcutaneous injection. All IMP applications will be done as separate injections into different injection sites.
  - Dose regimen: Placebo administered as 1 SC injection of placebo matching dupilumab 300 mg (2 mL).

Noninvestigational medicinal products(s)

Background therapy

Patients should continue the regular administration of their previous standard of care background therapy for COPD throughout the study, including:

Triple therapy: ICS + LABA + LAMA (Double therapy: LABA + LAMA allowed if ICS is contraindicated)

- Formulation: dry powder inhaler (DPI), metered dose inhaler (MDI) or pocket nebulizer.
- Route(s) of administration: Oral inhalation.
- Dose regimen: As prescribed.
- Background medication should not be adjusted during Screening. Patients are strongly encouraged to maintain their background therapy for the entire duration of their treatment therapy. After 1 severe or 2 moderate exacerbations of COPD, dose adjustments in background therapy, if required will be permitted for symptom control and as needed for the remainder of the trial period.

Reliever medication

- Patients may use albuterol/salbutamol or levalbuterol/levosalbutamol (including ipratropium or ipratropium/short acting β-agonist [SABA] combinations or terbutaline) as reliever medications as needed during the study.
- Formulation: MDI, nebulizer solutions or DPI.
- Route of administration: oral inhalation.
- Dose regimen: as prescribed.

Statistical considerations:

- Analysis populations
  - The efficacy population will be the intention-to-treat (ITT) population, defined as all randomized patients analyzed according to the treatment group allocated by randomization.
  - The safety population will include all patients who actually received at least one dose or a partial dose of the IMP, analyzed according to the treatment actually received.
- **Primary analysis:** 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 occurring during the 52-week treatment period as the response variable, with the treatment group, region (pooled country), ICS dose (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV_1), 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. Patients who permanently discontinue the study treatment will be encouraged to complete the study as planned and the additional off-treatment exacerbation events up to Week 52 will be

included in the primary analysis. Sensitivity analyses for handling missing data may include pattern mixture model by multiple imputation and tipping point analyses.

- **Analysis of key secondary endpoints:**

  The change from baseline in pre-bronchodilator FEV_1 at Week 12 will be analyzed using mixed-effect model with repeated measures (MMRM). The model will include change from baseline in FEV_1 values up to Week 12 as response variables, and factors for treatment group, age, sex, baseline height, region (pooled country), ICS dose (high dose ICS dose [yes/no]), smoking status at screening (current smokers or not), visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1, and FEV_1 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. For patients discontinued the study treatment, off-treatment FEV_1 values will be included in the analysis. Sensitivity analyses for handling missing data may include pattern mixture model by multiple imputation and tipping point analyses.

  The change from baseline in pre-bronchodilator FEV_1 at Week 52 will be analyzed in a similar way as change from baseline in pre-bronchodilator FEV_1 at Week 12 and the model will include values up to Week 52 as response variables.

  The change from baseline in SGRQ total score at Week 52 will also be analyzed in a similar way except that the MMRM model will include the following covariates: treatment group, region (pooled country), ICS dose (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.

  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 (high dose ICS [yes/no]), smoking status at screening (current smokers or not), and baseline SGRQ total score as covariates. Patients with missing SGRQ total score at Week 52 will be considered as non-responders.

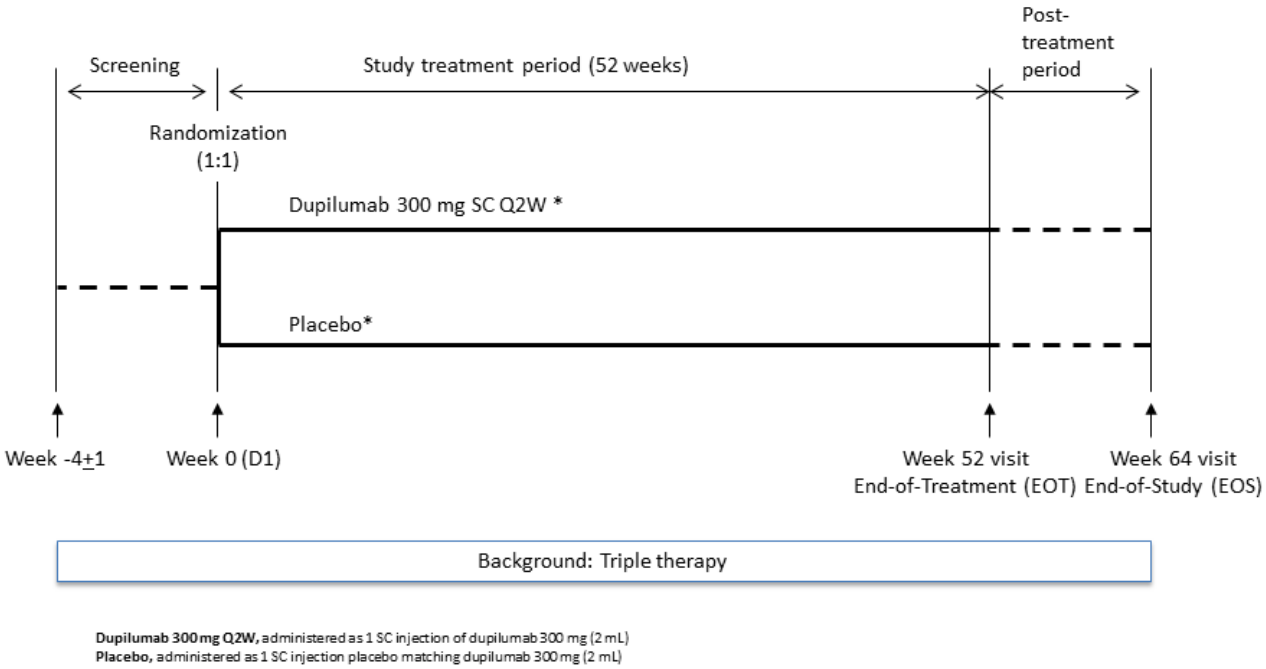
- **Multiplicity considerations:** Multiplicity is considered for testing multiple endpoints. The overall type-I error rate will be controlled at the two-sided 0.05 level. Details will be provided in Section 9.4.1.1.
- **Safety analyses:** The safety variables, including adverse events (AEs), laboratory parameters, vital signs, electrocardiography, and physical examinations will be summarized using descriptive statistics.
- An interim analysis will be performed during the study. See Section 9.5 for further details.

Data Monitoring Committee: Yes

- A data monitoring committee (DMC), independent from Sponsor, will be established for this study. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety and efficacy data during the course of the trial, review interim analysis results and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

1.2 SCHEMA

Figure 1 - Graphical study design



Dupilumab 300 mg Q2W, administered as 1 SC injection of dupilumab 300 mg (2 mL)
Placebo, administered as 1 SC injection placebo matching dupilumab 300 mg (2 mL)

1.3 SCHEDULE OF ACTIVITIES (SOA)

The schedule of activities (SoA) for patients who complete the planned treatment is described in Section 1.3.1. Patients who withdraw from treatment prematurely must complete the ETD visit and follow the assessment in Section 1.3.2 for the remaining visits.

1.3.1 Schedule of activities for patients who complete the planned treatment

	Screening	Randomization/ Baseline																												
VISIT	1	2[a,b]	3	4		5		6		7[s]		8[s]		9		10[s]		11[s]		12		13[s]		14		15[s]		16[c]	17[s]	18[s]	19
WEEK[a]	W-4 to W0	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52 (EOT)	56	60	64 (EOS)
Informed consent	X																													
Patient demography	X																													
Previous medical and surgical history	X																													
Chest X-ray[e]	X																													
Inclusion/exclusion	X	X																												
BODE score, includes 6-minute walk test and mMRC Dyspnea scale[r]		X																									X			
Smoking status	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Prior & concomitant medications	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Study treatment administration																															
Call IVRS/IWRS	X	X	X	X		X		X						X						X				X				X			X
Randomization		X																													
IMP administration[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Review electronic diary[g]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X			X
Safety																															
Physical examination[h]	X	X												X														X			X
Vital signs[i]	X	X	X	X		X		X						X						X				X				X			X
Electrocardiogram (12 lead)[d]	X	X						X						X						X								X			X

	Screening	Randomization/ Baseline																												
VISIT	1	2[a,b]	3	4		5		6		7[s]		8[s]		9		10[s]		11[s]		12		13[s]		14		15[s]		16[c]	17[s]	18[s]	19
WEEK[a]	W-4 to W0	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52 (EOT)	56	60	64 (EOS)
Hematology, biochemistry, Urinalysis including cotinine[j,k]	X	X		X		X		X						X						X								X			X
Hepatitis and HIV Serology tests	X																														
Pregnancy (β-HCG blood) test[l]	X																														
Urine pregnancy test[l]		X		X		X		X		X		X		X		X		X		X		X		X		X		X			X
Adverse event reporting, including SAEs	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Pharmacokinetics																															
Serum PK samples for dupilumab concentration[o]		X	X	X		X		X						X						X								X			X
Anti-dupilumab antibody[o]		X						X						X														X			X
Biomarkers																															
FeNO post-bronchodilator		X		X		X		X						X						X								X			X
PARC		X																										X			X
Eotaxin-3		X		X				X						X														X			X
Total IgE		X						X																				X			X
Fibrinogen		X												X														X			X
Whole blood RNA (optional)		X												X														X			
DNA (optional)		X[p]																													
Serum/plasma for archival samples (optional)		X		X				X						X						X								X			

	Screening	Randomization/ Baseline																													
VISIT	1	2[a,b]	3	4		5		6		7[s]		8[s]		9		10[s]		11[s]		12		13[s]		14		15[s]		16[c]	17[s]	18[s]	19
WEEK[a]	W-4 to W0	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52 (EOT)	56	60	64 (EOS)
Efficacy																															
COPD exacerbation reporting by the Investigator		X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Spirometry (pre-BD)[m,n]	X	X	X	X		X		X						X						X				X				X			X
Spirometry (post-BD)[m,n]	X	X	X	X		X		X						X						X								X			X
EXACT[g]	Every day (diary) from screening to Week 52																														
SGRQ[g]		X		X				X						X						X								X			X
EQ-5D-5L[g]		X												X														X			
Health care utilization[q]		X		X		X		X		X		X		X		X		X		X		X		X		X		X			X

β-hCG = Human chorionic gonadotropin-beta; BD = bronchodilator; BID = twice daily assessments; BODE= Body-mass index, airflow Obstruction, Dyspnea, and Exercise; continuous = subsequent visits during the treatment period; COPD = chronic obstructive pulmonary disease; cont. = continuous; CT = computed tomography, DNA = Deoxyribonucleic acid ; ECG = Electrocardiogram , EDTA = Ethylenediaminetetraacetic acid ; EOS = End of Study; EOT = End of treatment; EQ-5D-5L = Euro Quality of Life-5 Dimension 5-Level questionnaire; EXACT = Exacerbations of COPD tool; FeNO = Fractional exhaled nitric oxide; HBV = hepatitis B virus, HCB = hepatitis C virus, HIV = human immunodeficiency virus; IgE = Immunoglobulin E; IMP = Investigational Medicinal Product; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LABA = Long-acting β2 agonists; LAMA = Long-acting muscarinic antagonist; mMRC = Modified Medical Research Council Dyspnea Scale; PARC = Pulmonary and activation-regulated chemokine;
PGX = pharmacogenetic; PK = Pharmacokinetic; RNA = Ribonucleic acid; SABA = Short-acting β-agonists; SAEs = Serious adverse events; SC = subcutaneous; SGRQ = St. George's Respiratory Questionnaire.

a Randomization/baseline visit is defined as Day 1. The visit schedule should be adhered to within ±1 week for the 4-week screening period, ±3 days for the randomized IMP treatment period and ±5 days for the post IMP treatment period. If more than 12 weeks since last on-site scheduled visit, then unscheduled visit is required within 3 weeks of missed scheduled visit (eg, if missed scheduled visit at Week 24, then unscheduled visit must be performed by Week 27; If missed scheduled visit at Week 36, then unscheduled must be performed by Week 39). All the assessments of the missed scheduled on-site visit will need to be carried out at the unscheduled visit.

b All assessments at Visit 2 (Day 1) are to be conducted pre-IMP dose with the exception of the assessment of local tolerability of SC injections.

c End-of-treatment visit: See Section 7.1.1 for patients who discontinue treatment prematurely.

d ECG to be centrally collected & read.

e Chest X-ray to be performed unless a <6-month-old chest x-ray/chest CT/chest MR is available. In case chest-X-ray is not feasible due to local regulations, magnetic resonance imaging (MRI) will be performed.

f IMP (Dupilumab or placebo) is to be administered every 2 weeks by patient, caregiver or healthcare professional at the patient's home or in a health care facility. Last dose will be given at Week 50. If the patient or Investigator decides not to administer IMP at home, the IMP injections can be performed at the site by way of unscheduled visits. The IMP can be administered at home after training and at least 1 IMP injection at the site and supervised by the Investigator. Patients will be monitored at the study site for a minimum of 30 minutes after injections. See Section 6.1.1 for details. If the patient is unable or unwilling to administer IMP at home, injections can be performed at the site; or arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site.

g Electronic diary is used for recording of patient's answers to the EQ-5D-5L, EXACT and SGRQ questionnaires. This handheld device is dispensed at Screening Visit 1 (including instructions for use) and recorded information is reviewed on the other indicated days. At EOT visit the electronic diary is downloaded from the device and returned to the site.

h Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

i Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate will be measured at screening, baseline 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.

j Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count, differential count, and total red blood cell count. Serum chemistry will include creatinine, blood urea nitrogen, glucose, lactate dehydrogenase, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. 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. Clinical laboratory testing at Screening Visit 1 will include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). In case of results showing HBs Ag (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. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

k Refer to central lab manual for collection details.

l Only for women of childbearing potential. Pregnancy will lead to definitive treatment discontinuation in all cases. In case of positive urinary test, a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. Pregnancy testing should be done monthly, female participants will be supplied with dipsticks for between on-site visits.

m Spirometry will be done locally according to European Respiratory Society (ERS)/American Thoracic Society (ATS) 2005 guidance but measured by a central laboratory. Spirometry will be performed during a trough 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 ipratropium for at least 8 hours, withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for 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 other SABA). See Section 8.1.1.2 for details.

n Following randomization and during the treatment period - if spirometry is not performed at the scheduled visit it should be performed at the following on-site visit for all visits prior to Week 12. If not performed at Week 12 or at subsequent scheduled on-site visits, an unscheduled assessment is required within 3 weeks of the missed scheduled.

o PK and ADA samples to be collected prior to the administration of the drug.

p If collection is not completed at randomization, sample can be taken at a following visit.

q Includes collection of sick days, lost usual activities, and additional physician visits or other health care utilization.

r To be completed prior to IMP administration.

s Telephone visit.

1.3.2 Reduced schedule of events for patients after early treatment discontinuation

	ETD[a]																												
VISIT		3	4		5		6		7[j]		8[j]		9		10[j]		11[j]		12		13[j]		14		15[j]		16	17[j]	18[j]	19
WEEK		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64 (EOS)
BODE score, includes 6-minute walk test and mMRC Dyspnea scale	X																													
Smoking status	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Prior & concomitant medications	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Study treatment administration																														
Call IVRS/IWRS	X																													X
Review electronic diary	X																										X			X
Safety																														
Physical examination [c]	X												X														X			X
Vital signs[d]	X		X		X		X						X						X				X				X			X
Electrocardiogram (12 lead)[b]	X						X						X						X								X			X
Hematology, biochemistry, urinalysis including cotinine [e, f]	X						X						X						X								X			X
Urine pregnancy test [g]	X		X		X		X		X		X		X		X		X		X		X		X		X		X			X
Adverse event reporting, including SAEs	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Pharmacokinetics																														
Serum PK samples for dupilumab concentration	X						X						X						X								X			
Anti-dupilumab antibody	X						X						X														X			
Biomarkers																														
FeNO post-bronchodilator	X						X						X						X								X			X
PARC	X																													
Eotaxin-3	X																													X
Total IgE	X																													X
Fibrinogen	X																													X
Whole blood RNA (optional)	X																													
Serum/plasma for archival samples (optional)	X																													

	ETD[a]																												
VISIT		3	4		5		6		7[j]		8[j]		9		10[j]		11[j]		12		13[j]		14		15[j]		16	17[j]	18[j]	19
WEEK		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64 (EOS)
Efficacy																														
COPD exacerbation reporting by the Investigator	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Spirometry (pre-BD)[h]	X		X		X		X						X						X				X				X			X
Spirometry (post-BD)[h]	X		X		X		X						X						X								X			X
EXACT[i]	X																													
SGRQ[i]	X						X						X						X								X			X
EQ-5D-5L[i]	X																													
Health care utilization	X																										X			

BD = bronchodilator; BID = twice daily assessments; BODE = Body-mass index, airflow Obstruction, Dyspnea, and Exercise; continuous = subsequent visits during the treatment period; COPD = chronic obstructive pulmonary disease; cont. = continuous; ECG = Electrocardiogram, EDTA = Ethylenediaminetetraacetic acid ; EOS = End of Study; EOT = End of treatment; EQ-5D-5L= Euro Quality of Life-5 Dimension 5-Level questionnaire; ETD = early treatment discontinuation; EXACT = Exacerbations of COPD tool; FeNO = fractional exhaled nitric oxide; IgE = Immunoglobulin E; IMP = Investigational Medical Product; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LABA = Long-acting β2 adrenergic agonists; LAMA = Long-acting muscarinic antagonists; mMRC = Modified Medical Research Council Dyspnea Scale; PARC = Pulmonary and activation-regulated chemokine; PGX = pharmacogenetic; PK = Pharmacokinetic; RNA Ribonucleic acid; SABA = Short-acting β-agonists; SAEs = Serious adverse events; SC = subcutaneous; SGRQ = St. George's Respiratory Questionnaire.

a Patients who withdraw from study treatment (prior to completing the planned duration of IMP treatment) will perform, as soon as possible, the early treatment discontinuation (ETD) visit. Once the ETD visit is performed, patients should follow the ETD SoA based on the original visit number and the visit schedule should be adhered to within ±5 days. Please see Section 7.1.1 for more details.

b ECG to be centrally collected & read.

c Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

d Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate will be measured at every subsequent on-site visit. Body weight (kg) will be measured at EOT/EOS visits.

e Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count, differential count, and total red blood cell count. Serum chemistry will include creatinine, blood urea nitrogen, glucose, lactate dehydrogenase, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. 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.

f Refer to central lab manual for collection details.

g Only for women of childbearing potential. Urine pregnancy test at ETD and every 4 weeks through Visit 16 and at EOS. In case of positive urinary test, a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. Pregnancy testing should be done monthly, female participants will be supplied with dipsticks for between on-site visits.

h Spirometry will be done locally according to European Respiratory Society (ERS)/American Thoracic Society (ATS) 2005 guidance but measured by a central laboratory. Spirometry will be performed during a trough 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 ipratropium for at least 8 hours, withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for 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 other SABA).

i The EQ-5D-5L, EXACT, and SGRQ are to be completed in the patient's electronic diary.

j Telephone visit.

2 INTRODUCTION

Dupilumab is a systemic targeted immunomodulatory agent, inhibiting the Th2 pathway. It is a fully human monoclonal antibody (mAB) directed against the interleukin 4 receptor alpha (IL-4Rα) subunit, a component of IL-4 receptors Type I and Type II, which mediate signaling by IL-4 (both receptors) and by IL-13 (Type II receptor). The IL-4R alpha receptor is present on multiple cell types known to be involved in the Type 2 inflammatory process. Dupilumab is being studied as a potential novel treatment for COPD in those patients with evidence of Type 2 inflammation as identified by the biomarker of blood eosinophils.

2.1 STUDY RATIONALE

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease, associated with significant economic burden, and for which available standard-of-care therapies show insufficient treatment effect on symptoms, lung function, exacerbations and long-term progression of the disease. This study is designed to investigate the efficacy and safety profile of dupilumab over one year in patients with COPD who are in need of an additional treatment added to their current management. The presence of a placebo arm is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab. All patients will receive standard of care background medication throughout the study. The proposed study design provides the opportunity to investigate the efficacy of dupilumab on multiple COPD domains including lung function, prevention of moderate and severe exacerbations and symptom control. The effect on lung function and symptom control will be evaluated over short term and long term.

2.2 BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common, heterogeneous disease associated with an abnormal inflammatory immune response of the lung to noxious particles and gases (1). It results in progressive airflow obstruction that is mainly irreversible or only partially reversible and in many cases loss of alveolar tissue and emphysema. The disease typically starts in small airways, where the chronic inflammation causes structural changes including narrowing of the small airways, and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. The inflammation component of COPD is thought to involve many cell types including structural cells, T lymphocytes, neutrophils, macrophages, and their biological products. Though the inflammatory component in COPD is typically thought to be neutrophilic, there has been an identified subgroup of COPD which is characterized by a concomitant elevation in blood eosinophils which suggests a Type 2 inflammatory component of their disease. COPD is most commonly caused by smoking tobacco, but may also be caused by particulate and noxious gas inhalation through outdoor or indoor air pollution including occupational exposures to vapors, gas, dust (including silica) and fumes. The most common clinical symptoms include chronic dyspnea, cough and/or sputum production. COPD exacerbations are important contributors to the disease burden, particularly in severe COPD. Exacerbations are often triggered by viral and/or bacterial infections, but tend to occur

also more frequently in patients with COPD with Type 2 inflammatory signature, where they may be preceded by increases in sputum eosinophils. Exacerbations may trigger a major inflammatory response followed by tissue destruction and frequent exacerbations which are associated with forced expiratory volume in 1 second (FEV1) decline, more rapid disease progression and increased risk of mortality.

In particular, current smokers with COPD have an accelerated decline in lung function, which is heterogeneous, exhibits considerable inter- and intra-individual variability and FEV_1 decline can reach more than 100 ml/year in some patients with COPD. Smoking cessation attenuates the accelerated loss of lung function, but neither smoking cessation nor current therapies result in a substantial recovery of lung function lost at the time of smoking cessation (2).

"Type 2 inflammation" exists across a spectrum of diseases. This inflammatory cascade is regulated by T-helper Type 2 cells and is driven by activation of IL-4, IL-5, and IL-13 cytokines. (3). Peripheral and airway eosinophils are present in asthmatics with Type 2 inflammation (4). Markers of Type 2 inflammation, including sputum IL-4 and IL-5 have been identified in subgroups of patients with COPD and are linked to peripheral eosinophils (5, 6). In addition, peripheral eosinophilia (>300), as a marker of Type 2 inflammation, appears to identify a subgroup of COPD patients with distinct clinical features (6, 7) including more frequent respiratory exacerbations (8) as well as worse overall mortality. At the same time, this group, similar to asthmatics with Type 2 inflammation (9), also appears to be more responsive to ICS (6). Additional biomarkers for Type 2 inflammation have been identified in asthma populations, including IgE, FeNO, and Periostin, but to date they have been less well studied in COPD.

Dupilumab blocks the IL4Ra, leading to inhibition of the Type 2 cytokines IL-4 and IL-13. In addition, IL-13 has been shown to block mucus secretion. We hypothesize that blocking key mediators of Type 2 inflammation as well as reducing mucus production in COPD will lead to a reduction in inflammatory exacerbations as well as an improvement in lung function. We will use peripheral eosinophilia to identify COPD patients with Type 2 inflammation.

Chronic obstructive pulmonary disease is a highly prevalent, serious, and progressive disease resulting in significant morbidity, mortality, and economic burden (10, 11). Based on the BOLD and other large scale epidemiological studies, it is estimated that the number of COPD cases in the world was 384 million in 2010, with a global prevalence of 11.7% (95% confidence interval: 8.4%-15.0%) (10). In the US alone there are more than 12 million diagnosed patients and the incidence of COPD is expected to grow rapidly with an aging population. COPD is a progressive and irreversible inflammatory lung disease that is periodically punctuated by disease exacerbations that result in long-term disability and mortality, in the US, COPD is the third most common cause of death. In Europe the number of cases is estimated to be 66.4 million in 2010 among people aged 30 years or more, with a prevalence of 13.7% (13.5% - 13.9%) (10). Globally there are around 3 million deaths attributed to COPD annually. With the increasing prevalence of smoking in developing countries, and aging populations in high-income countries, the prevalence is expected to rise and the number of deaths to reach 4.5 million by 2030. Medical comorbidities such as cardiovascular disease, diabetes, lung cancer, skeletal muscle dysfunction, osteoporosis, psychological disturbances, and metabolic syndrome are common among COPD patients and occur across the spectrum of disease severity.

The Standard of Care for moderate COPD starts with daily use of bronchodilators, mostly long-acting muscarinic antagonists (LAMA) and/or long-acting β_2-agonists (LABA). As disease progresses, in particular in patients with frequent exacerbations, bronchodilators are combined with anti-inflammatory drugs such as inhaled corticosteroids (ICS), and phosphodiesterase Type 4 (PDE-4) inhibitors (roflumilast) (12, 13, 14). The major limitations of the existing agents for COPD include modest efficacy and for inhaled corticosteroids an increased risk of respiratory infections including pneumonia, in particular at high doses of potent molecules and in patients with severe COPD. While inhaled corticosteroids have a consistent effect in reducing the risk of moderate COPD exacerbations defined by a COPD deterioration requiring the use of systemic corticosteroids and/or antibiotics, there is no consistent benefit on severe exacerbations requiring hospitalizations. There is increasing evidence that this treatment effect is primarily driven by patients with more that 2% blood eosinophils (15).

Systemic, mostly oral corticosteroids are largely reserved for the treatment of exacerbations given their unacceptable safety profile with heightened concerns for a COPD population. No approved therapeutic agent blocks the decline in FEV_1 over time or modifies the progressive disease course of COPD. Thus there is a high unmet need for more effective treatment of this disease.

Currently, no targeted biological treatments addressing the immunological underpinnings of COPD are approved. In Phase 3 trials, the anti-interleukin (IL-5) mAb mepolizumab showed a modest 18%-20% reduction of exacerbations in COPD patients with high blood eosinophils (16). The anti-IL-5 receptor mAb benralizumab recently announced results from its Phase 3 studies and both studies did not meet the primary endpoint of statistically significant reduction of COPD exacerbations. Details on factors that may have contributed to these results are not publicly available. Data from the Phase 2a trial with benralizumab suggest that the FEV_1 improvement versus placebo averaging 150 mL over time is mainly driven by the subgroup of patients with high blood eosinophils. In this study, no reduction of exacerbations was seen in the per-protocol population, and a numerical, but not statistically significant, reduction of exacerbation was seen in the subgroup of patients with high blood eosinophils (17).

Thus, significant unmet medical needs continue to exist in the growing population of patients with COPD. The main objective for new treatments is to further improve COPD symptoms, lung function, and prevent exacerbations, while optimizing adherence to the treatment.

2.2.1 Dupilumab anti-IL4Rα monoclonal antibody

Candidate gene studies and GWAS have identified IL-4 and IL-13 variants that occur more frequently in COPD patients than in controls (18), and Type 2 gene expression score has been identified in ~20% of COPD patients (19, 20). It is known that dupilumab decreases tissue eosinophils and therefore may improve COPD control in patients with COPD and eosinophilia. Eosinophilic airway inflammation is evident in 20%-40% of COPD patients (21, 7) with increased levels of eosinophils in blood, sputum, and bronchial biopsies reported during acute exacerbations (21, 12). Additionally, through dupilumab's blockade of the IL-13 pathway, it is postulated that dupilumab may play a unique role in treating the mucous hypersecretion and goblet cell hyperplasia which is evident in chronic bronchitis subtype of COPD.

Dupilumab by binding to the IL-4Rα subunit blocks signaling of the signature Type 2 cytokines (IL-4 and IL-13) has a broader impact on Type 2 inflammation and therefore may have an improved potential to treat aspects of COPD inflammation which are driven by Type 2 inflammatory tone.

Dupilumab is currently approved for the treatment of atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyposis (CRSwNP), and is in late stage development for eosinophilic esophagitis. At the time of protocol finalization, dupilumab has been submitted for regulatory approval for asthma in the US and in Europe. In asthma, it has demonstrated satisfactory safety and excellent efficacy in a broad spectrum of asthma patients, including severe asthma patients and previous smokers. The planned Phase 3 program including this study will provide evidence on the efficacy and safety of dupilumab in COPD patients with evidence of Type 2 inflammation as reflected by blood eosinophil counts (≥0.3 Giga/L) at screening.

2.3 BENEFIT/RISK ASSESSMENT

Dupixent® (dupilumab) 150 mg/mL solution for injection is authorized for marketing in over 40 countries worldwide including the United States (US), European Union (EU) (Centralized Procedure), and Japan for the adult moderate-to-severe AD indication. The marketing authorization for treatment of adult AD in the US was approved on 28 March 2017. The European Commission (EC) granted marketing authorization for dupilumab on 26 September 2017 for use in adults with moderate-to-severe AD who are candidates for systemic therapy. Dupilumab was also authorized in the US on 11 March 2019 for use in adolescent patients (≥12 years) with inadequately controlled moderate-to-severe AD. It was also approved as an add-on maintenance treatment for CRSwNP in the US on 26 June 2019 and in the EU on 29 October 2019. Approval was received for dupilumab from the US Food and Drug Administration (FDA) on 19 October 2018 for use in adults and adolescents (≥12 years) with moderate-to-severe asthma. In the EU, the EC issued a positive decision on 07 May 2019 for use in adults and adolescents (≥12 years) with severe asthma with type 2 inflammation. In Japan, dupilumab received Pharmaceuticals and Medical Devices Agency (PMDA) approval on 26 March 2019 for use in adults and adolescents (≥12 years) with severe or refractory bronchial asthma.

Dupilumab has shown clinically relevant benefit in several Type 2 mediated immune disorders including AD, bronchial asthma, CRSwNP, and eosinophilic esophagitis. In patients with moderate to severe uncontrolled asthma, dupilumab reduced the risk of severe exacerbations compared to placebo by 46 to 70%, and consistently improved lung function (FEV_1), including in oral corticosteroid dependent patients with severe asthma, in whom despite a reduction in oral corticosteroid use, an improvement of 220 ml compared to placebo was observed. A subgroup analysis of "COPD-like" patients (eg, patients with age of onset asthma >40, prior smoking history, and post-bronchodilator FEV_1/forced vital capacity [FVC]<0.7) included in the Phase 3 asthma study (Study EFC13579; QUEST) showed similar treatment effects in this subpopulation compared to the overall population.

For dupilumab, the safety data observed so far in completed and currently ongoing studies in AD, CRSwNP, and asthma patients (at the same or higher doses than that proposed for this study) have demonstrated a satisfactory safety profile. Considering the high mortality of COPD patients, all

deaths will be adjudicated. Considering that cardiovascular disease is a frequent and important comorbidity of COPD, cardiac events will also be adjudicated throughout the study. The program will have an Adjudication Committee for the aforementioned events and a Data Monitoring Committee (DMC), which will review the benefit risk including the cardiac safety on a regular basis.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of dupilumab may be found in the Investigator's Brochure, Participant Information Leaflet, Package Insert, Development Safety Update Report or Summary of Product Characteristics.

The Sponsor also recognizes that the "Coronavirus Disease 2019" (COVID-19) pandemic may have an impact on the conduct of clinical trials. The Sponsor will monitor the situation closely and ensure the integrity of the trial conduct and data (see Section 8).

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of dupilumab 300 mg q2w in patients with moderate or severe COPD as measured by • Annualized rate of acute moderate or severe COPD exacerbation (AECOPD).	• Annualized rate of moderate* or severe** COPD exacerbations 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 observation for >24 hours in an emergency department/urgent care facility or resulting in death. For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days.
Key Secondary	
To evaluate the effect of dupilumab 300 mg q2w on • Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) 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 FEV_1 over 52 weeks compared to placebo.	• Change in pre-bronchodilator FEV_1 from baseline to Week 12 compared to placebo. • Change from baseline to Week 52 in SGRQ total score compared to placebo. • Proportion of patients with SGRQ improvement $\geq$4 points at Week 52. • Change in pre-bronchodilator FEV_1 from baseline to Week 52 compared to placebo.
Other Secondary Evaluate the effects of dupilumab 300 mg q2w on lung function assessments.	• Change in pre-bronchodilator FEV_1 from baseline to weeks other than 12 and 52 (ie, Weeks 2, 4, 8, 24, 36, and 44) compared to placebo. • Change in post-bronchodilator FEV_1 from baseline to Week 2, 4, 8, 12, 24, 36 and 52 compared to placebo. • Change in forced expiratory flow (FEF) 25-75% from baseline to Weeks 2, 4, 8, 12, 24, 36, 44, and 52.
Evaluate the effect of dupilumab on moderate and severe COPD exacerbations.	• 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.
Safety and Immunogenicity • To evaluate safety and tolerability. • To evaluate dupilumab systemic exposure and incidence of antidrug antibodies (ADA).	• Adverse events (AEs)/treatment-emergent adverse events (TEAEs). • Potentially clinically significant laboratory abnormalities in hematology, biochemistry and urinalysis. • ADA against dupilumab.

Objectives	Endpoints
Tertiary/exploratory	
To evaluate the drug concentration of dupilumab in serum over time.	Serum functional dupilumab concentrations and PK profile.
To explore the association of biomarkers with treatment response.	• Pharmacodynamic response of selected biomarkers. - Pulmonary and activation-regulated chemokine (PARC). - Eotaxin-3. - Fractional exhaled nitric oxide(FeNO; postbronchodilator). - Total IgE. • Fibrinogen. • Optional: Messenger ribonucleic acid (mRNA) sequencing or whole transcriptome analysis from blood. • Optional: Deoxyribonucleic acid (DNA) for assessment of pharmacogenomic effects. Predictive effects of selected biomarkers on treatment response.
To evaluate the effects of dupilumab compared with placebo on FEV_1 and FVC.	• Annualized loss of lung function as assessed by a FEV_1 slope analysis. • Change from baseline in FVC (% predicted and absolute values in mL) from baseline to Week 12, Week 24 and Week 52.
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 COPD exacerbations assessed by the EXACT over 52 week.
To evaluate the effects of dupilumab compared to placebo on treatment failure requiring background medication change.	• Increase in number of controller medication after exacerbation. • Increase in patient total daily dose of controller medication after exacerbation.

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments used in this study are standard for the evaluation of therapy in patients with COPD.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Multinational, randomized, double-blind, placebo-controlled, parallel groups (2 groups), 52-week Phase 3 study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-to-severe Type 2 inflammatory COPD such as that driven by activation of IL-4, IL-5, and IL-13 on an established LABA, LAMA and/or ICS background therapy (triple therapy unless ICS contraindicated). Study treatments are dupilumab 300 mg q2w or placebo q2w administered during the 52-week treatment period. The study includes 3 study periods.

- Screening period (4 weeks ±1 week).
- Randomized investigational medicinal product (IMP) treatment period (52 weeks ±3 days).
- Post IMP treatment period (12 weeks ±5 days).

Patients who satisfy the inclusion and exclusion criteria will be randomized (1:1) to one of the following IMP treatment period groups to be administered for 52 weeks:

- Dupilumab 300 mg, administered as 1 SC injection q2w.
- Placebo administered as 1 SC injection of placebo matching dupilumab 300 mg.

Randomization will be stratified by country, ICS dose (high dose ICS [yes/no]) at baseline, and smoking status at screening (current smokers or not). As an example, the adult high dose of ICS for fluticasone propionate is >500 mcg (DPI or HFA) or 401-800 mcg (HFA) for Japanese population (please refer to Section 10.18 for definition of high dose for the most common ICS). Alerts will be built into the interactive voice/web response system (IVRS/IWRS) to limit enrolling patients who are current smokers (as defined by smoking status at screening) to less than or equal to 30% or 278 patients out of the total enrolled patients.

Study intervention discontinuation follow-up

Patients who discontinue the study intervention prematurely (prior to completing the 52-week treatment period) will perform, as soon as possible, the early treatment discontinuation (ETD) visit with all assessments normally planned for the end of treatment (EOT) visit, to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment is available. In addition, to allow assessment of patient outcomes over the stipulated study period, patients will be asked and encouraged to complete all remaining study visits, and participate in all safety follow-up assessments according to the visit schedule. For these patients the assessment schedule will be reduced (see Section 1.3.2) and visits during the planned treatment period may be conducted by phone (except for planned EOT) if patient is unable to come in for a site visit. Assessments not completed via phone should be performed at the next scheduled visit.

Post IMP-treatment follow-up:

Upon completing the 52-weeks randomized IMP treatment period, patients will continue their triple background ICS/LABA/LAMA therapy (unless ICS is contraindicated) and enter 12-week safety follow-up period. Adjustment of background medication will be allowed at the discretion of the Investigator as clinically indicated during the post-treatment period.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, placebo-controlled study design where the effects of the IMP are assessed on top of optimized background therapy is considered to be the most appropriate design to explore the efficacy and safety of a novel biologic therapy in COPD. Similar study designs and endpoints have been employed for recent studies with other biologics and are considered "state-of-the-art" for studies in COPD (16, 17). The selection of the dose of IMP and duration of study treatment are explained in Section 4.3 and Section 9.2, respectively.

4.3 JUSTIFICATION FOR DOSE

The proposed dose for this study is dupilumab 300 mg administered SC every other week. This dose has proven to be effective and to have an acceptable safety profile in various Type 2 inflammatory diseases. The 300 mg q2w dose is the approved dose for AD, is an approved dose for asthma in the US, and is the only selected Phase 3 dose for the CRSwNP program, currently ongoing. Efficacy results from the completed pivotal studies in patients with moderate-to-severe asthma demonstrated that the 300 mg q2w dose had a clinically meaningful and statistically significant effect in reducing exacerbations, improving lung function, asthma control and quality of life with a satisfactory safety profile. In addition, dupilumab 300 mg q2w showed a significant steroid-sparing effect while significantly reducing exacerbations and improving lung function in a population of severe corticosteroid-dependent asthmatics.

In the dupilumab asthma program, doses of 200 mg q2w and 300 mg q2w demonstrated comparable efficacy and safety in reducing exacerbations and improving FEV_1 in patients with moderate-to-severe asthma not chronically using concomitant oral corticosteroids (OCS). However, analysis of the exposure-response relationships using descriptive exposure quartile and model-based analyses for these two efficacy endpoints showed that increasing dupilumab exposure resulted in a greater effect for both efficacy endpoints in patients with uncontrolled moderate-to-severe asthma. The lung function improvement and severe exacerbation rate reduction approached a maximum at the exposure of 200 mg and 300 mg q2w, with a 5 to 9% greater reduction in exacerbations for 300 mg q2w. FEV_1 response was also predicted to be better maintained over the dosing interval for 300 mg q2w. In severe OCS-dependent asthma patients, an exposure response relationship was noted at 300 mg q2w, with more patients achieving OCS-free asthma control at the exposure range at 300 mg q2w (mean C_{trough} approximately 70 mg/L) than that at 200 mg q2w (mean C_{trough} approximately 39 mg/L). Furthermore, the 300 mg q2w dose is expected to saturate the target receptor in the vast majority of patients and therefore a higher regimen is not expected to provide additional efficacy.

Considering that the proposed COPD population to be enrolled in this study has the potential for significant risk for morbidity and mortality associated with impairment of their lung function, similar to the patients in the OCS-sparing Phase 3 asthma study (Study EFC13691), the Sponsor is including the 300 mg q2w dose regimen to achieve the optimal benefit/risk ratio in this difficult to treat COPD patient population.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the end of study visit.

The end of the study is defined as completion of the last patient last visit (the End of Study Visit) which will occur at the end of a 12-week safety follow-up period for those patients who complete the study as per protocol.

For patients who permanently discontinue the planned treatment, the recommended follow-up is described in Section 4.1.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be ≥40 to ≤85 years of age, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with a physician diagnosis of COPD who meet the following criteria at screening:

- Current or former smokers with a smoking history of ≥10 pack-years.
  - Current smokers are defined as those patients who are active smokers with ≥10 pack-years of smoking (active smoking includes cigarettes, e-cigarettes, cigars, pipes, etc).
  - Former smokers are defined as those patients who were active smokers with ≥10 pack-years of smoking (active smoking includes cigarettes, e-cigarettes, cigars, pipes, etc) and who have stopped smoking for at least 6 months prior to Visit 1.
- Moderate to severe COPD (post-bronchodilator FEV_1/FVC ratio <0.70 and post-bronchodilator FEV_1 % predicted >30% and ≤70%).
- Medical Research Council (MRC) Dyspnea Scale Grade ≥2.
- Patient-reported history of signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening in the absence of other known causes of chronic cough.
- Documented history of high exacerbation risk defined as exacerbation history of ≥2 moderate* or ≥1 severe** within the year prior to inclusion.

  At least one exacerbation should have occurred while the patient was taking ICS/LAMA/LABA (or LAMA/LABA if ICS is contradicted).

  * Moderate exacerbations are recorded by the Investigator and defined as AECOPD that require either systemic corticosteroids (intramuscular (IM), intravenous, or oral) and/or antibiotics. One of the two required moderate exacerbations has to require the use of systemic corticosteroids.

  ** Severe exacerbations are recorded by the Investigator and defined as AECOPD requiring hospitalization or observation >24 hours in emergency department/urgent care facility.
- Background triple therapy (ICS + LABA + LAMA) for 3 months prior to randomization with a stable dose of medication for ≥1 month prior to Visit 1: (Double therapy: LABA + LAMA allowed if ICS is contraindicated).

I 03. Evidence of Type 2 inflammation: Patients with blood eosinophils ≥300 cells/microliter at Visit 1 (Screening).

Weight

I 04. Body mass index (BMI) ≥16 kg/m^2.

Sex

I 05. Male or Female.

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4], not breastfeeding, and at least one of the following conditions applies:
   - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4),

     OR
   - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the intervention period and for at least 12 weeks after the last dose of study intervention.

Informed Consent

I 06. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Study methodology

E 01. COPD diagnosis for less than 12 months prior to randomization.

E 02. A patient with current diagnosis of asthma or history of asthma according to the Global Initiative for Asthma (GINA) guidelines, or other accepted guidelines.

E 03. Significant pulmonary disease other than COPD (eg, lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, bronchiectasis, Churg-Strauss Syndrome, etc) or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts.

E 04. Cor pulmonale, evidence of right cardiac failure.

E 05. Long-term treatment with oxygen >4.0 L/min OR if a participant requires more than 2.0 L/min in order to maintain oxygen saturation >88%.

E 06. Hypercapnia requiring BiPAP.

E 07. Acute exacerbation of COPD (AECOPD, as defined above in I 02) within 4 weeks prior to or during the screening period.

E 08. Respiratory tract infection within 4 weeks prior to screening, or during the screening period.

E 09. History of, or planned pneumonectomy or lung volume reduction surgery. Patients who are participating in the acute phase of a pulmonary rehabilitation program, ie, who started rehabilitation <4 weeks prior to screening (Note: patients in the maintenance phase of a rehabilitation program can be included).

E 10. Diagnosis of α-1 anti-trypsin deficiency.

E 11. Inability to follow the procedures of the study (eg, due to language problems, psychological disorders) or unable to read, understand and fill out a questionnaire or use an e-Diary without any help.

E 12. Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days prior to Visit 1 or any other biologic therapy (including anti-IL5 mAb) or immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.) as well as other diseases within 2 months or 5 half-lives prior to Visit 1, whichever is longer.

E 13. Exposure to another investigative drug (small molecules as well as monoclonal antibodies) within a time period prior to Visit 1 that is less than 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 1.

E 14. History of systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients.

E 15. Patients receiving medication or therapy that are prohibited as concomitant therapy (see Section 6.5).

E 16. Patient is the Investigator, or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.

E 17. Clinically significant abnormal electrocardiogram (ECG) at randomization that may affect the conduct of the study in the judgment of the Investigator, eg, prolonged QTc interval [male >450 msec, female >470 msec, Fredericia correction].

E 18. A patient with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory (other than COPD), gastrointestinal, cerebrovascular disease/condition, substance and/or alcohol abuse disorder, or history of or current other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to poorly controlled insulin-dependent diabetes, uncontrolled hypertension.

Prior history of malignancy or active malignancy, including lymphoproliferative diseases (except successfully treated carcinoma in-situ of the cervix, non-metastatic squamous cell or basal cell carcinoma of the skin) within 5 years prior to baseline.

E 19. Active tuberculosis or non-tuberculous mycobacterial infection, latent untreated tuberculosis or a history of incompletely treated tuberculosis will be excluded from the

study unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.

E 20. Acute myocardial infarction <6 months from screening visit.

E 21. TIA or stroke <6 months from screening visit.

E 22. Hospitalization for any CV or cerebrovascular event <6 months from screening visit.

E 23. Heart failure NYHA Class III or IV.

E 24. Patients on cardiac medications not on a stable dose during the last 6 months, eg, antiarrythmics, antihypertensives, and antidiuretics, etc. Dose modification of cholesterol-modifying agents and anticoagulants is allowed.

E 25. Cardiac arrhythmias including paroxysmal (eg, intermittent) atrial fibrillation are excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (ie, selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) and stable appropriate level of anticoagulation for at least 6 months may be considered for inclusion.

E 26. Unstable ischemic heart disease or other relevant cardiovascular disorder such as pulmonary embolism, deep vein thrombosis within ≤6 months from enrollment that in Investigator's judgment may put the patient at risk or negatively affect the study outcome.

E 27. Patients who are <80% compliant with controller therapy during screening.

E 28. Previous use of dupilumab.

E 29. Females who are lactating, breastfeeding or who are pregnant.

E 30. Women of childbearing potential (pre-menopausal female biologically capable of becoming pregnant) who (also see Appendix 4, Section 10.4):

- Do not have a confirmed negative serum beta-hCG test at Visit 1 or negative urine pregnancy test at Visit 2.
- Who are not willing to use one of the acceptable forms of effective contraception for the duration of the study as per Table 14 (Appendix 4).
- Postmenopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception.

E 31. Diagnosed active parasitic infection (helminthes), suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.

E 32. History of HIV infection or positive HIV 1/2 serology at Visit 1.

E 33. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per Investigator’s judgment.

E 34. Evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1, significant viral infections within 4 weeks before Visit 1 that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).

E 35. Live, attenuated vaccinations within 4 weeks prior to Visit 1 or planned live, attenuated vaccinations during the study; see Section 10.7 (Appendix 7) for list of prohibited live, attenuated vaccines.

E 36. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc).

E 37. Patients with any of the following result at screening:
- Positive (or indeterminate) HBsAg or
- Positive IgM HBc Ab or
- Positive total HBc Ab confirmed by positive HBV DNA or
- Positive HCV Ab confirmed by positive HCV RNA.

E 38. Clinically significant laboratory tests at screening:
- Alanine transaminase (ALT) >3 times upper limit of normal range (ULN).
- Hemoglobin <10 g/100 mL for male and <9 g/100 mL for female.
- Platelets <100 000/mm3.
- Creatinine ≥150 µmol/L.

E 39. Patients on macrolide (eg, azithromycin) therapy, unless on stable therapy for >12 months.

E 40. Patient who has withdrawn consent before enrollment/randomization.

E 41. Despite screening of the patient, enrollment/randomization is stopped at the study level.

5.3 LIFESTYLE CONSIDERATIONS

The use of e-cigarettes or vaping is not permitted during the conduct of this study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Patients who are eligible for rescreening may be rescreened once during the open screening period of the study for the following reasons only:

- In the case of technical malfunction of equipment.
- Previously did not meet the criteria for participation in the study.

Retesting of eosinophil values is allowed up to three times during the screening period to meet inclusion criteria for showing eosinophil count ≥300 cells/microliter (I 03) before randomization. A patient who is unable to complete a successful spirometry effort as defined by ATS criteria can be retested one additional time during the screening period of the study.

There is no requirement for a waiting period between the screen-failure date and the rescreening date. The IVRS/IWRS report will flag rescreened patients. Patients that are rescreened must sign a new consent form. If subject is rescreened, a different patient identification number will be issued, and all Visit 1 procedures must be repeated.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

Study intervention name	Dupilumab 300 mg q2w	Placebo q2w
Dosage formulation	Dupilumab 300 mg for SC administration is supplied as 150 mg/mL solution in 2.25 mL prefilled glass syringes to deliver 300 mg in 2.0 mL.	Placebo for dupilumab will be provided in identically matched glass pre-filled syringe to deliver 2 mL which will match dupilumab 300 mg.
Unit dose strength(s)/Dosage level(s)	300 mg	Not applicable
Route of administration	Subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive injections.	Subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive injections.
Dosing instructions	Every 14 ±3 days	Every 14 ±3days
Packaging and labeling	Dupilumab will be supplied as one glass pre-filled syringe packed in a patient kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement.	Placebo will be supplied as one glass pre-filled syringe packed in a patient kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement.

6.1.1 Investigational Medicinal Product(s)

The investigational medicinal product (IMP) is administered every 14 ±3 days (q2w) during the 52-week treatment period (Table 2).

Investigational medicinal product (IMP) will be administered by the Investigator/health care professional or designee following clinic procedures and blood collection. Patients should be monitored for at least 30 minutes after administration of all IMP injections. The monitoring period may be extended as per country specific or local site-specific requirements.

Subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive administrations.

The first IMP administration will be done by the Investigator or delegate. The patients are allowed to self-inject IMP at home after at least 1 injection at investigational site, supervised by the Investigator or delegate. To train patients how to prepare and inject IMP the Investigator will

first train the patient at the on-site visit during the treatment period. At this visit the patient will perform the injection under the supervision of the Investigator or delegate. This training must be documented in the patient's study file. Patient injection should only be performed in the abdomen or upper thighs. Patient should also be instructed to monitor for any reaction for at least 30 minutes (or longer per country specific or local site-specific requirements) following injection.

If the patient cannot take all the allocated IMP kits at home (eg. due to a storage issue), the DTP (Direct to Patient) service can be used or the patient may come to the site to pick-up the IMP kits. For doses not given at the study site, diaries will be provided to record information related to the injections. The diary will be kept as source data in the patient's study file.

If the patient is unable or unwilling to administer IMP at home, injections can be performed at the site; or arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site.

6.1.2 Non-investigational Medicinal Product(s)

Background therapy

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).

Formulation: dry powder inhaler (DPI), metered dose inhaler (MDI) or pocket nebulizer.

Route(s) of administration: Oral inhalation.

Dose regimen: As prescribed.

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.

Background therapy will be supplied from the time of randomization on by Sponsor's local affiliate as locally required or by sites. Reimbursement will be provided when deemed necessary and as per country regulation.

Reliever Medication

Reliever medications will be supplied by sites and reimbursed as per country regulation or by Sponsor's local affiliate as locally required.

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.

Formulation: MDI, nebulizer solutions or DPI.

Route of administration: oral inhalation.

Dose regimen: as prescribed.

Study personnel will convert salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use as shown on the following tables:

Table 3 - Reliever medication - Salbutamol/Albuterol nebulizer solution

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
2.5	4
5.0	8
7.5	12
10	16

*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs.

- Example of salbutamol/albuterol nebulizer-to-puff conversion: Patient received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 and 11 AM. Total daily =7.5 mg or 12 puffs.

Table 4 - Reliever medication - Levosalbutamol/Levalbuterol nebulizer solution

Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
0.63	2
1.25	4
2.5	8
3.75	12
5	16

*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs.

- Example of levosalbutamol/levalbuterol nebulizer-to-puff conversion: Patient received 3 levosalbutamol/levalbuterol nebulizer treatments (1.25 mg/treatment) between 7 and 11 AM. Total daily =3.75 mg or 12 puffs.

Table 5 - Reliever medication - Ipratropium or Ipratropium/short-acting β agonists [SABA] nebulizer solutions

Total Daily Dose of Ipratropium (mg) in Ipratropium or Ipratropium/SABA Nebulizer Solutions	Number of Puffs*
0.5	4
1.0	8
1.5	12
2.0	16

*Conversion factor: ipratropium or ipratropium/short-acting β agonists (SABA) nebulizer solution (with 0.5 mg Ipratropium) corresponds to 4 puffs.

- Example of ipratropium or ipratropium/SABA nebulizer-to-puff conversion: Patient received 3 ipratropium or ipratropium/SABA nebulizer treatments (0.5 mg Ipratropium/treatment) between 7 and 11 AM. Total daily =1.5 mg or 12 puffs.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Storage and handling

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP/noninvestigational medicinal product (NIMP) in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

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

The expiry date is mentioned on the IMP labels (when required by country regulation), and storage conditions are written on the IMP labels.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention and NIMP received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention and NIMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention and NIMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of used and unused study interventions are provided in a Pharmacy manual.

Preparation of IMP

Dupilumab or matching placebo in glass pre-filled syringes will be dispensed to the patients.

Responsibilities

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

All IMP/NIMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP/NIMP issued and returned is maintained. For doses not given at study site, the home dosing diary will be used to record injections.

Any quality issue noticed with the receipt or use of an IMP/NIMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.9).

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

Under no circumstances will the Investigator supply IMP/NIMP to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor, the local regulation may apply as well as the participant approval), allow the IMP/NIMP/device to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP/device in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Methods of assigning patients to treatment group

A randomized treatment kit number list will be generated centrally by Sanofi for the IMPs. The IMPs (dupilumab or matching placebo) will be packaged in accordance with the list. The Sanofi Clinical Supply Chain team will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system (IVRS/IWRS). This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the IMPs to the patients. The Investigator obtains treatment kit number at randomization and subsequent scheduled visits via an IVRS/IWRS that will be available 24 hours a day. Patients will be randomized in a 1:1 ratio to receive SC administrations of either:

- Dupilumab 300 mg q2w.
- Matching placebo for dupilumab q2w.

Randomization will be stratified by country, ICS dose (high dose ICS [yes/no]) at baseline, and smoking status at screening (current smokers or not). As an example, the adult high dose of ICS for fluticasone propionate is >500 mcg (DPI or HFA) or 401-800 mcg (HFA) for Japanese population (see Section 10.18 for definition of high dose for the most common ICS). Alerts will be built into the IVRS/IWRS to limit enrolling patients who are current smokers (as defined by

smoking status at screening) to less than or equal to 30% or 278 patients out of the total enrolled patients.

Investigational medicinal products will be dispensed at the study visits summarized in SoA (Section 1.3).

Returned IMP from the patient's home should not be re-dispensed to the participants.

6.3.2 Methods of blinding

Dupilumab and placebo will be provided in identically matched 2 mL pre-filled syringes.
To protect the blind, each treatment kit of 2 mL (dupilumab / placebo) glass pre-filled syringes will be prepared such that the treatments (dupilumab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number.

In accordance with the double-blind design, study patients, Investigators, and study site personnel will remain blinded to study treatment and will not have access to the randomization arm or to the IMP content (dupilumab or placebo) except under circumstances described in Section 6.3.3.

6.3.3 Randomization code breaking during the study

In case of an AE, the code must only be broken in circumstances when knowledge of the IMP is required for treating the patient.

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

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

Patients who are withdrawn from treatment should be encouraged to remain in the study and the Investigator should discuss with them the key visits to attend (see Section 7.2).

6.4 STUDY INTERVENTION COMPLIANCE

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP/NIMP received, dispensed, used, unused and returned/destroyed. The product accountability and inventory form/system is to be updated each time IMP/NIMP is dispensed. It must be established with the Investigator or other personnel designated by the Investigator and countersigned by the Investigator and the monitoring team. The study monitor will periodically check the supplies of the IMP held by the Investigator or pharmacist to verify accountability and inventory.

Treatment kit number has to be recorded on the appropriate page of the electronic Case Report Form (eCRF) and also on the product accountability and inventory form/system.

All used, partially used, or unused treatments will be destroyed at each respective site, after accountability and reconciliation have been performed. The site must not destroy the unused IMP/NIMP unless the Sponsor provides written authorization. Confirmation of destruction will be provided to the Sponsor.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The following concomitant medications are not permitted during the study from screening onwards:

- Use of any biologic agent within 5 half-lives of that compound before study entry (6 months if half-life is not known) and during the course of the study.
- Use of PDE4 inhibitors (roflumilast) and of theophylline during the course of the study unless stable >6 months prior to screening visit.
- New chronic use of macrolide antibiotics (eg, azithromycin) with the exception of AECOPD, in which case macrolides may be used up to 28 days.
- Systemic immunosuppressants (eg, methotrexate, any anti-TNF mAbs, B and/or T-cell targeted immunosuppressive therapies) including chronic use of systemic corticosteroids.
- Intravenous immunoglobulin (IVIG) therapy.
- Live attenuated vaccines, refer to Appendix 7 (Section 10.7).
- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with dose stable 1 month prior to Visit 1).
- Other investigational drugs.

Note: The following is a list of permitted concomitant medications during the study, refer to Section 6.1.2 for expected background therapy and allowed reliever medications.

- Maintenance treatment of COPD with ICS, LABA, LAMA, at a stable dosage.
- Systemic corticosteroids in case of acute exacerbation up to a maximum of 6 weeks.
- Rescue medication with SABA or short acting antimuscarinics (eg, atrovent).

6.6 DOSE MODIFICATION

Not applicable.

6.7 INTERVENTION AFTER THE END OF THE STUDY

Upon completion of the treatment period (52 weeks), or after early termination, study drug will no longer be provided to participants.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Withdrawal of consent for treatment (ie, treatment discontinuation at patient request) should be distinguished from (additional) withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up (eg, medical record checks). The site should document any case of withdrawal of consent.

7.1 DISCONTINUATION OF STUDY INTERVENTION

The IMP should be continued whenever possible.

In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF.

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant remains in the study to be evaluated for as per Section 1.3.2 (see the SOA for data to be collected at the time of discontinuation of study intervention).

Permanent intervention discontinuation is any intervention discontinuation associated with the definitive decision from the Investigator not to re-expose the patient to the IMP at any time during the study, or from the patient not to be re-exposed to the IMP whatever the reason.

List of criteria for permanent discontinuation of study intervention

All efforts should be made to document the reason(s) for discontinuation of study intervention and this should be documented in the eCRF.

Patients must be withdrawn from the study intervention for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation on the study intervention would be detrimental to the patient's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Any code broken requested by the Investigator will lead to permanent discontinuation of study intervention.
- Pregnancy.

- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (see Section 10.16, Appendix 16).
- Serum ALT >3 ULN and Total Bilirubin >2ULN (see Section 10.6, Appendix 6).
- Serum ALT >5 ULN if baseline ALT ≤2 ULN or ALT >8 ULN if baseline ALT >2 ULN (see Section 10.6, Appendix 6).
- If the patient misses more than 3 consecutive doses, the patient will be permanently discontinued from the study intervention.

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

See the SoA (Section 1.3.2) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Handling of participants after permanent study intervention discontinuation

Patients who discontinue the study intervention prematurely (prior to completing the 52-week treatment period) will perform, as soon as possible, the ETD visit with all assessments normally planned for the EOT visit (Visit 16), to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment is available. In addition, to allow assessment of patient outcomes over the stipulated study period, patients will be asked and encouraged to complete all remaining study visits, and participate in all safety follow-up assessments according to the visit schedule with a ±5-day window. For these patients the assessment schedule will be reduced (see Section 1.3.2) and visits during the planned treatment period may be conducted by phone (except for planned EOT) if patient is unable to come in for a site visit. Assessments not completed via phone should be performed at the next scheduled visit.

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion (ie, EOS, see Section 1.3), or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Patients who discontinue early from treatment may be asked to return to the clinic to have additional antidrug antibody (ADA) samples collected for analysis based on the overall assessment of antibody titers and/or clinical presentation at the time of discontinuation.

All cases of permanent discontinuation of study intervention should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation of study intervention

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

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

- Infections or infestations that do not respond to medical treatment.
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix 6 (Section 10.6).

If a patient is unable to return to clinic for a given visit within the specified visit window, patient should follow-up with all visit follow-up procedures planned for the subsequent visit (excluding randomization and EOT). If more than 12 weeks since last on-site scheduled visit, then unscheduled visit is required within 3 weeks of missed scheduled visit (eg, if missed scheduled visit at Week 24, then unscheduled visit must be performed by Week 27; if missed scheduled visit at Week 36, then unscheduled must be performed by Week 39). All the assessments of the missed scheduled on-site visit will need to be carried out at the unscheduled visit.

For all temporary discontinuations of study intervention, duration must be recorded by the Investigator in the eCRF. Following a temporary interruption or missed dose, the IMP treatment should be reinitiated at the next scheduled dose, maintaining the original dose.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- See SoA (Section 1.3.2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Patients who withdraw from study treatment (prior to completing the planned duration of IMP treatment) will perform the ETD visit and will be asked and encouraged to complete all remaining study visits. Patients who withdraw from the study during the post-treatment phase should be encouraged to return for the EOS visit (for details see Section 1.3.2 and Section 7.1.1). The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

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

In addition, a patient may withdraw his/her consent to participate in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

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

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a systemic drug concentration sample, if appropriate, and the Post treatment Period Visits.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

In light of the public health emergency related to COVID-19 (or in case of any other pandemic requiring public health emergency), the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, eg, phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff. Implementation of such mechanisms may differ country by country, depending on country regulations and local business continuity plans. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 (or any other pandemic) will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

8.1 EFFICACY ASSESSMENTS

8.1.1 Disease-specific efficacy measures

8.1.1.1 Severity of COPD exacerbations as defined by the protocol

"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 observation for >24 hours in emergency department/urgent care facility or resulting in death.

All other exacerbations will be classified as "mild".

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

Clinical symptoms of exacerbations of COPD

In addition to the protocol-defined exacerbations of COPD listed above, clinical signs and symptoms of exacerbations of COPD will be captured in the eCRF (including, but not limited to increase in dyspnea, increase in wheezing, increase in cough, increase in sputum volume and/or increase in sputum purulence).

Management of exacerbations of COPD

Exacerbations of COPD should be treated as deemed necessary by the Investigator.
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. 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.

Protocol defined COPD exacerbation events are collected as efficacy endpoints via the exacerbation eCRF. These events should not be reported as AEs unless they fulfill a seriousness criterion.

8.1.1.2 Spirometry

Spirometry at clinical site visits should be performed in accordance with the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (22) and prior to administration of investigational product.

For pre-bronchodilator measured parameters, including FEV_1, 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.

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

8.1.2 Clinical outcome assessments

8.1.2.1 Patient reported outcome questionnaires

At screening (Visit 1), patients will be issued an electronic diary. Patients will be instructed and trained by members of the clinical staff on the use of the device, and written instructions on the use of the electronic device will be provided to the patients. Recorded information is downloaded from this device on the other indicated days (Section 1.3).

On a daily basis during screening and treatment, the patient will use an electronic diary to:

- Respond to the COPD exacerbation and symptom scale questions of the EXACT tool.
- Record use of established controller inhalation therapy.

The electronic diary will be used for other patient related questionnaires such as SGRQ from the protocol.

In the Post IMP Treatment Period, the patient's response in the electronic diary will not be recorded daily; electronic questionnaires will only be administered at on-site visits as outlined in the SoA.

Patient-reported outcome questionnaires at a site visit should be completed prior to any other assessments or procedures.

8.1.2.1.1 St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire (SGRQ [23, 24]) is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation. A global score ranges from 0 to 100. Scores by dimension are calculated for three domains: Symptoms, Activity and Impacts (Psycho-social) as well as a total score. Lower score indicates better quality of life (QoL) (see Appendix 10: St. George's Respiratory Questionnaire, Section 10.10).

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. The SGRQ has been used in a range of disease groups including asthma, COPD and bronchiectasis.

8.1.2.1.2 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 12: Exacerbations of Chronic obstructive pulmonary disease tool [EXACT], Section 10.12). 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).
- Scared or worried (1 item).

Development and validation history of the tool is consistent with guidelines proposed by the FDA, EMA and well-known measurement principles. The EXACT total score assesses COPD exacerbations. The higher the score, the more severe are the symptoms.

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 RS-Total score represents respiratory symptom severity, overall. Three subscales can be used that assess: 1) breathlessness (RS-Breathlessness), 2) cough and sputum (RS-Cough and Sputum), and 3) chest-related symptoms (RS-Chest Symptoms). The higher the score the more severe are the symptoms.

8.1.2.1.3 The 5-level Euro Quality of Life-5 Dimension questionnaire (EQ-5D-5L)

EQ-5D-5L is a standardized health-related QoL questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. EQ 5D is designed for self-completion by patients. The EQ-5D consists of a descriptive system and the EQ Visual Analog Scale (VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, (Appendix 14, see Section 10.14).

8.1.2.2 Other clinical outcome assessments

8.1.2.2.1 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 (25). It comprises

4 domains: 1) Degree of pulmonary impairment (FEV_1); 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 13, Section 10.13).

8.2 SAFETY ASSESSMENTS

The same safety assessments will be applied across both arms.

Adverse events, including SAEs and adverse events of special interest (AESI), will be collected at every visit. The assessments for AE, SAE and AESI are described in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

A complete physical examination will include 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.

Refer to Section 1.3 for the schedule of physical examinations performed throughout this study.

Investigators should pay special attention to clinical signs related to previous serious illnesses or signs of infection.

Any new clinically significant finding or worsening of previous finding should be reported as a new adverse event.

8.2.2 Vital signs

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate will be measured at screening, baseline 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 EOT/EOS visits. Refer to Section 1.3 for the schedule of vital signs performed throughout this study.

8.2.3 Electrocardiograms

Recording of a standard 12-lead ECG will be performed at the site. Refer to Section 1.3 for the schedule of ECG performed throughout this study. 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; the triplicate ECGs are required. Refer to ECG reading manual for more details. All ECG recordings will be centrally read by independent experts.

8.2.4 Clinical safety laboratory assessments

The clinical laboratory tests are planned to be conducted at a central laboratory.

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 98 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

The clinical laboratory parameters that will be measured are described in Appendix 2: Clinical laboratory tests (Section 10.2). Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix 6: Liver and Other Safety: Suggested Actions and Follow-up Assessments (Section 10.6).

For patient(s) who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes (Appendix 17: Future Use of Samples, see Section 10.17.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting (Section 10.3).

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following

up AEs that are serious, considered related to the IMP or study procedures, or that caused the participant to discontinue the IMP (Section 7).

8.3.1 Adverse event of special interest

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

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described in Section 8.3.2, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF. If an SAE or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe injection site reactions lasting longer than 24 hours, occurs in a patient, blood samples should be collected for determination of functional dupilumab concentration, and ADA assessment at or near the onset and completion of the occurrence of the event, if possible (see Section 8.5.3 for details).

- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms).
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Appendix 15, Section 10.15).
- Severe injection site reactions that last longer than 24 hours.
- Any infection meeting at least one of the following criteria:
  - Any serious infection (SAE).
  - Requires parenteral (intravenous, intramuscular, subcutaneous) antimicrobial therapy.
  - Requires oral antimicrobial therapy for longer than 2 weeks.
  - Is a parasitic infection.
  - Is an opportunistic infection (see Appendix 16, Section 10.16).

Note: antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents

- Any severe type of conjunctivitis or blepharitis.
- Keratitis.
- Significant ALT elevation:
  - ALT >5 × the upper limit of normal (ULN) in patients with baseline ALT ≤2 × ULN, or
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP.
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.

  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix 4 [Section 10.4]).
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Symptomatic overdose (serious or nonserious) with IMP/NIMP.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form and symptoms, if any, entered on separate adverse event forms.
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the maximum daily dose as specified in a drug label, within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form and symptoms, if any, entered on separate adverse event forms.

Asymptomatic overdose should also be reported on the overdose form.

8.3.2 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3), or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

All SAEs and AESI will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.3 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and non-serious AEs of special interest (as defined in Section 8.3.1), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.5 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.6 Pregnancy

See AESI (Section 8.3.1).

8.3.7 Adjudication Committee

Adjudication will be performed by experts independent of sponsor for the evaluation of whether deaths, cardiovascular SAEs and respiratory SAEs meet criteria for certain safety 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.

8.3.8 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

In this study, some AEs are considered related to the underlying condition. Specifically, for patients with COPD worsening of underlying condition is not considered an AE unless it meets serious criteria as defined in Appendix 3 (Section 10.3).

8.3.9 Guidelines for reporting product complaints / medical device incidents (including malfunctions)

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

Symptomatic overdose is an AESI (defined in Section 8.3.1). No antidote is available for dupilumab.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically.
3. Obtain a serum sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

8.5.1 Sampling time

Blood samples will be collected for determination of functional dupilumab and anti-dupilumab antibodies in serum as specified in the SoA (Section 1.3). Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. The date and time of collection should be recorded in the patient e-CRF.

8.5.2 Handling procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of systemic drug concentration and ADA is provided in Table 6.

Table 6 - Summary of handling procedures for dupilumab

Sample type	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Blood sample volume	5 mL	5 mL
Anticoagulant	None	None
Blood handling procedures	See Operational Manual	See Operational Manual
Serum aliquot split	2 aliquots	2 aliquots
Storage conditions	<6 months: below -20°C <24 months: below -80°C (preferred)	<6 months: below -20°C <24 months: below -80°C (preferred)
Serum shipment condition	In dry ice	In dry ice

8.5.3 Bioanalytic method

Serum PK and ADA samples will be assayed using validated methods as described in Table 7.

Table 7 - Summary of bioanalytical methods for dupilumab and anti-dupilumab antibodies

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

ELISA=enzyme-linked immunosorbent assay.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Note: In case of a suspected SAE or any AESI event like anaphylactic reactions or systemic hypersensitivity that may be related to IMP and require treatment, or severe and serious injection site reactions lasting more than 24 hours, if feasible, additional blood samples may be collected for the determination of functional dupilumab concentration and ADA assessment at or near the event. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled systemic drug concentration page in the eCRF must be completed as well. If necessary for safety monitoring, additional ADA samples may be collected after the EOS visit until resolution of SAE or AESI.

Specifically for PK, any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6 PHARMACODYNAMICS

8.6.1 Pharmacodynamic variables/biomarkers

- Pharmacodynamic response of selected biomarkers.
  - PARC.
  - Eotaxin-3.
  - FeNO (postbronchodilator).
  - Total IgE.
  - Fibrinogen.
- Serum/plasma for archival purposes.

For timing of PD sample collection refer to SoA (Section 1.3).

Assay methodologies are briefly summarized below. More detailed information on the collection, handling, transport, and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate laboratory manual.

Specific procedures for collection, storage and shipping of samples collected for pharmcodynamics will be provided in a lab manual.

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. Blood eosinophil and neutrophil counts will be measured at timepoints additional to hematology (Section 1.3).

Plasma/serum biomarkers

PARC will be assayed using a validated enzyme immunoassay.

Fibrinogen assay: (development of immunoassay method ongoing).

Eotaxin-3 will be measured in heparinized plasma with a validated enzyme immunoassay.

Total IgE will be measured with a quantitative method (eg, Phadia ImmunoCAP) approved for diagnostic testing.

Exhaled nitric oxide

FeNO will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be done after pre-bronchodilator spirometry and before post bronchodilator spirometry. Further details on the procedure for measuring exhaled nitric oxide with NIOX will be provided in a separate instruction manual.

8.7 PHARMACOGENOMICS

Pharmacogenetic/Pharmacogenomic testing is optional and voluntary. Written informed consent must be obtained before sampling.

For those patients who consent to the optional pharmacogenetic/pharmacogenomic sample collection section of the informed consent form (ICF), blood samples for exploratory genetic analysis of DNA or RNA will be collected at the study visit as specified in the SoA (Section 1.3), and these samples will be stored for future analysis. Specific procedures for collection, storage and shipping of pharmacogenetic/pharmacogenomic samples will be provided in a lab manual.

For patient(s) who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes (Appendix 17: Future use of samples, see Section 10.17).

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

8.8 BIOMARKERS

Pharmacodynamic and pharmacogenetics biomarkers are described in Section 8.6.1 and Section 8.7, respectively.

8.9 HEALTH CARE RESOURCE UTILIZATION

A questionnaire of health care resource utilization (reliever medication, physician visit, hospitalization, emergency or urgent medical care facility visit, sick leaves including loss of usual activity days) will be collected by the Investigator for all participants throughout the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The statistical hypotheses used to test dupilumab 300 mg q2w against placebo on the primary endpoint of annualized rate of moderate-to-severe COPD exacerbations over the 52-week treatment period are as follows:

- Null hypothesis: $r_{dupilumab}/r_{placebo} = 1$.
- Alternative hypothesis: $r_{dupilumab}/r_{placebo} \neq 1$.

Where $r_{dupilumab}$ and $r_{placebo}$ represent exacerbation rate in the dupilumab and placebo groups, respectively.

The statistical hypotheses used to test dupilumab 300 mg q2w against placebo on the key secondary endpoint of pre-bronchodilator FEV1 from baseline to Week 12 are as follows:

- Null hypothesis: $c_{dupilumab} = c_{placebo}$.
- Alternative hypothesis: $c_{dupilumab} \neq c_{placebo}$.

Where $c_{dupilumab}$ and $c_{placebo}$ represent change in pre-bronchodilator FEV_1 in the dupilumab and placebo groups, respectively.

The statistical hypotheses to be tested on other key secondary endpoints, change in pre-bronchodilator FEV_1 from baseline to Week 12 and change from baseline to Week 52 in the SGRQ total score compared to placebo, can be specified similarly as those on the change in FEV_1 at Week 12. For the proportion of patients with SGRQ improvement ≥4 points at Week 52, the null hypothesis is the odds ratio of response between the dupilumab and placebo group is equal to 1, while the alternative hypothesis is the odds ratio is unequal to 1.

9.2 SAMPLE SIZE DETERMINATION

The sample size of the study is determined based on power calculations for the primary endpoint of annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period. Assuming the number of exacerbations following a negative binomial distribution with a dispersion parameter of 1, a placebo annualized rate of exacerbations being 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 =0.05. With the addition of an interim analysis, the final alpha may be reduced to 0.049, which maintains approximately 90% power (see Section 9.5 for further details).

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

smoking status at screening (current smokers or not). As an example, the adult high dose of ICS for fluticasone propionate is >500 mcg (DPI or HFA) or 401-800 mcg (HFA) for Japanese population (please refer to Section 10.18 for the most common ICS). Alerts will be built into the IVRS/IWRS to limit enrolling patients who are current smokers (as defined by smoking status at screening) to less than or equal to 30% or 278 patients out of the total enrolled patients.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 8):

Table 8 - Populations for analyses

Population	Description
Screened	All patients who signed the ICF.
Randomized	The randomized population includes all patients with a treatment kit number allocated and recorded in the IRT database, and regardless of whether the treatment kit was used or not. Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population, but will be included in the safety population.
Intent-to-treat (ITT)	All randomized patients analyzed according to the treatment group allocated by randomization.
Efficacy	The ITT population.
Safety	The safety population includes all patients who actually received at least one dose or partial of a dose of the IMP, analyzed according to the treatment actually received. Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For patients on dupilumab but accidentally receive different treatment from the planned, the actual treatment group allocation for as-treated analysis will be the dupilumab group. The pharmacodynamic (PD) analyses will be performed on the safety population.
Pharmacokinetic (PK)	The PK population includes all patients in the safety population with at least one non-missing result for functional dupilumab concentration in serum after first dose of the study treatment. Patients will be analyzed according to the treatment actually received.
Antidrug antibody (ADA)	ADA population includes all patients in the safety population who have at least one non-missing ADA result after first dose of the study treatment. Patients will be analyzed according to the treatment actually received.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock for the interim analysis (see Section 9.5) and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy analyses

Table 9 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary Annualized rate of moderate and severe COPD exacerbations over 52-week treatment period.	The annualized rate of moderate and severe COPD exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 52-week treatment period as the response variable, with the treatment group, region (pooled country), ICS dose (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV_1), 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. Patients who permanently discontinue the study treatment will be encouraged to complete the study as planned and the additional off-treatment exacerbation events up to Week 52 will be included in the primary analysis. Sensitivity analyses for handling missing data may include pattern mixture model by multiple imputation and tipping point analyses. Subgroup analysis To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoints with respect to age, gender, region, race, weight, BMI, smoking status, ICS dose (high dose ICS [yes/no]), disease severity (as % predicted post-bronchodilator FEV_1), number of moderate-or-severe COPD exacerbation events within one year prior to the study, pre-bronchodilator FEV_1, and other factors that will be specified in SAP. Baseline biomarker-by-treatment interaction on the efficacy endpoints will be analyzed to evaluate the potential predictive effect of baseline biomarkers on the treatment response.
Key secondary Change in pre-bronchodilator FEV_1 from baseline to Week 12.	The change from baseline in pre-bronchodilator FEV_1 at Week 12 will be analyzed using mixed-effect model with repeated measures (MMRM). The model will include change from baseline in FEV_1 values up to Week 12 as response variables, and factors for treatment group, age, sex, baseline height, region (pooled country), ICS dose (high dose ICS [yes/no]), smoking status at screening (current smokers or not), visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1, and FEV_1 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 FEV_1 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 FEV_1 values will be included in the analysis. Sensitivity analyses for handling missing data may include pattern mixture model by multiple imputation and tipping point analyses.
Change in pre-bronchodilator FEV_1 from baseline to Week 52.	The change from baseline in pre-bronchodilator FEV_1 at Week 52 will be analyzed in a similar way as change from baseline in pre-bronchodilator FEV_1 at Week 12 and the model will include values up to Week 52 as response variables.
Change in the SGRQ total score from baseline to week 52.	The change from baseline in SGRQ total score at Week 52 will be analyzed in a similar way as change in pre-bronchodilator FEV_1 at Week 52 except that the MMRM model will include the following covariates: treatment group, region (pooled country), ICS dose (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.

Endpoint	Statistical Analysis Methods
Proportion of patients with SGRQ improvement ≥4 points at Week 52.	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 (high dose ICS [yes/no]), smoking status at screening (current smokers or not), and baseline SGRQ total score as covariates. Patients with missing SGRQ total score at Week 52 will be considered as non-responders.
Other secondary Change in pre-bronchodilator FEV_1 from baseline to Weeks other than 12 & 52.	The change in pre-bronchodilator FEV_1 from baseline at other time points will be analyzed in the same way as the change from baseline in pre-bronchodilator FEV_1 at Week 52.
Change in post-bronchodilator FEV_1, change in forced expiratory flow (FEF) 25-75%.	The change in the spirometry parameters from baseline will be analyzed similarly as the change in pre-bronchodilator FEV1 except that the corresponding baseline of the parameter will replace baseline pre-bronchodilator FEV_1 to be adjusted for in the MMRM model.
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 (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. The Kaplan-Meier method will be used to derive the probabilities that a patient would experience event up to specific timepoints for each treatment group.
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.
Exploratory	Analysis of Exploratory endpoints will be described in the SAP finalized before database lock for the interim analysis.

If the primary endpoint is statistically significant at the interim analysis then for the continuous and proportion type endpoints at Week 52, only participants who have the opportunity to reach Week 52 assessments at the time of the interim analysis cut-off date (ie, completed the Week 52 study period or would have completed had they not discontinued) will contribute to the inferential analyses.

9.4.1.1 *Multiplicity considerations*

Multiplicity is considered for performing an interim analysis and for testing multiple endpoints. The overall Type-I error rate will be controlled at the two-sided 0.05 level.

An interim analysis will be performed using the Kim-DeMets spending function (26) when the information fraction for the primary endpoint is ≥0.92 (see Section 9.5). A hierarchical testing procedure will be used for the testing primary, key secondary and other endpoints. The annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period will be first tested with an alpha as determined in Table 12. Only upon rejection of the null hypothesis for the annualized rate of moderate and severe COPD exacerbations can the key secondary endpoint, change in pre-bronchodilator FEV_1 from baseline to Week 12 be tested.

Multiplicity adjustment for the other efficacy endpoints will be described in the study SAP.

9.4.2 Safety analyses

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the Safety Population. The baseline value is defined generally as the last available value before randomization. The treatment emergent adverse event (TEAE) period is defined as the time between the first administration of study medication to the last administration of the IMP +98 days.

Table 10 - Safety analyses

Endpoint	Statistical Analysis Methods
AE, SAE, AE leading to death, AE leading to permanent treatment discontinuation.	Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Proportion of patients with at least one TEAE, treatment emergent SAE, TEAE leading to death, and TEAE leading to permanent treatment discontinuation will be tabulated by treatment group. In addition TEAEs will be described according to maximum intensity and relation to the study drug. AEs that occur outside the treatment-emergent period will be summarized separately.
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.
AESI and other AE groupings	Incidence of each type of AESI and other AE groupings will be tabulated by treatment group. For each type of AESI, the following analysis will be generated. • A summary of the number (%) of patients with - Any TEAE. - Any SAE (regardless of treatment-emergent status). - Any treatment-emergent SAE. - Any AE leading to death. - Any TEAE leading to death. - Any TEAE leading permanent treatment discontinuation. - Any TEAE related to IMP reported by Investigator. - Number of patients with the TEAE per 100 patient-years. - Any TEAE by maximum intensity, corrective treatment, and final outcome. • Kaplan-Meier (K-M) estimates of probability of having at least one TEAE at specific time points, and K-M curve to depict the course of event onset over time. The method to identify AESIs and other AE groupings will be specified in the SAP.
Death	The following deaths summaries will be generated: • Number (%) of patients who died by study period (TEAE, on-study) summarized on the safety population by treatment received. • Death in nonrandomized patients or randomized and not treated patients. Treatment-emergent AE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Endpoint	Statistical Analysis Methods
Laboratory parameters	Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. The following definitions will be applied to laboratory parameters. • 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. • PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage. The proportion of patients who had at least one incidence of PCSA at any time during the TEAE period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

9.4.3 Other analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

Table 11 provides a summary of the planned statistical analyses of the other endpoints.

Table 11 - Other analyses

Endpoint	Statistical Analysis Methods
PK	Serum concentrations of SAR231893 (REGN668) will be summarized for the dupilumab treatment group using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time.
ADA	The incidence of treatment-emergent ADA response for SAR231893 (REGN668) will be provided by treatment groups, including characterization of the response with titers and neutralizing antibody status. Association of ADA with impact on drug concentration profile, efficacy and safety may be explored. ADA analysis will be detailed in the SAP.
PD	For all PD parameters, raw data at each visit, absolute changes from baseline, and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point. Summary plots (mean ± standard error of the mean) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment groups.

Data collected regarding the impact of the COVID-19 or other pandemics on the participants will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 or other events requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

9.5 INTERIM ANALYSES

An interim analysis is planned when the information fraction is ≥0.92 based on follow-up time for the primary endpoint of annualized rate of moderate or severe COPD exacerbations over a 52-week treatment period. All participants will have complete follow-up for the key secondary endpoint of change from baseline in FEV_1 at Week 12. The purpose of this interim analysis is to potentially demonstrate efficacy when ≥92% of the information fraction for the primary endpoint is available, but prior to all patients completing the 52-week treatment period, as COPD is a disease with a high unmet medical need.

To control the overall type I error at α=0.05, the Kim-DeMets approach (26) will be used with the power parameter rho (ρ) determined based on the information fraction observed at the time of the interim analysis and to maintain an α=0.049 at the final analysis (Table 12).

Table 12 - Kim-DeMets alpha spending function to control the overall alpha at 0.05

Information fraction	Rho (ρ)	α at interim analysis	α at final analysis
0.92 to <0.93	12	0.018	0.049
0.93 to <0.94	12	0.020	0.049
0.94 to <0.95	13	0.022	0.049
0.95 to <0.96	14	0.024	0.049
0.96 to <0.97	15	0.027	0.049

If the primary endpoint does not demonstrate efficacy at this interim analysis then the study will remain blinded and the primary endpoint will be retested at the final analysis with an α=0.049.

If the primary endpoint demonstrates efficacy at this interim analysis then the rest of the multiplicity-controlled endpoints will be tested with α=0.05. Further details will be provided in the study SAP.

This interim analysis will be performed by independent statisticians that support the DMC and are separated from personnel involved in the trial conduct. The DMC will review the unblinded result of the primary endpoint and will communicate if the criterion for efficacy is met as prespecified in the SAP. The DMC is established and will continue the regular review of unblinded safety data as described in the DMC charter. In the event that statistical significance is demonstrated on the primary endpoint the additional analyses will be performed by the unblinded Sponsor team. To maintain study integrity with respect to the subsequent visits, follow-up and analyses after this interim analysis, a dissemination plan will be written. This plan will clearly identify two independent study teams (blinded team and unblinded team) and provide further details on the unblinding plan. People involved in the conduct of the study (patients, Investigators, Site Staff, and the blinded Study and Project Team) will have no access to unblinded patient level data, individual patient treatment codes, or unblinded tables or figures (see the Dissemination plan for details).

If efficacy at the interim analysis is not demonstrated the database lock for primary 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 of the CSR. Additional data between this database lock and last patient completing last visit will be summarized in a CSR addendum.

If efficacy at the interim analysis is demonstrated, then the interim analysis database lock will be considered the primary analysis for all endpoints. The database lock for final analysis is planned when all patients complete the Week 52 visit or discontinue from the study before Week 52, but may occur when all patients complete the Week 64 visit or discontinue from the study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted, as required by local regulation, to an IRB/IEC and to the Health Authorities (competent regulatory authority) by the Investigator or Sponsor and, where further required by regulation, reviewed and approved by the IRB/IEC and Health Authorities before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.3 Data protection

- All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation). Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.
- Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the PMDA in Japan).
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.4 Committees structure

Study committees

The study data will be reviewed by a DMC and adjudication committee.

10.1.4.1 Data Monitoring Committee (DMC)

A DMC, independent from sponsor will be established for this study. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety

data during the course of the trial, review interim analysis results and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

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

10.1.4.2 Adjudication committee

Adjudication will be performed by experts independent of sponsor for the evaluation of whether deaths, cardiovascular SAEs and respiratory SAEs meet criteria for certain safety 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.

10.1.5 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

10.1.6 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Reference Manual.

10.1.8 Study and site closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

10.1.9 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 13 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 13 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Hematology	To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count and total red blood cell count.
Clinical chemistry	To include creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase.
Routine urinalysis	To include urine dipstick analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
Other tests	Clinical laboratory testing at Screening Visit 1 will include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). In case of results showing HBs Ag (negative), HBs Ab (negative) and HBc Ab (positive), an HBV DNA testing may 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. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- AECOPD unless it meets the criteria for SAE.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE.

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death.

b) Is life-threatening.

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity.

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect.

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor’s representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor’s representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.

The Investigator will submit any updated SAE data to the Sponsor/Sponsor's representative within 24 hours of receipt of the information.

REPORTING OF SAES

SAE reporting to the Sponsor's representative via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Protocol.

SAE reporting to the Sponsor's representative via paper CRF (if eCRF is not available)

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Protocol.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal.
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 14.

Table 14 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable

Highly effective methods that are user independent[a]
• Progestin only Implants • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral Tubal Ligation
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

PREGNANCY TESTING:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test (at Screening). Urine pregnancy tests will be performed monthly subsequently.

Additional pregnancy testing as shown in the SoA (Section 1.3) and as follows.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

COLLECTION OF PREGNANCY INFORMATION:

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

Male participants with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

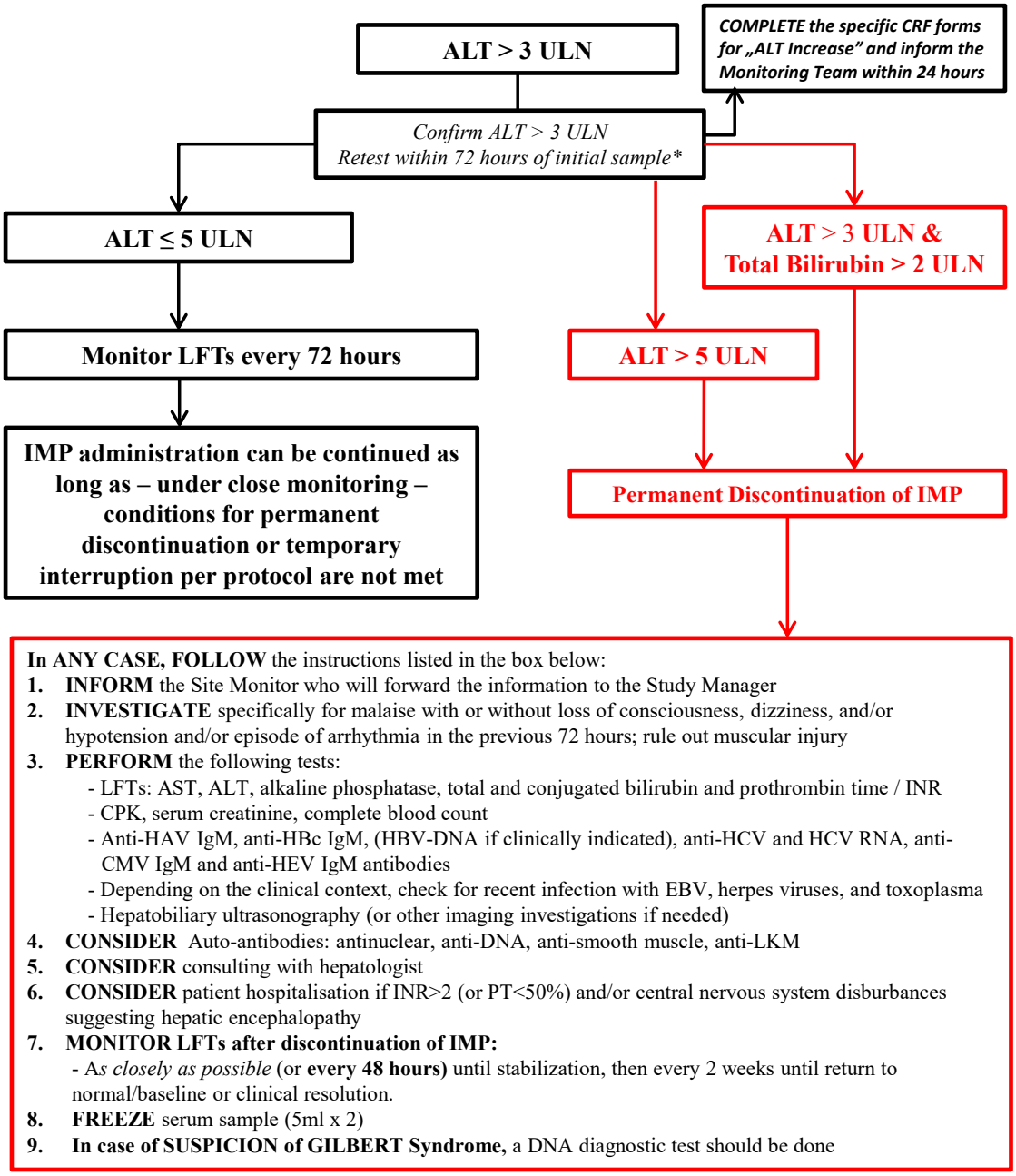
10.5 APPENDIX 5: GENETICS

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

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

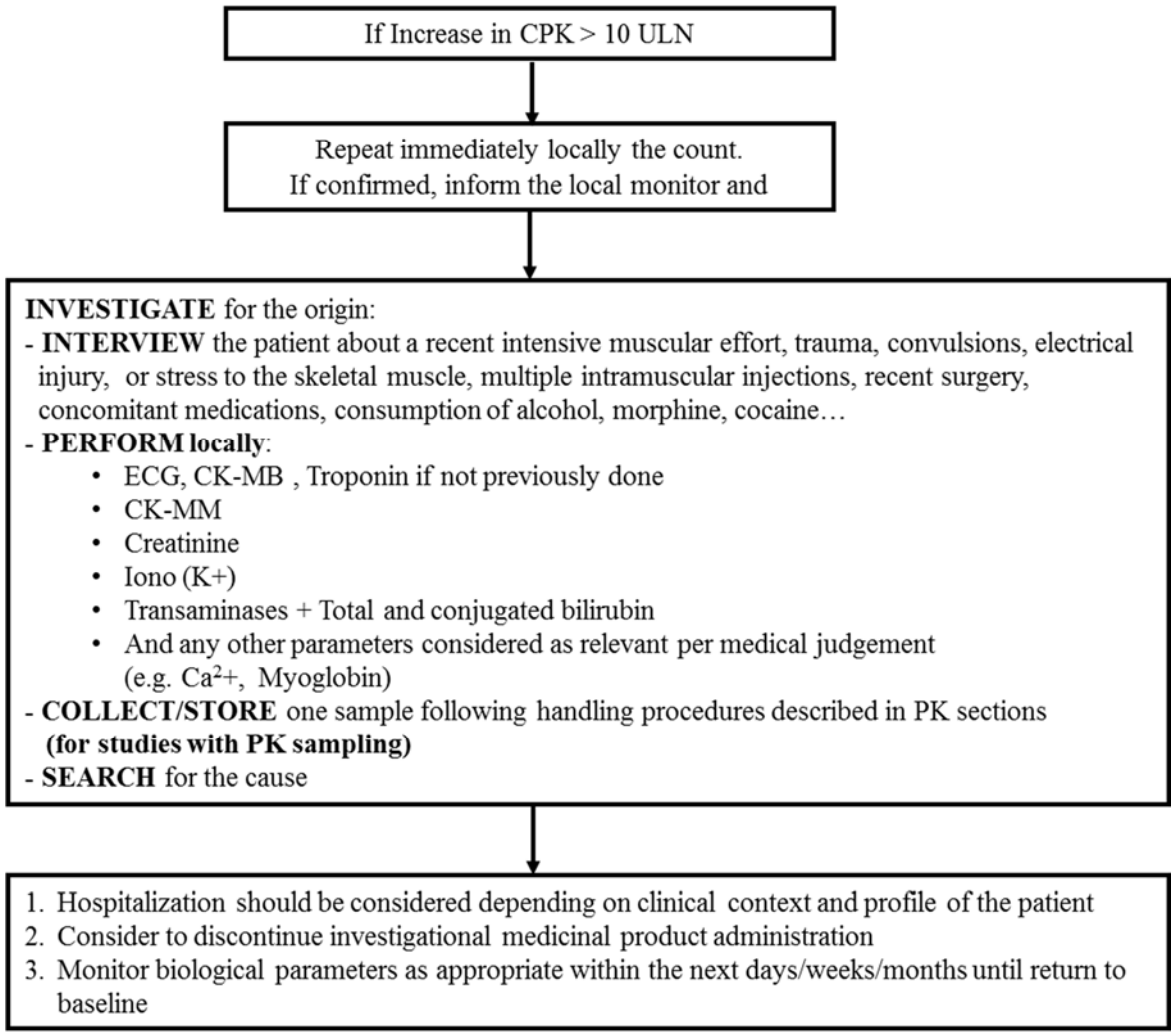
10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

INCREASE IN ALT



*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note: "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit.
The algorithm does not apply to the instances of increase in ALT during screening.
See Section 10.3 for guidance on safety reporting.
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.3 is met.

10.7 APPENDIX 7: LIST OF PROHIBITED LIVE ATTENUATED VACCINES

- Bacillus Calmette-Guérin (BCG) antituberculosis vaccine.
- Chickenpox (Varicella).
- Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted.
- Measles (Rubeola).
- Measles-mumps-rubella (MMR) combination.
- Measles-mumps-rubella-varicella (MMRV) combination.
- Mumps.
- Oral polio (Sabin).
- Oral typhoid.
- Rotavirus.
- Rubella.
- Smallpox (Vaccinia).
- Varicella Zoster (shingles).
- Yellow fever.

This list is indicative and not exhaustive.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.9 APPENDIX 9: ABBREVIATIONS

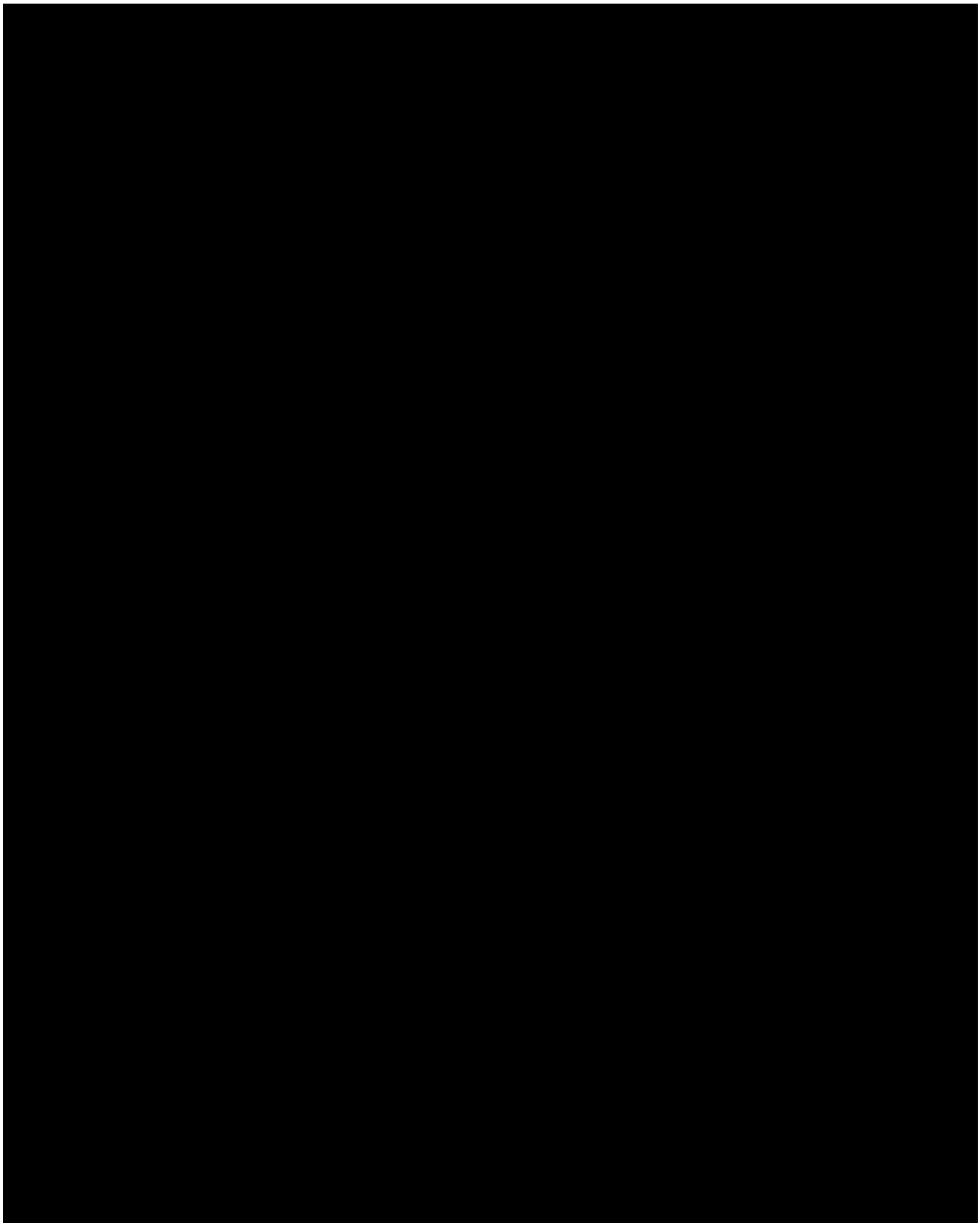
AC:	Audit Committee
AD:	atopic dermatitis
ADA:	antidrug antibody
AE:	adverse event
AECOPD:	acute exacerbation of chronic obstructive pulmonary disease
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANA:	anti-nuclear antibody
AST:	aspartate aminotransferase
ATS:	American Thoracic Society
BCG:	Bacillus Calmette-Guérin
BD:	bronchodilator
BID:	twice daily assessments
BiPAP:	bi-level positive airway pressure
BMI:	Body-Mass Index

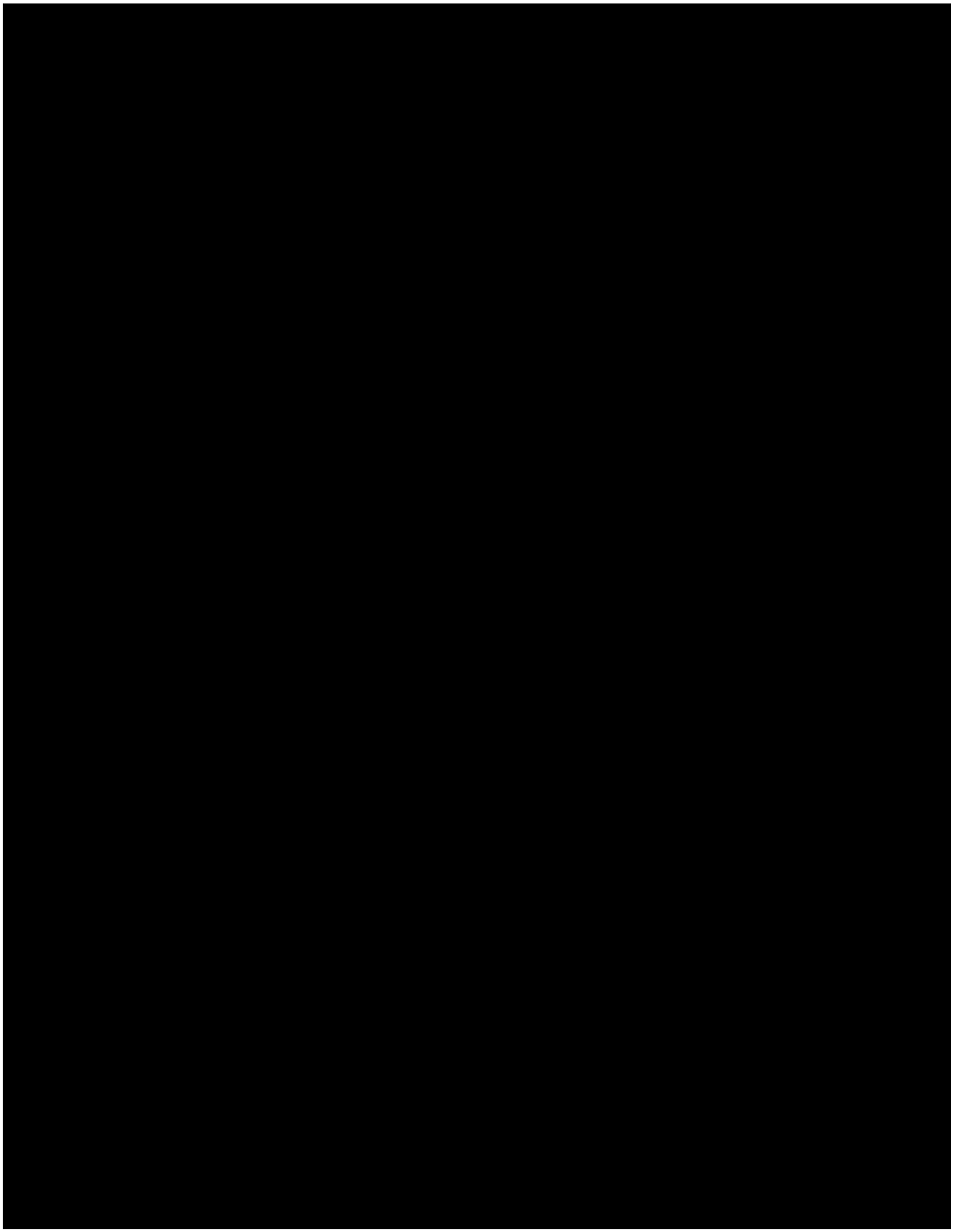
BODE:	Body-mass index, airflow Obstruction, Dyspnea, and Exercise
CAT:	COPD assessment test
CFR:	Code of Federal Regulations
CI:	confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
CONSORT:	Consolidated Standards of Reporting Trials
COPD:	chronic obstructive pulmonary disease
CRF:	Case Report Form
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSR:	clinical study report
CT:	computed tomography
CV:	cardiovascular
DMC:	Data monitoring Committee
DNA:	deoxyribonucleic acid
DPI:	dry powder inhaler
DTP:	Direct to Patient
EC:	European Commission
ECG:	electrocardiogram
eCRF:	electronic Case Report Form
ELISA:	enzyme-linked immunosorbent assay
EOS:	End of Study
EOT:	end of treatment
EQ-5D-5L:	Euro Quality of Life-5 Dimension 5-Level questionnaire
E-RS:	Evaluating Respiratory Symptoms
ETD:	early treatment discontinuation
EU:	European Union
EudraCT:	European Union Drug Regulating Authorities Clinical Trials
EXACT:	Exacerbations of Chronic Pulmonary Disease Tool
FDA:	US Food and Drug Administration
FEF:	forced expiratory flow
FeNO:	fractional exhaled nitric oxide
FEV1:	forced expiratory volume in first second
FSH:	follicle stimulating hormone
FVC:	forced vital capacity
GCP:	Good Clinical Practices
GDPR:	Global Data Protection Regulation
GINA:	Global Initiative for Asthma
GSO:	Global Safety Officer
GWAS:	genome-wide association study
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HFA:	hydrofluoroalkane
HIPAA:	Health Insurance Portability and Accountability Act
HIV:	Human Immunodeficiency Virus
HLGT:	high-level group term
HLT:	high level term

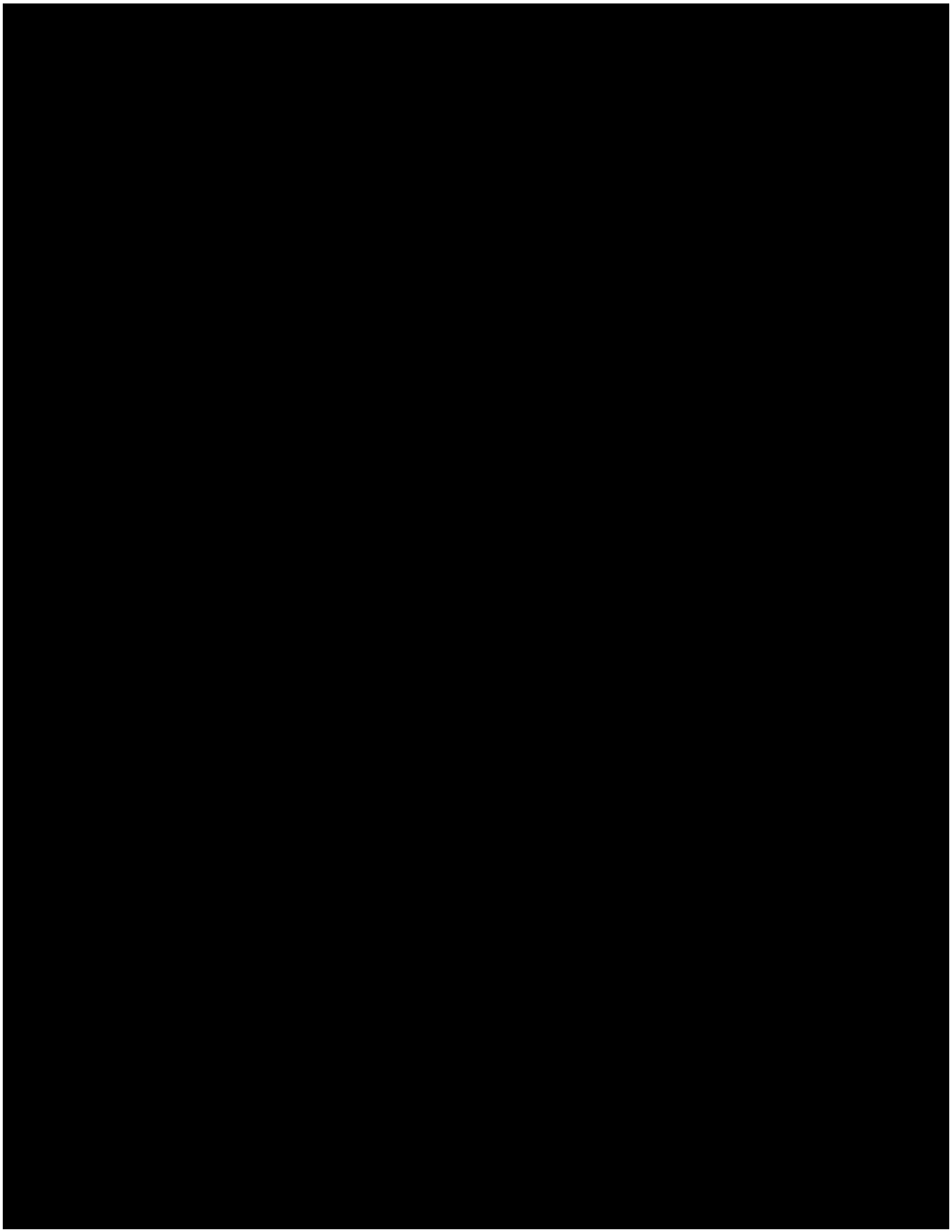
HRT:	hormonal replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS:	inhaled corticosteroid
IEC:	Independent Ethics Committee
IgE:	Immunoglobulin E
IL-13:	Interleukin 13
IL-4:	interleukin 4
IL-4Rα:	Interleukin-4 receptor alpha
IL-5:	Interleukin-5
IMP:	investigational medicinal product
INN:	International Nonproprietary Names
IRB:	Institutional Review Board
IRT:	Interactive Response Technology
ITT:	intent-to-treat
IUD:	Intrauterine device
IUS:	Intrauterine hormone-releasing system
IVIG:	intravenous immunoglobulin
IVRS:	interactive voice response system
IWRS:	interactive web response system
LABA:	long acting beta agonist
LAMA:	long acting muscarinic antagonist
LS:	least square
mAbs:	monoclonal antibodies
MDI:	metered dose inhaler
MMR:	Measles-mumps-rubella
mMRC:	Modified Medical Research Council Dyspnea Scale
MMRM:	mixed-effect model with repeated measures
MMRV:	Measles-mumps-rubella-varicella
MRI:	magnetic resonance imaging
NIMP:	noninvestigational medicinal product
NYHA:	New York Heart Association Functional Classification
OCS:	oral corticosteroids
PARC:	pulmonary and activation-regulated chemokine
PCSA:	potentially clinically significant abnormality
PMDA:	Pharmaceuticals and Medical Devices Agency
PT:	preferred term
SABA:	short-acting β agonists
SAP:	statistical analysis plan
SGRQ:	St. George's Respiratory Questionnaire
SoA:	schedule of activities
SOC:	system organ class
SOP:	standard operating procedure
SUSAR:	suspected unexpected serious adverse reactions

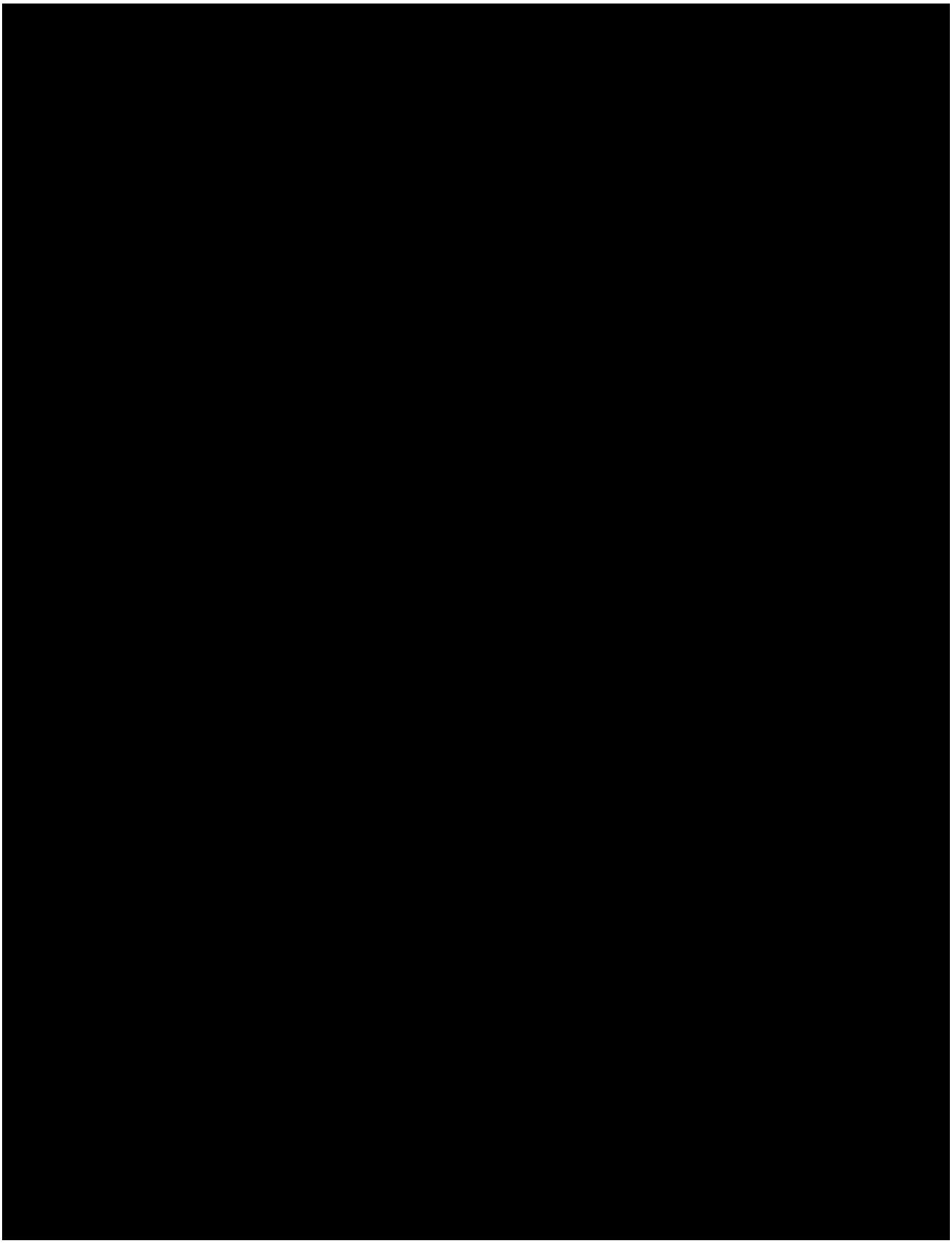
TEAE:	treatment emergent adverse event
TIA:	transient ischemic attack
TNF:	tumour necrosis factor
ULN:	upper limit of normal
US:	United States
VAS:	Visual Analog Scale
WBC:	white blood cells
WHO:	World Health Organization
WOCBP:	woman of childbearing potential
β-hCG:	Human chorionic gonadotropin-beta

10.10 APPENDIX 10: ST. GEORGE'S RESPIRATORY QUESTIONNAIRE









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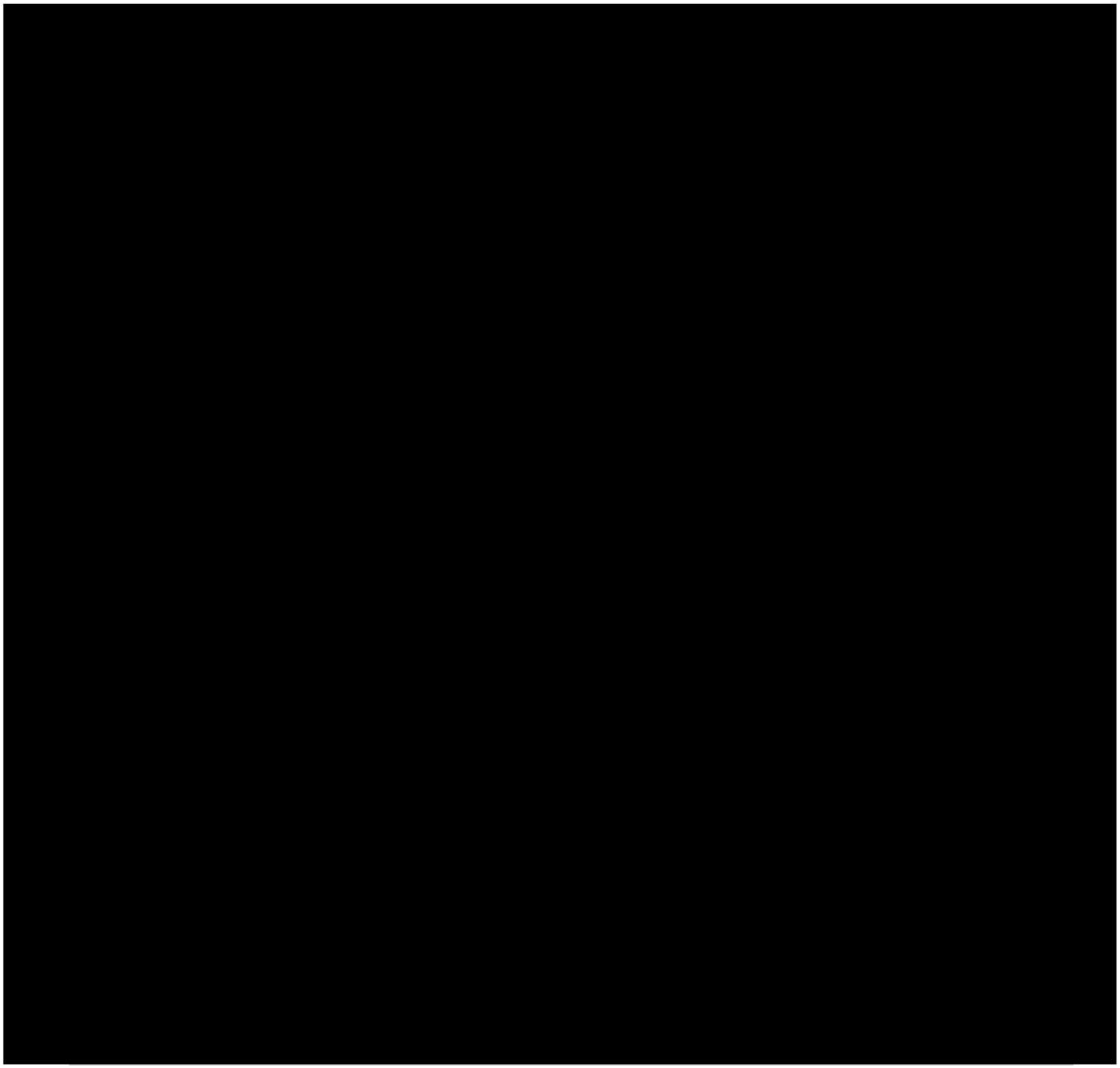
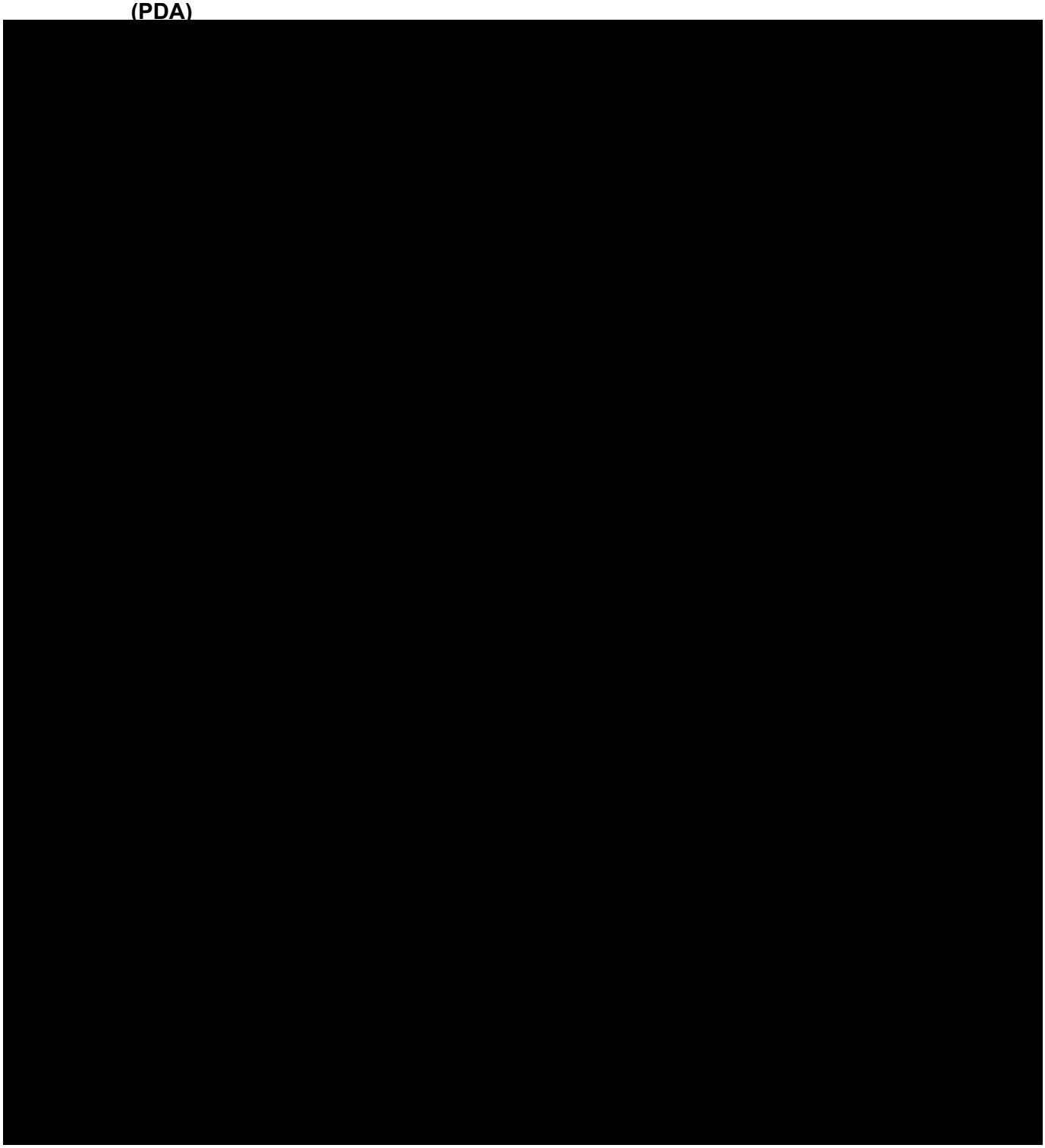
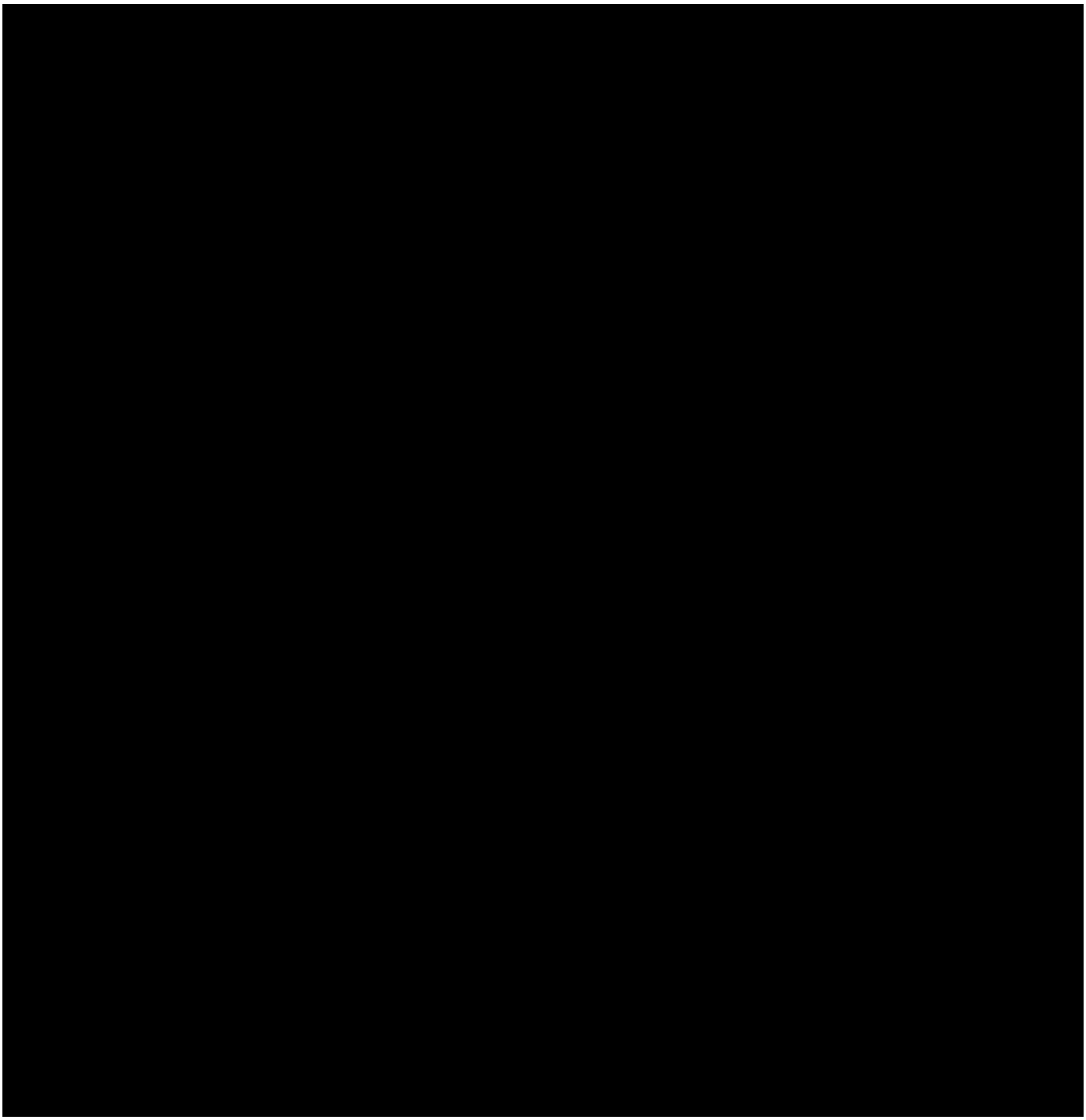
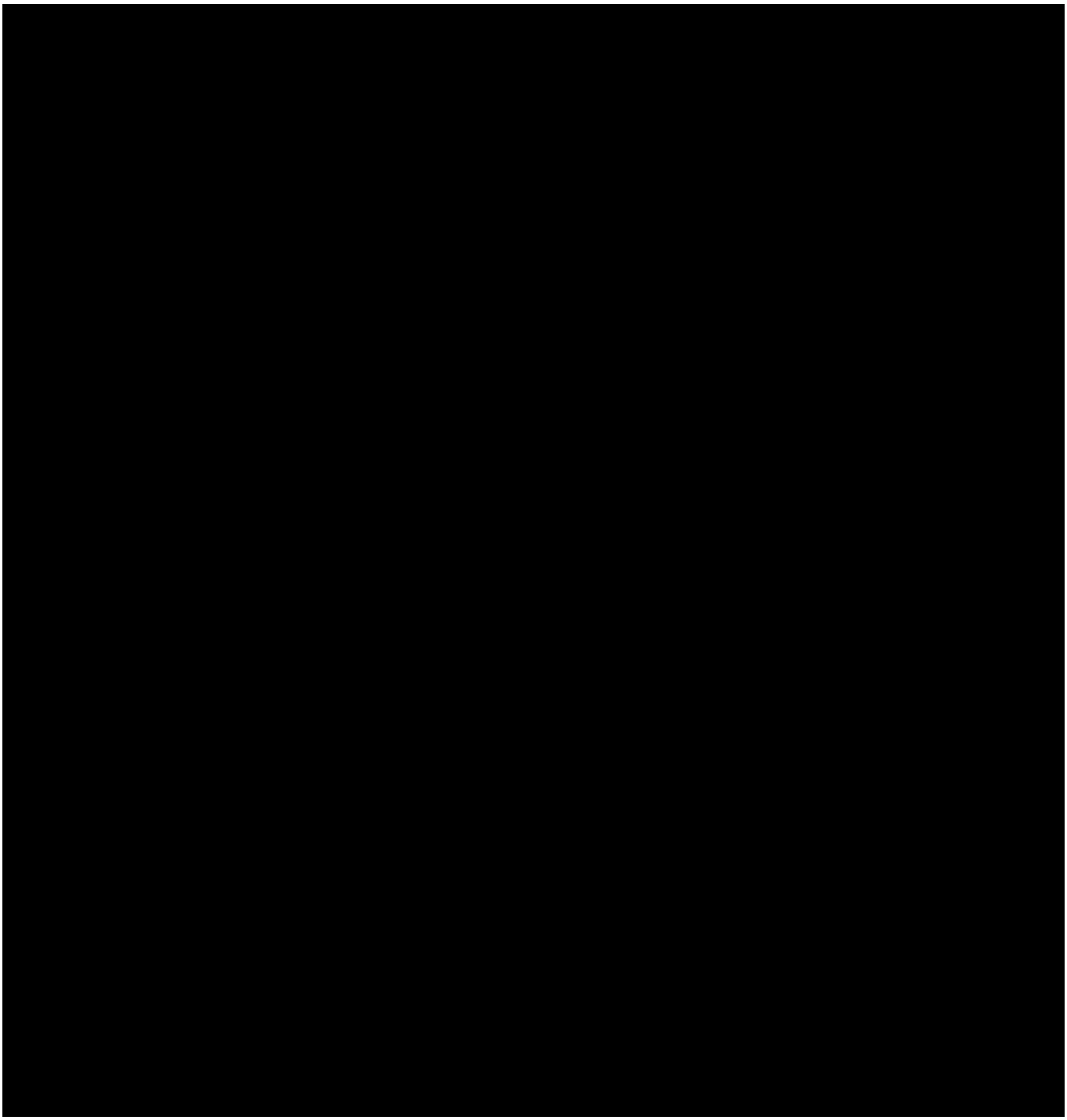


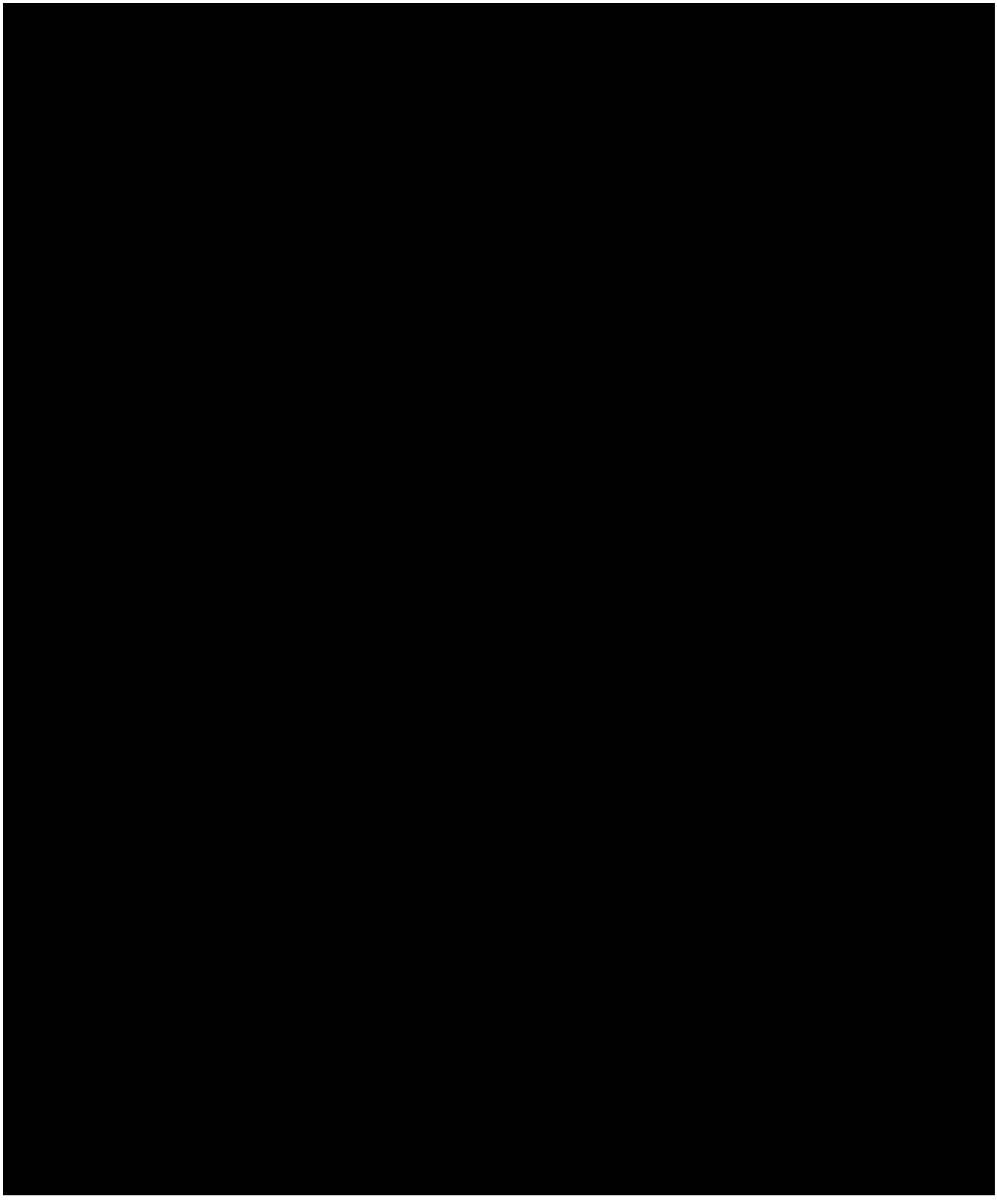
10.11 APPENDIX 11: THE EXACT AS FORMATTED FOR PERSONAL DIGITAL ASSISTANT (PDA)

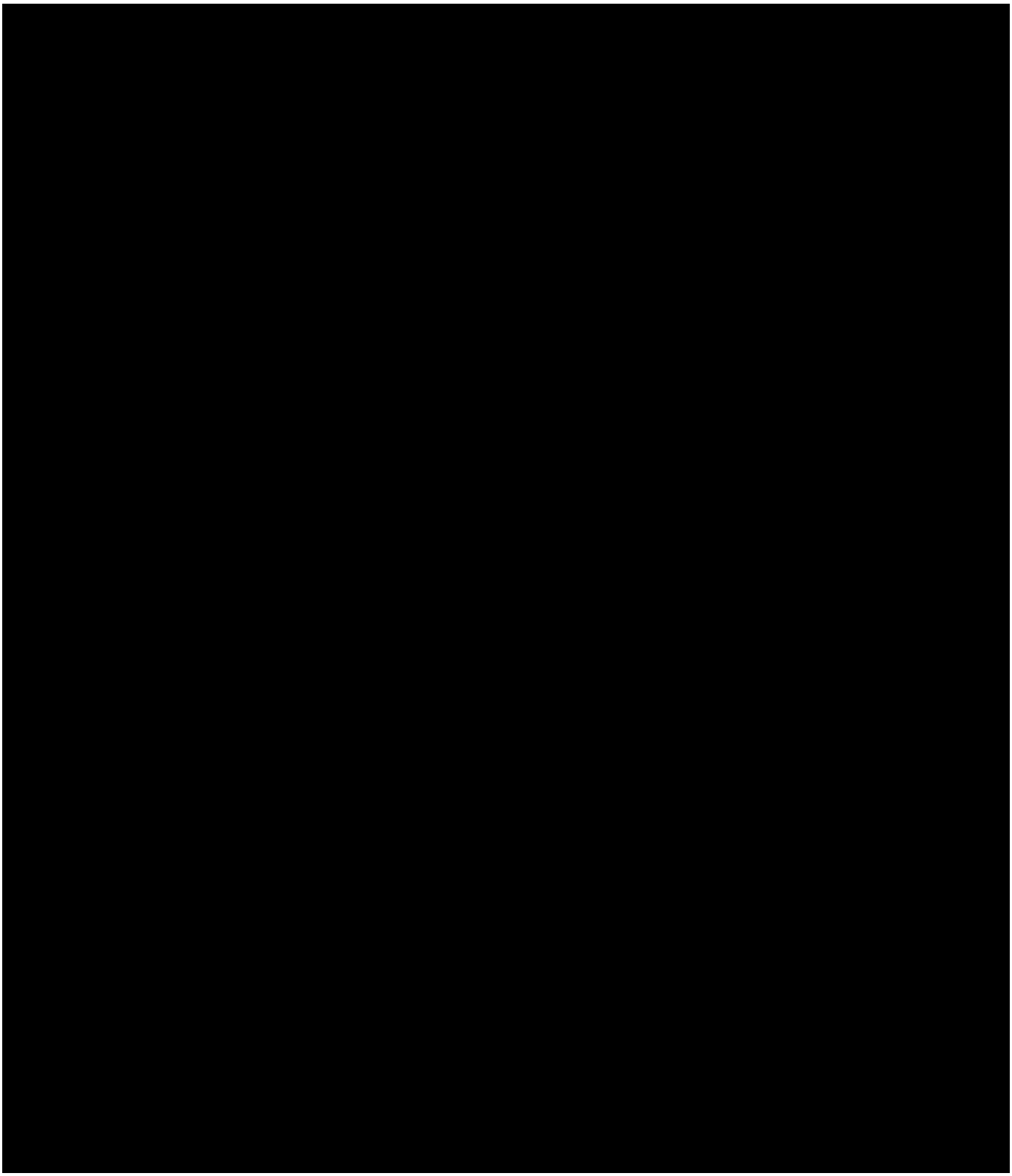


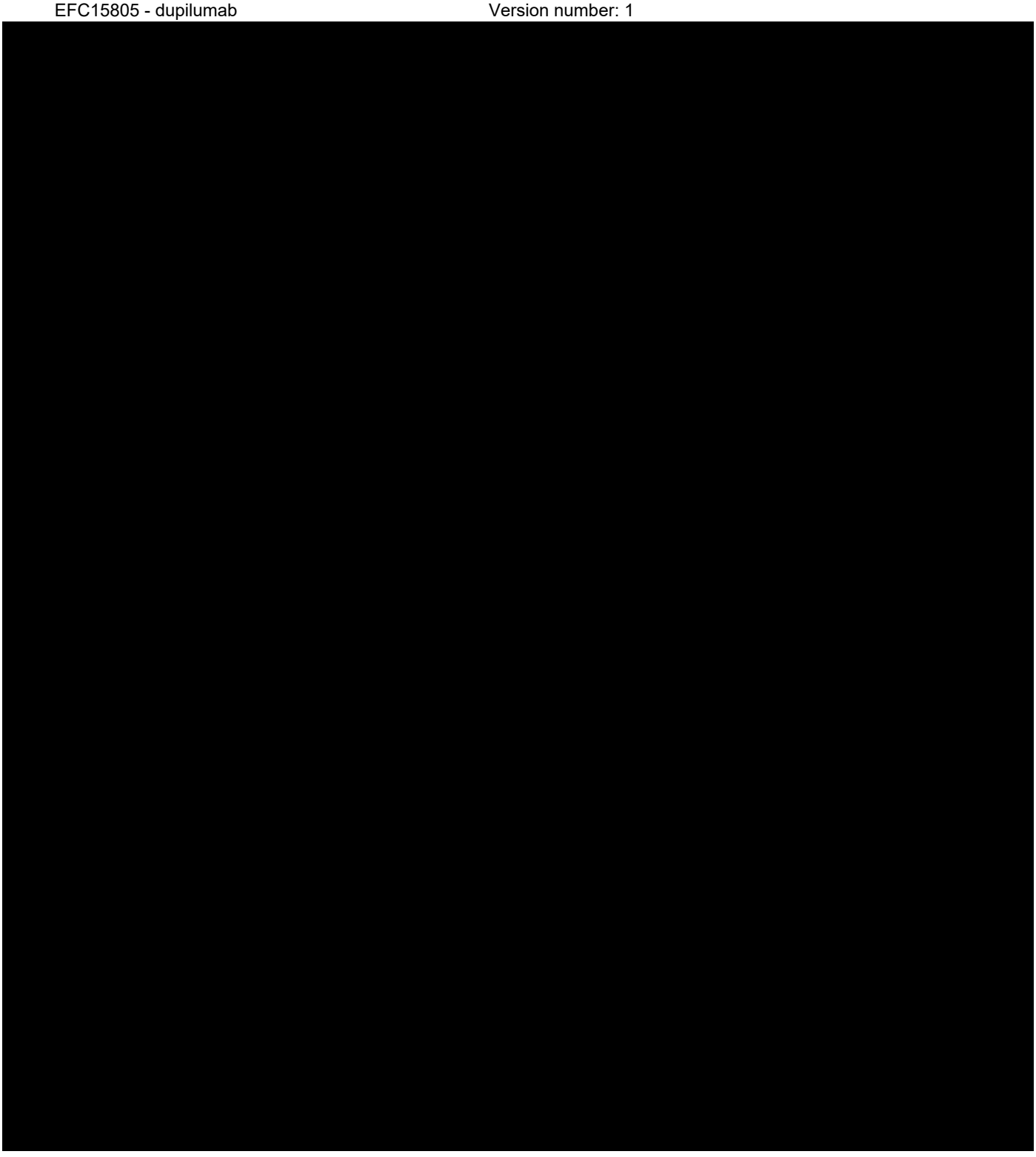




10.12 APPENDIX 12: EXACT QUESTIONNAIRE







10.13 APPENDIX 13: 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

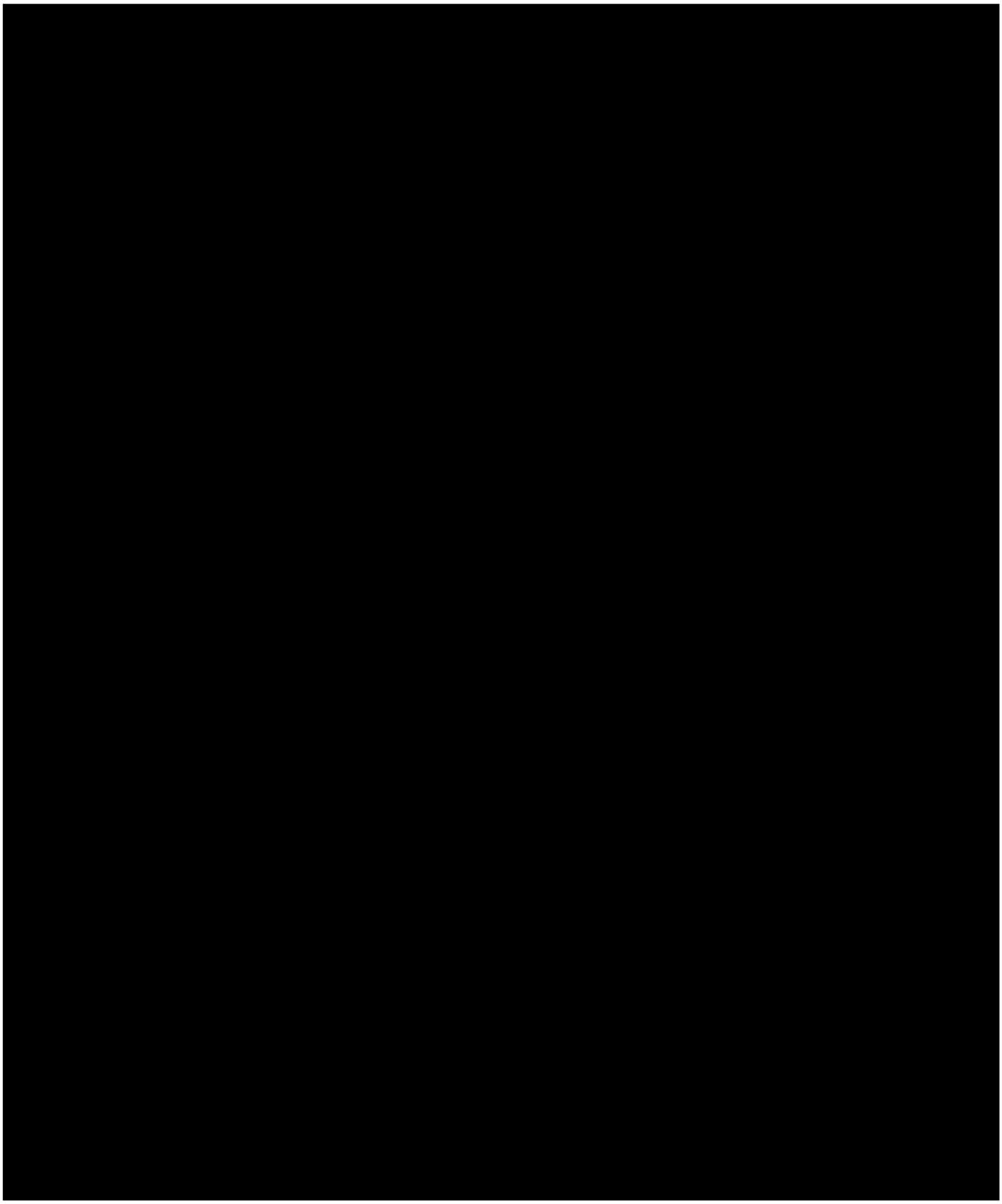
	0	1	2	3
FEV_1% pred	≥65	50-64	36-49	≤35
6MWD (m)	≥350	250-349	150-249	≤149
MMRC	0-1	2	3	4
BMI ($kg.m^{-2}$)	>21	≤21		

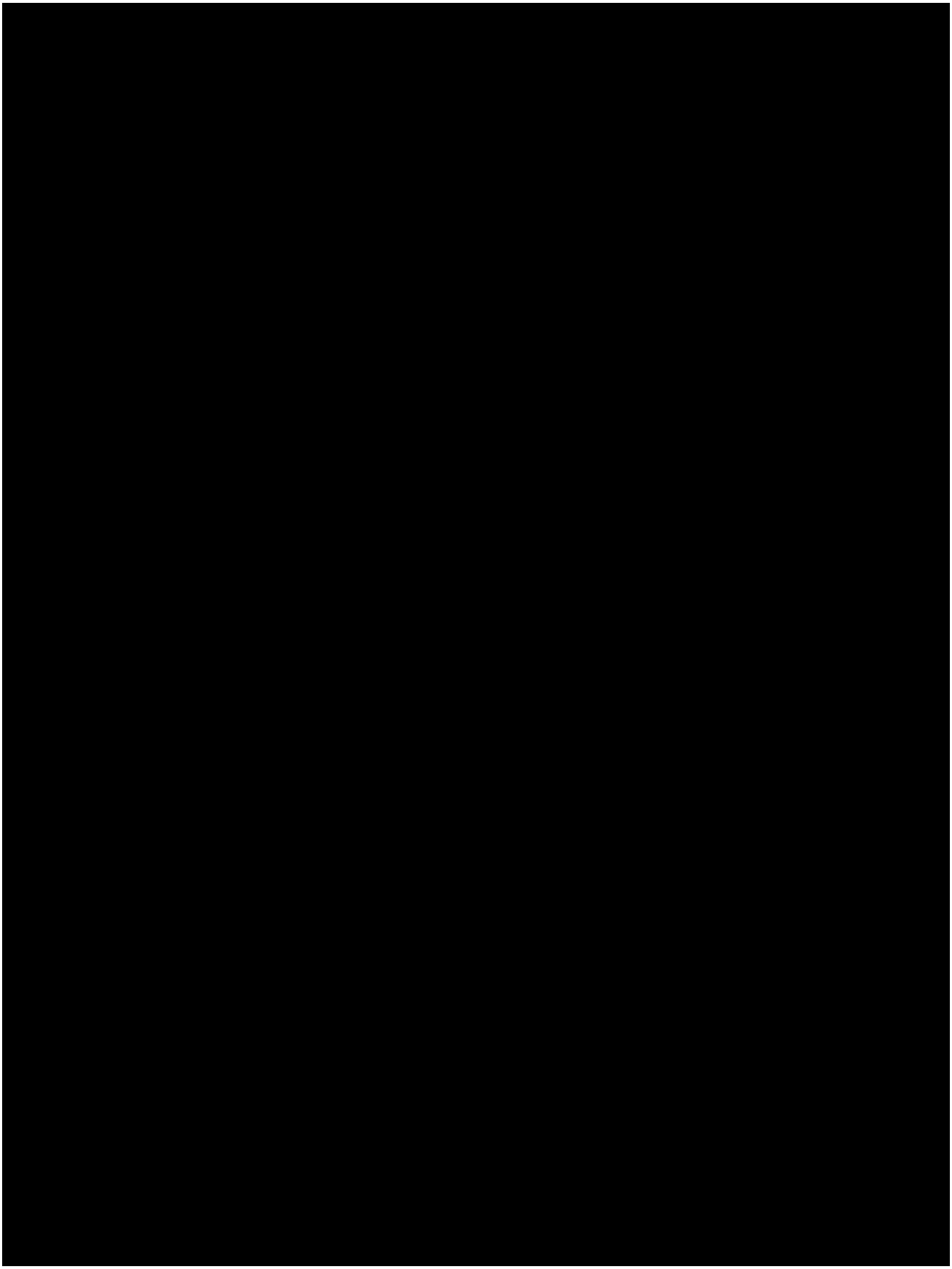
Total BODE Index score = 0 to 10 units

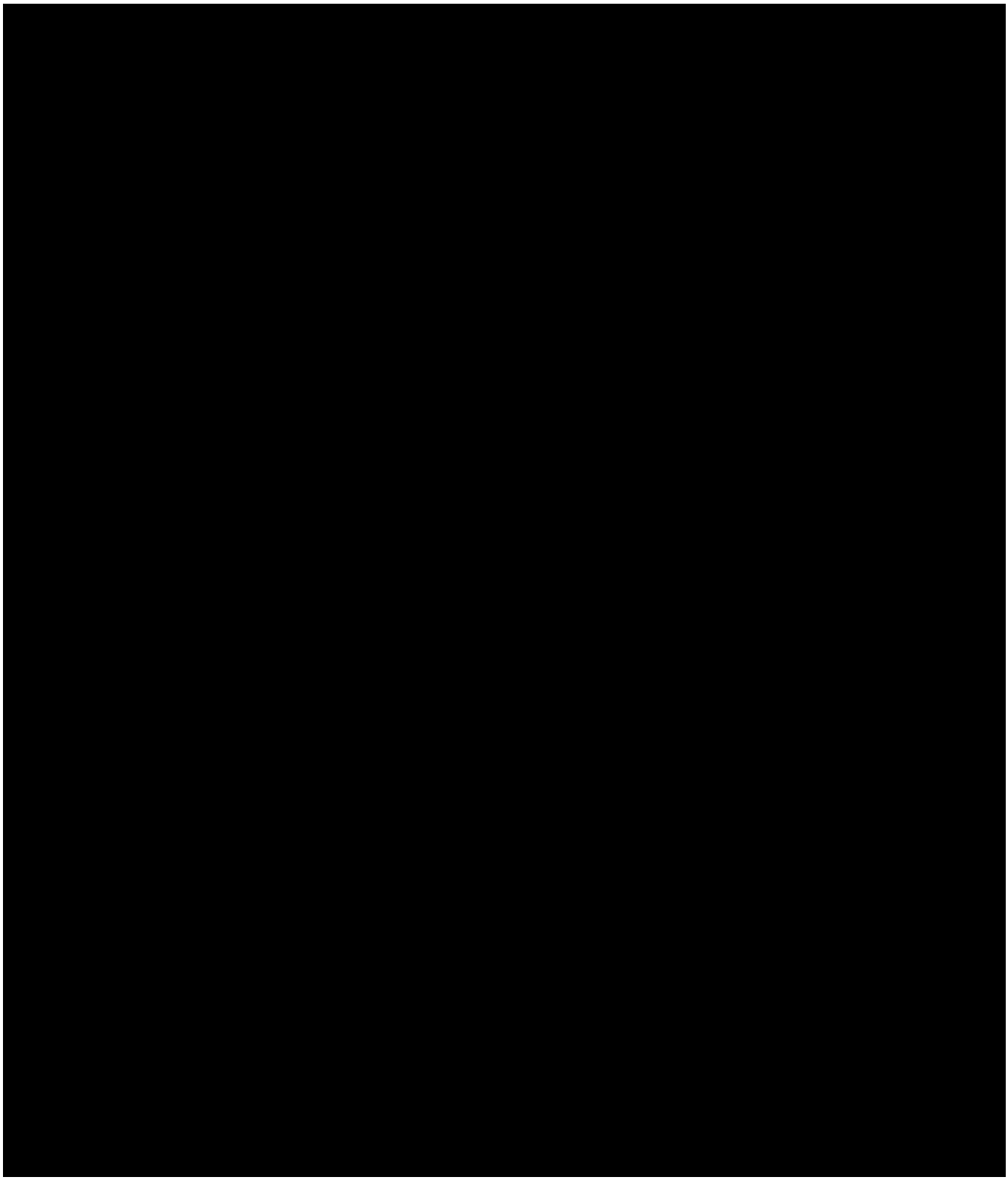
(FEV1% pred = predicted amount as a percentage of the forced expiratory lung volume in one second; 6MWD = six minute walking distance; MMRC = modified medical research council dyspnea scale; BMI = body mass index)

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

10.14 APPENDIX 14: EQ-5D-5L







10.15 APPENDIX 15: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (27)."

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.

10.16 APPENDIX 16: LIST OF OPPORTUNISTIC INFECTIONS

- Aspergillosis.
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers).
- Candidiasis - only systemic or extensive mucosal or cutaneous candidiasis.
- 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 tuberculosis.
- Mycobacterium avium.
- Nontuberculosis mycobacteria.
- Pneumocystis pneumonia (PCP).

This list is indicative and not exhaustive.

10.17 APPENDIX 17: FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For patient(s) who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes (any genetic analysis subject to additional consent per Section 8.7). For patients who have consented to it, archival blood samples will be collected at the visits specified in the study flow chart (see Section 1.3). Additional details will be provided in the laboratory manual.

These archived serum and plasma samples, and any residual or leftover serum, plasma or blood remaining from planned laboratory work, may be used for research purposes related to COPD or other respiratory diseases such as asthma or inflammatory diseases (eg, exploratory biomarkers of disease or drug effect), pathway biology, additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol. These samples will remain labelled with the same identifiers as the ones used during the study (ie, Subject ID, sample ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (Section 10.1.3).

10.18 APPENDIX 18: 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.

Note: The reported ICS doses in the Tables below refer to METERED dose.

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

Inhaled corticosteroid	Daily dose (mcg)	
	High dose	Lower doses
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.

10.19 APPENDIX 19: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.19.1 Amended protocol 01 (Amendment 01) (29-September-2020)

This amended protocol 01 (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The overall rationale for the changes implemented in the protocol amendment is to decrease the study burden on patients, to minimize COVID-19 pandemic-related risks in this vulnerable and elderly population of COPD patients, and to update the AESIs with the updated Sponsor safety information related to eye disorders.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Added the NCT number	Addition of NCT number
1.3.1 Schedule of activities for patients who complete the planned treatment And 1.3.2 Reduced schedule of events for patients after early treatment discontinuation	Replaced the following on-site visits with telephone visits:V7 (w16), V8 (w20), V10 (w28), V11 (W32), V13 (w40), V15 (w48), V17 (w56), V18 (w60). Footnotes added and updated to reflect this change. The assessments were adjusted accordingly.	To decrease the burden of on-site visits for patients while maintaining patient safety and data quality; to minimize COVID-19 pandemic-related risks in vulnerable and elderly population of COPD patients.
	BODE score added at EOT/ETD	Omission corrected
1.3.1 Schedule of activities for patients who complete the planned treatment	Added EQ-5D-5L assessment at w24 and w52.	To develop the economic model
	Clarifying in table and footnote 'l' that the urine pregnancy test can be performed monthly at home using 'urine dipsticks', in between on-site visits.	Update
	Updated footnote 'a' to clarifiy in case of missed scheduled on-site visits.	Update
	Updated footnote 'm' to explain in case of missed spirometry assessments during on-site visits.	Update

Section # and Name	Description of Change	Brief Rationale
1.3.1 Schedule of activities for patients who complete the planned treatment And 6.1.1 Investigational Medicinal Product(s)	Updated text/footnote 'f' to reflect that after at least 1 injection supervised by the Investigator or delegate and after the training has been completed and documented, the patient can be allowed to self-inject the IMP.	Dupilumab is currently marketed and self administration after proper training in subcutaneous injection technique aligns with approved label.
	Added below text: If the patient is unable or unwilling to administer IMP at home, injections can be performed at the site; or arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site.	Provided further clarity for administration of IMP
1.3.2 Reduced schedule of events for patients after early treatment discontinuation	Added urine pregnancy test to be performed on w4, w8, w16, w20, w28, w32, w40, w44, and w48. Updated footnote 'g' to clarify that the urine pregnancy test can be performed monthly at home using 'urine dipsticks', in between on-site visits.	Update
	Removed pharmacokinetic assessments in case of ETD (early treatment discontinuation) at End of Study.	Correction
	Whole blood RNA (optional) sampling added at ETD	Correction
	EQ-5D-5L questionnaire added at ETD and updated footnote 'i'.	To develop the economic model.
2.3 Benefit/Risk Assessment, 8 Study Assessments And Procedures 9.4.3 Other analyses	Statement regarding study conduct in Emergency situation like Covid-19 is added.	To align with recent regulatory requests seeking to understand the Sponsor's risk mitigations during the COVID-19 pandemic.
3 Objectives and Endpoints	Updated a 'tertiary/exploratory' endpoint wording from ("removed moderate to severe"): • Annualized rate of moderate to severe COPD exacerbations assessed by the EXACT over 52 week. To: • Annualized rate of COPD exacerbations assessed by the EXACT over 52 week.	Correction on type of COPD exacerbations assessed by the EXACT.
	Updated the endpoints of "Other Secondary Objective" to reflect the deletion of pre-bronchodilator forced expiratory volume in first second (FEV1) at w16, w20, w28 and w48; and deletion of forced expiratory flow (FEF) at w16, w28.	Update based on deleted assessments for FEV1 and FEF because of replacement of on-site visits to telephone visits.
5.1 Inclusion Criteria	Updated I 02 to: Participants with a physician diagnosis of COPD who meet the following criteria at screening. "at screening" was added.	Clarity
5.2 Exclusion Criteria	E 33: removed "tuberculosis" from examples of invasive opportunistic infections.	Clarity
	E38: deleted the phrase "randomization (Visit 1)". Revised text: Clinically significant laboratory tests at screening:…	Correction

Section # and Name	Description of Change	Brief Rationale
5.4 Screen Failures	Updated the bullet point for rescreening criteria from: • Fail to meet exclusion criteria. To: • Previously did not meet the criteria for participation in the study.	To allow more flexibility for rescreening of patients.
	Moved the following sentence to another paragraph under same heading: If subject is rescreened, a different patient identification number will be issued.	Clarity
6.1.1 Investigational Medicinal Product(s)	Added below text: If the patient cannot take all the allocated IMP kits at home (eg. due to a storage issue), the DTP (Direct to Patient) service can be used or the patient may come to the site to pick-up the IMP kits. For doses not given at the study site, diaries will be provided to record information related to the injections. The diary will be kept as source data in the patient's study file.	Provided further clarity for supply of IMP.
6.2 Preparation/ Handling/ Storage/ Accountability - Responsibilities	Added provision for local regulation application for DTP (Direct to Patient) shipment.	Clarity
6.5 Concomitant Therapy	Added reference to Section 6.1.2 for expected background therapy and allowed reliever medications.	Clarity
	The phrase " are allowed during the study " was removed from the sentence and updated as below (under permitted concomitant medications list): • Maintenance treatment of COPD with ICS, LABA, LAMA, at a stable dosage.	Clarity
7.1.1 Permanent discontinuation	In the list of criteria for permanent discontinuation of study intervention, replaced the phrase "in the study" by "on the study intervention" and updated the point as below: • If, in the Investigator's opinion, continuation on the study intervention would be detrimental to the patient's well-being. Updated the below sentence from: "Patients must be withdrawn from the study for the following reasons: To: "Patients must be withdrawn from the study intervention for the following reasons:	Typographical correction
	Moved the following point from temporary study intervention discontinuation to permanent discontinuation of study intervention: • If the patient misses more than 3 consecutive doses, the patient will be permanently discontinued from the study intervention.	Clarity
7.1.2 Temporary discontinuation of study intervention	Created subheading 7.1.2 Temporary discontinuation of study intervention under 7.1 Discontinuation of Study Intervention.	Clarity
	Added text to clarifiy in case of missed scheduled on-site visits.	Update
8.2.3 Electrocardiograms	Updated the wording to clarify that the triplicate ECGs are required.	Clarity

Section # and Name	Description of Change	Brief Rationale
8.3.1 Adverse event of special interest	Added following AESIs: • Any severe type of conjunctivitis or blepharitis. • Keratitis.	To align the AESIs with safety evaluation regarding eye related disorders with updated product information in IB edition 14.
	Replaced the word “verbatim” by “overdose form” and updated the IMP overdose text as below: • An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form and symptoms, if any, entered on separate adverse event forms.	Clarity
	Updated the NIMP overdose text to as below: • An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the maximum daily dose as specified in a drug label, within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form and symptoms, if any, entered on separate adverse event forms.	Clarity
	Replaced below text: Of note, asymptomatic overdose has to be reported as a standard AE. by: Asymptomatic overdose should also be reported on the overdose form.	Clarity
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting	Updated the text in definition of SAE from: If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease). To: If an event is not an AE per definition above, then it cannot be an SAE.	Clarity
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Added pregnancy data collection information for male participants with partners who become pregnant.	To align with Sponsor standard operating procedure (SOP).
	Clarifying that the urine pregnancy test will be performed monthly instead of only on site visits.	Update
Throughout	Correction of small errors (eg, comma errors, duplication of words); slight rewordings for clarity, removal of repeated footnote markers in SoA table, and updation of abbreviations.	Correction

10.19.2 Amended protocol 02 (Amendment 02) (16-December-2021)

This amended protocol 02 (amendment 2) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The overall rationale for the changes implemented in the protocol amendment is to provide flexibility for participant enrollment criteria while maintaining the favorable benefit risk profile and scientific objectives of the study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Text in Inclusion Criterion I01: "participant must be ≥40 to ≤80 years of age" was replaced with "participant must be ≥40 to ≤85 years of age".	Upper age limit is increased to allow participation of older COPD patients who could potentially benefit from dupilumab while maintaining favorable benefit-risk profile.
Section 5.2 Exclusion Criteria	Exclusion Criterion E02 wordings updated from: "A patient with current diagnosis of asthma or history of asthma according to the 2018 Global Initiative for Asthma (GINA) guidelines, or other accepted guidelines" To "A patient with current diagnosis of asthma or history of asthma according to the Global Initiative for Asthma (GINA) guidelines, or other accepted guidelines".	For clarification.
	Exclusion Criterion E05 revised from: "treatment with oxygen of more than 12 hours per day" To "Long-term treatment with oxygen >4.0 L/min OR if a participant requires more than 2.0 L/min in order to maintain oxygen saturation >88%".	To allow COPD patients on long-term oxygen therapy to participate in the study who could potentially benefit from dupilumab while maintaining favorable benefit-risk profile.
	Exclusion Criterion E17: updated wording by adding "eg," within the sentence to clarify the exclusion criteria	For clarification.
	Exclusion Criterion E18: Moved the following sentence to a new paragraph under the same exclusion criterion. "Prior history of malignancy or active malignancy, including lymphoproliferative diseases (except successfully treated carcinoma in-situ of the cervix, non-metastatic squamous cell or basal cell carcinoma of the skin) within 5 years prior to baseline".	For clarification.
Section 6.1 Study Intervention(s) Administered	The term "consecutive visits" was replaced with "consecutive injections" in Table 2.	For clarification.

Section # and Name	Description of Change	Brief Rationale
Section 8.4 Treatment of Overdose	A word “symptomatic” was added at the beginning of the following sentence: ‘Symptomatic overdose is an AESI (defined in Section 8.3.1). No antidote is available for dupilumab.’	For clarification.
Section 10.18 Appendix 18	Added a note for the tables, “the reported ICS doses in the Tables below refer to METERED doses”.	For clarification.
Throughout	Minor editorial and document formatting revisions are made.	Correction.

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