AMENDED CLINICAL TRIAL PROTOCOL 01

Protocol title:	**A randomized, double-blind, placebo-controlled, parallel-group, Proof-of-Concept (PoC) study to assess the efficacy, safety and tolerability of SAR440340, in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)**
Protocol number:	**ACT15104**
Amendment number:	**01**
Compound number (Trademark/INN):	**SAR440340/REGN3500**
Short title:	**Proof-of-Concept study to assess the efficacy, safety and tolerability of SAR440340 (anti-IL-33 mAb) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)**
Sponsor name:	
Legal registered address:	

Regulatory agency identifying number(s):

EudraCT number:	2017-003290-34	**NCT03546907**
IND number:	134401	
UTN number:	Not yet available	

Approval Date: 11-Jun-2018 Total number of pages: 113

Sponsor signatory:

Please refer to the last page of this document for electronic signatures including date and time

Monitoring Team's Representative Name and Contact Information:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	All	11-Jun-2018, Version 1 (electronic 1.0)
Original Protocol		30-Mar-2018, Version 1 (electronic 2.0)

Amended protocol [01] (Day Month Year)

This amended protocol (Amendment 01) 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

This amendment incorporates recommendation from the European Union clinical trial review.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Activities	Footnote added to blood eosinophils and neutrophils to specify that a complete hematology panel will be performed at Visit 4, Visit 12 and follow-up Visit F1	Clarification for the biomarker (blood eosinophils and neutrophils) collection visits is provided in order to address the request from the Health Agencies review.
4.3 Justification for Dose	Details added to the justification for dose	Requested during the Health Agencies review of the clinical trial application.
5.2 Exclusion Criteria	Deleted E08: Participants with COPD diagnosed within the 6 months prior to randomization	During the Health Agencies' review of the clinical trial application, an inconsistency was identified in the duration of COPD diagnosis required for study inclusion. As per inclusion criterion I01, patients with a diagnosis of COPD for at least 1 year are eligible for inclusion, whereas exclusion criterion E08 excluded participants with COPD diagnosed within the 6 months prior to randomization. The study intends to include patients diagnosed with for at least 1 year, therefore E08 is now deleted.
	Modified E26: Known allergy to doxycycline or related compounds.	Per the Healthy Agencies' request, the criterion is being modified to also exclude patients with a history of systemic hypersensitivity to any excipients of the IMP.

Section # and Name	Description of Change	Brief Rationale
	Modified E34: Patients with cardiovascular diseases/conditions: for uncontrolled hypertension	Per the Health Agencies' request, the exclusion criterion related to uncontrolled hypertension has been modified in order to exclude patients with grade 3 hypertension (high cardiovascular risk).
6.5 Concomitant Therapy	Removed intra-articular steroids from permitted concomitant therapy	Resolve an inconsistency as relevant systemic exposure may occur with intra-articular steroids. Systemic steroids are not permitted during the screening or treatment phases.
8.1.1.1 COPD exacerbation	Added “Any course of systemic steroids/antibiotics started <7 days of finishing a previous course should be considered as treatment for a single exacerbation”	Further clarification has been provided as regards reporting of COPD exacerbations.
8.1.2 Patient reported outcomes questionnaires	Added “Record use of systemic corticosteroids and/or antibiotics taken for COPD exacerbation”	An inconsistency between set-up of e-diary and the protocol e-diary language has been corrected.
Section 10.10 - Appendix 10	Added Appendix 10 and renumbered other appendices	This is the appendix for Protocol Amendment History
All sections	Minor inconsistencies corrected, spelling and grammar corrected	Improve the quality of the document

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A randomized, double-blind, placebo-controlled, parallel-group, Proof-of-Concept (PoC) study to assess the efficacy, safety and tolerability of SAR440340, in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

Short title: Proof-of-Concept study to assess the efficacy, safety and tolerability of SAR440340 (anti-IL-33 mAb) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

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. Interleukin-33 (IL-33) is a pro-inflammatory cytokine that initiates and amplifies innate and adaptive inflammatory cascades, in response to epithelial cell stress or damage due to exposure to airborne allergens, viruses, cigarette smoke, and air pollutants. The objective of the current study is to investigate the effects of 300 mg SAR440340 (a human monoclonal antibody that targets IL-33), administered SC once every 2 weeks as compared to placebo on reducing the incidence of exacerbations in patients with moderate-to-severe COPD.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To investigate effects of SAR440340 (anti-IL 33 mAb) compared with placebo, on the annualized rate of moderate-to-severe acute exacerbations of COPD (AECOPD) over up to 52 weeks of treatment.	- Annualized rate of moderate*-to-severe** AECOPD over the treatment period. - *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, emergency medical care visit or resulting in death.
Key secondary	
• To investigate effects of SAR440340 compared with placebo, on improving respiratory function, as assessed by pre bronchodilator FEV1 over 24 weeks.	• Average change from baseline to Week 16-24*** in FEV1 (pre-bronchodilator) *** Model-based averages across Weeks 16, 20 and 24 will be compared between the treatment groups

Overall design:

Multinational, randomized, double-blind, placebo controlled, parallel group (2 groups), Proof of Concept (PoC) study that is designed to assess the efficacy, safety, and tolerability of SAR440340 in patients with moderate-to-severe COPD on an established Long-acting β2 adrenergic agonist (LABA), Long-acting muscarinic antagonist (LAMA), and/or ICS background therapy (double or triple therapy). Patients will be treated with SAR440340 or placebo for a minimum of 24 weeks and up to a maximum of 52 weeks*, and a 20-week safety follow-up period.

* *This study employs a variable treatment duration from 24 to 52 weeks to maximize data for the primary endpoint (annualized rate of exacerbation) in a time-efficient manner. Patients enrolled in the trial will remain in the treatment period for up to a maximum of 52 weeks or until the last patient randomized completes a minimum treatment period of 24 weeks. Of note, the accrual and drop-out rates will be closely monitored. If the accrual rates are significantly lower than planned and/or the drop-out rates are higher than expected, the minimum treatment duration may be extended to achieve the desired amount of total exposure. The maximum treatment duration of 52 weeks will not be changed.*

The study duration is outlined below:

- Screening period (10 days to 4 weeks)
- Randomized investigational medicinal product (IMP) treatment period (24 to 52 weeks)
- Post IMP safety follow-up treatment period (20 weeks).

At screening, patients must be on standard of care background therapy, for 3 months prior to Visit 2/Randomization and at a stable dose for at least 1 month prior to the Screening Visit 1, including either:

- Double therapy: LABA + LAMA or ICS + LABA or ICS + LAMA.

OR

- Triple therapy: ICS + LABA + LAMA.

Patients who satisfy the inclusion and exclusion criteria will be randomized (1:1) to:

- SAR440340 (300 mg) administered as 2 SC injections every 2 weeks (q2w) for 24 to 52 weeks
- Matching placebo for SAR440340 administered as 2 SC injections q2w for 24 to 52 weeks

It is planned to enroll approximately 50% of patients on ICS-containing background therapy (ICS+LABA; ICS+LAMA or ICS +LABA+LAMA).

Patients must be willing to stay on their established background medication for COPD throughout the duration of the study.

Visits up to 52-week IMP treatment period will occur every other week and will be followed by a 20-week observational follow-up period.

Treatment discontinuation follow-up:

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 visit (ETD) with all assessments normally planned for the EOT visit, to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment is available. In addition, and to allow assessment of patient outcomes over the stipulated study period, patients will be asked and encouraged to complete all remaining study treatment visits, and participate in all safety follow-up assessments according to the visit schedule with a +/-5 day window. For such patients the assessment schedule will be reduced (See study flowchart for patients after permanent treatment discontinuation in Section 1.3.2) and alternate visits during the planned treatment period may be conducted by phone (those with odd visit numbers, except for the planned EOT), as can visits F1 and F2.

Under exceptional circumstances when a patient cannot come to the site for a scheduled visit, a phone contact can be made. During the phone contact, at least information about AEs, concomitant medication and COPD exacerbation events should be collected.

Post IMP treatment follow-up:

Upon completing the 24-52 weeks randomized IMP treatment, patients will continue background therapy and enter the 20-week safety follow-up period.

Number of participants:

Approximately 340 patients will be randomized in this study (170 patients per arm) of which approximately 50% of patients should present with a blood eosinophil count of ≥ 250 /mm^3 and about 50% of patients with a blood eosinophil count of <250 /mm^3. All randomized participants who receive at least 1 dose of IMP will be included in the efficacy and safety analysis. See Section 9.2 for sample size determination and Section 9.3 for analysis populations.

Intervention groups and duration:

Study participation for each patient will be up to a total of approximately 46 weeks to 76 weeks, including up to 4 weeks of screening, 24 weeks to 52 weeks of IMP treatment period, and 20 weeks of post IMP treatment period.

Study intervention(s)

Investigational medicinal products(s)

SAR440340

- Formulation: Sterile SAR440340 will be provided in one 20 mL vial containing 287 mg of lyophilisate drug product. One vial of lyophilisate drug product (287 mg) is reconstituted with 2.5 mL of sterile water for injection resulting in 2.9 mL of 100 mg/mL SAR440340. A volume of 1.5 mL per injection will be withdrawn from the vial. Patients will receive 2 injections per dose

- Route(s) 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 visits)
- Dose regimen: 2 SC injections q2w for 24-52 weeks.

Matching placebo for SAR440340

- Formulation: Sterile placebo will be provided in one 20 mL vial containing lyophilisate placebo. One vial of lyophilisate is reconstituted with 2.5 mL of sterile water for injection resulting in 2.9 mL IMP. A volume of 1.5 mL per injection will be withdrawn from the vial. Patients will receive 2 injections per dose
- Route(s) 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 visits)
- Dose regimen: 2 SC injections q2w for 24-52 weeks.

Noninvestigational medicinal products(s)

Background therapy

Patients should continue their established standard of care background therapy for COPD throughout the study (double therapy [LABA + LAMA or ICS + LABA or ICS + LAMA] or triple therapy [ICS + LABA + LAMA]).

- Formulation: Dry powder inhaler (DPI), metered dose inhaler (MDI) or pocket nebulizer
- Route(s) of administration: Oral inhalation
- Dose regimen: As prescribed

Patients must be willing to stay on their established background medication for COPD throughout the duration of the study. After successful management of an acute exacerbation of COPD (e.g. 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.

Reliever Medication

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

- Formulation: Dry powder inhaler (DPI), metered dose inhaler (MDI) or pocket nebulizer
- Route(s) of administration: Oral inhalation

Dose regimen: As prescribed.

Statistical considerations:

- **Primary efficacy analysis:**

  For the primary efficacy endpoint the annualized exacerbation rate, a negative binomial regression model will be used to assess treatment differences. The model will include the total number of events occurring during the treatment period (up to Week 52) as response variable, and the treatment group, the baseline eosinophil strata and region (pooled countries) as covariates. Log-transformed observation duration will be the offset variable. Parameters will be estimated using the maximum likelihood method with the Newton-Raphson algorithm.

  Comparison of the annualized event rates between the treatment group and the placebo group will be made within this model and the rate ratios and their 95% confidence intervals will be estimated.

  In the case of premature discontinuation of study drug, a secondary analysis will include events up to 14 days after the last dose.

  Using the same method, subgroup analyses will be performed separately by the baseline eosinophil levels (≥250 /mm3 versus <250 /mm3).

- **Analysis of secondary endpoints:**

  Key secondary endpoint

  The key secondary efficacy endpoint the average change from baseline to Week 16- 24 in pre-bronchodilator FEV1 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. Model-based averages across Weeks 16, 20 and 24 will be compared between the treatment groups. The dependent variable is the change from baseline in pre-bronchodilator FEV1 at each time points. The model will include baseline FEV1 value, treatment group, visit, and treatment-by-visit interaction, the baseline eosinophil strata, and region (pooled countries), as covariates. An unstructured correlation matrix will be used to model the within-patient correlations. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Additional covariates such as the background medications, age, height, gender, race and smoking status will be considered for inclusion in the analysis model based on evaluation of blinded data and the final analysis model documented in the statistical analysis plan (SAP).

  Comparison between the treatment group and the placebo group will be made within this model and the least square mean difference and their 95% confidence intervals will be estimated.

  In the case of premature discontinuation of study drug the primary analysis will include data up to 14 days after the last dose.

Subgroup analyses will be performed using the same method by baseline eosinophil levels (≥250 /mm3 versus <250 /mm3).

Other secondary efficacy endpoints:

Change from baseline to Week 24 in FEV1 post-bronchodilator will be analyzed in the same way as the key secondary endpoint.

Similar analytic method will be applied to analyze change from baseline to time points past Week 24 in FEV1 (both pre-bronchodilator and post-bronchodilator).

Time to first moderate or severe AECOPD will be analyzed using a Cox regression model with treatment, baseline eosinophil strata, and region (pooled country) as covariates. The Kaplan-Meier (K-M) method will be used to estimate the probabilities of first AECOPD at specific time points for each group. Additional covariates will be considered based on evaluation of blinded data and the final analysis model documented in the SAP.

- **Safety analysis**

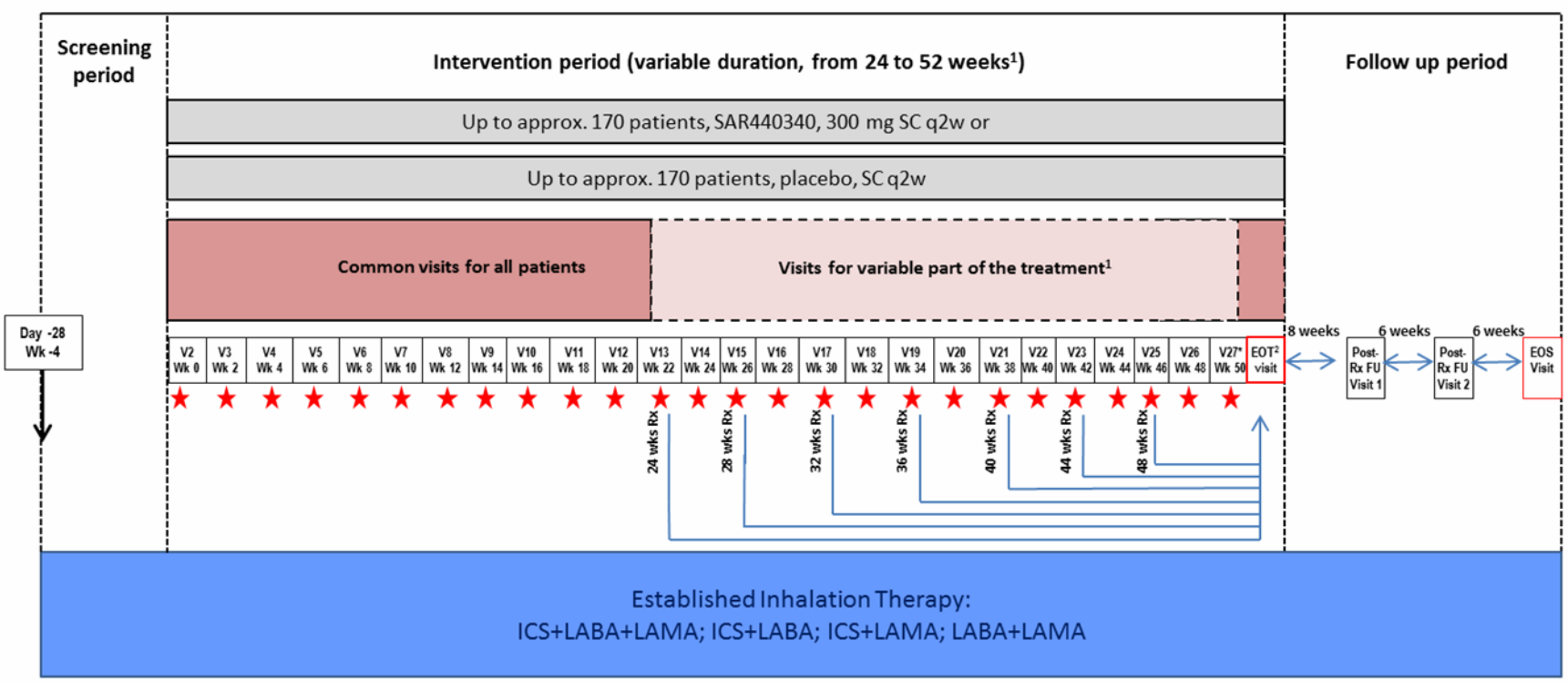
  Safety analyses will be descriptive, based on the safety population. The safety analysis will focus on the treatment-emergent adverse event (TEAE) period. This period is defined as the time from the first administration of the IMP to 22 weeks after the last administration of the IMP. During the study, unblinded data will be reviewed on an ongoing basis for safety and efficacy by a Data Monitoring Committee (DMC).

Data Monitoring Committee: Yes

An internal DMC will be comprised of individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC members are independent of the project/study teams and are not involved in the study conduct. The primary responsibilities of the DMC are to review and evaluate the study data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to project/study team.

1.2 SCHEMA

Figure 1 - Graphical study design



★ Treatment consisting of 2 injections of 1.5 mL each of SAR440340 or placebo.

[1] Variable treatment period determined by either completion of a 52 week treatment duration or the end of treatment of the last patient completing planned treatment (EOT visit), whichever occurs earlier, whichever occurs earlier Section 4.1.

[2] End of Treatment (EOT) visit to occur 2 weeks after last administration of IMP.

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 treatment must complete the Early Treatment Discontinuation (ETD) visit and follow the assessment in Section 1.3.2 for the remaining visits.

1.3.1 Schedule of Activities (SoA) for Patients who complete the Planned Treatment

	S	R/B																												
VISIT	**1**	**2[a,b]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**EOT[c]**	**F1**	**F2[d]**	**EOS**
WEEK	**W-4 to W-1**	**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**	**60**	**66**	**72**
Informed consent	X																														
Patient demography	X																														
Previous medical and surgical history	X																														
Chest X-ray[e]	X																														
Inclusion/exclusion	X	X																													
COPD Assessment Test (CAT)[f]	X	X																													
Smoking status	X	X	X	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	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Randomization		X																													
IMP administration[g]		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				
Dispense or upload electronic diary[h]	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	X	X	X		X
Safety																															
Physical examination[i]	X	X						X						X						X								X			X
Vital signs[j]	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	X	X	X		X
Electrocardiogram (12 lead)[k]	X	X						X						X						X								X			X
Hematology, biochemistry, urinalysis including	X	X				X				X				X						X								X			X

	S	R/B																												
VISIT	**1**	**2[a, b]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**EOT[c]**	**F1**	**F2[d]**	**EOS**
WEEK	**W-4 to W-1**	**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**	**60**	**66**	**72**
cotinine[l]																															
Hepatitis and HIV Serology tests[m]	X																														
Quantiferon Gold	X																														
Pregnancy (β-HCG blood) test[n]	X																														
Urine pregnancy test[n]		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	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics																															
Serum samples for SAR440340 concentration[o]		X	X	X		X		X		X				X						X								X	X		X
Anti-SAR440340 antibody[p]		X						X						X														X			X
Biomarkers																															
Blood eosinophils and neutrophils	X	X		X[q]		X		X[q]						X						X								X	X[q]		X
Total IL33 and sST2[o]	X	X		X		X		X						X														X	X		X
Calcitonin	X	X		X		X		X						X														X	X		X
PARC	X	X		X				X						X						X								X			
Eotaxin-3	X	X		X				X						X						X								X			
Total IgE	X	X		X				X						X														X			
Fibrinogen	X	X												X														X			
FeNO pre-bronchodilator (optional)[r]		X		X		X		X						X						X											
FeNO post-bronchodilator (optional)[r]		X		X		X		X						X						X											
Induced sputum (optional)[s]		X												X														X			
Blood samples for RNA sample (optional)	X	X		X										X														X			
Blood sample archival for exploratory research (optional)[t]	X	X		X				X						X						X								X			

	S	R/B																												
VISIT	**1**	**2[a, b]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**EOT[c]**	**F1**	**F2[d]**	**EOS**
WEEK	**W-4 to W-1**	**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**	**60**	**66**	**72**
DNA Pharmacogenomics analysis (optional)		X																												
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	X	X	X	X	X	X	X	X	X	X	X
Spirometry (pre-BD)[u, v]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X	X	X	X	X
Spirometry (post-BD) [u, v]	X	X	X	X		X		X						X						X								X	X		X
EXACT[w]	Every day (diary) from screening to week 52																													
SGRQ[w]		X		X		X		X						X						X								X	X		X
EQ-5D-5L[w]		X												X														X	X		X
Actigraphy Optional assessments (US/Canada only)	Con-tinuos						Con-tinuos						Con-tinuos																		
At-home spirometry (FEV1) Optional assessments (US/Canada only)	BID						BID						BID																		

S= Screening; **R/B**= Randomization/Baseline; **F**=Follow-up

β-hCG = Human chorionic gonadotropin-beta; BID = twice daily assessments; CAT = COPD Assessment Test; continuous = subsequent visits during the treatment period; COPD = chronic obstructive pulmonary disease; cont. = continuous; DNA = Deoxyribonucleic acid ; EDTA = Ethylenediaminetetraacetic acid ; EOS = End of Study; EOT = End of treatment; EQ-5D= Euro Quality of Life-5 Dimension questionnaire; EXACT = Exacerbations of COPD tool (EXACT); HIV = human immunodeficiency virus; IgE = Immunoglobulin E; IMP = Investigational Medical Product; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LABA = Long-acting β2 adrenergic agonist; LAMA = Long-acting muscarinic antagonist ;PARC = Pulmonary and activation-regulated chemokine; PK = Pharmacokinetic; RNA = Ribonucleic acid; SABA = Short-acting beta-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 ±3 days for the screening period and randomized IMP treatment period, and ±5 days for the 2 visits during the post IMP treatment period.

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 4.1 for patients who discontinue treatment.

d Can be performed with a phone call.

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

f The COPD Assessment Test (CAT) is to be registered through the patient's electronic diary.

g IMP (SAR440340 or placebo) to be administered every 2 weeks at the site. Last dose will be given 2 weeks prior to planned EOT visit eg, for patients with 52-week treatment period the last dose will be taken at Week 50, or earlier, as directed by the sponsor. Patients should be monitored by site personnel for at least 30 minutes after administration of all IMP injections. Monitoring period may be extended as per country specific requirements.

h Electronic diary is used for recording of patient's answers to the EXACT, SGRQ and EQ-5D-5L questionnaires, CAT assessment as well as for recording reliever medication. This device is dispensed at Screening Visit 1 (including instructions for use) and recorded information is downloaded from this device on the other indicated days. At EOS visit the electronic diary is downloaded and returned to the site.

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

j 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.

k ECG to be centrally collected & read.

l Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count with 5-part 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. Cotinine will be tested using the urine sample collected.

m 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 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).

n Only for women of childbearing potential: serum pregnancy test at Screening/V1 and urine pregnancy tests at every 4 weeks from Randomization through EOT and at EOS. A negative result must be obtained at V1 and at V2 prior to randomization. In case of positive urinary test the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases.

o Refer to central lab manual for collection details.

p If ADA assessment at week 12 is positive, additional measurements may be performed from PK samples collected at Week 4.

q The complete hematology panel will be performed.

r FeNO: measurement at sites only with access to FeNO equipment.

s Optional sputum sample at V2 should be collected post-randomization and prior to dosing with IMP, as long as patient consents to the optional collection. Only available at select sites in some countries.

t Archived samples 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.

u 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).

v Following randomization and during the treatment period - if spirometry is not performed at the scheduled visit it should be performed at the following visit during the treatment period.

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

1.3.2 Schedule of Activities (SoA) for Patients After Early Treatment Discontinuation

	ETD *a*																												
VISIT		3 *b*	4	5 *b*	6	7 *b*	8	9 *b*	10	11 *b*	12	13 *b*	14	15 *b*	16	17 *b*	18	19 *b*	20	21 *b*	22	23 *b*	24	25 *b*	26	27 *b*	EOT *c*	F1 *b*	F2 *b*	EOS
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	60	66	72
Smoking status	X	X	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	X	X	X	X	X	X	X	X	X	X	X
Call IVRS/IWRS	X																										X			X
Upload electronic diary *d*	Every on-site visit up to 12 weeks after ETD																													
Safety																														
Physical examination *e*	X						X						X						X								X			X
Vital signs *f*	X						X						X						X								X			X
Electrocardiogram (12 lead) *g*	X						X						X						X								X			X
Hematology, biochemistry, urinalysis including cotinine *h*	X				X				X				X						X								X			X
Urine pregnancy test *i*	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	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics																														
Serum samples for SAR440340 concentration *j*	X						X						X														X			X
Anti-SAR440340 antibody *k*	X						X						X														X			X
Biomarkers																														
Blood eosinophils and neutrophils	X				X				X				X						X								X			X
Total IL33 and sST2 *j*	X																													
Calcitonin	X																													
PARC	X																													
Eotaxin-3	X																													
Total IgE	X																													
Fibrinogen	X																													

	ETD *a*																												
VISIT		3 *b*	4	5 *b*	6	7 *b*	8	9 *b*	10	11 *b*	12	13 *b*	14	15 *b*	16	17 *b*	18	19 *b*	20	21 *b*	22	23 *b*	24	25 *b*	26	27 *b*	EOT *c*	F1 *b*	F2 *b*	EOS
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	60	66	72
Induced sputum (optional) *m*	X																													
Blood samples for RNA sample (optional)	X																													
Blood sample archival for exploratory research (optional) *n*	X																													
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	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry (pre-BD) *o, p*	X		X		X		X						X						X								X			X
Spirometry (post-BD) *o, p*	X		X		X		X						X						X								X			X
EXACT *q*	Every day (diary) up to 12 weeks after ETD																													
SGRQ *q*	X																													
EQ-5D-5L *q*	X																													
Actigraphy Optional assessments (US/Canada only)	X																													
At-home spirometry (FEV1) Optional assessments (US/Canada only)	X																													

F=Follow-up

β-hCG = Human chorionic gonadotropin-beta; BID = twice daily assessments; CAT = COPD Assessment Test; continuous = subsequent visits during the treatment period; COPD = chronic obstructive pulmonary disease; cont. = continuous; DNA = Deoxyribonucleic acid ; EDTA = Ethylenediaminetetraacetic acid ; EOS = End of Study; EOT = End of treatment; EQ-5D= Euro Quality of Life-5 Dimension questionnaire; EXACT = Exacerbations of COPD tool (EXACT); HIV = human immunodeficiency virus; IgE = Immunoglobulin E; IMP = Investigational Medical Product; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LABA = Long-acting β2 adrenergic agonist; LAMA = Long-acting muscarinic antagonist; PARC = Pulmonary and activation-regulated chemokine; PK = Pharmacokinetic; RNA = Ribonucleic acid; SABA = Short-acting beta-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 visit (ETD) visit. Once the ETD is performed, patients should follow the ETD SoA based on their original visit number, and the visit schedule should be adhered to within ±5 days.

b Visit may be performed by a phone call.

c End-of-treatment visit. For patients who discontinue treatment, this visit corresponds to the planned EOT visit.

d Electronic Diary will be used on daily basis for period of 12 weeks after ETD. The CAT assessment, and reliever medication will not be collected in patients after early treatment discontinuation.
e Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.
f Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate will be measured at on-site visits. Body weight (kg) will be measured at EOT/EOS visits.
g ECG to be centrally collected & read.
h Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count with 5-part 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 creatinine 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. Cotinine will be tested using the urine sample collected.
i Only for women of childbearing potential: urine pregnancy test at ETD and every 4 weeks through EOT and at EOS. In case of positive urinary test the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible.
j Refer to central lab manual for collection details.
k If ADA assessment at week 12 is positive, additional measurements may be performed from PK samples from Week 4.
l FeNO: measurement at sites only with access to FeNO equipment.
m Optional sputum sample at ETD should be collected post-randomization and prior to dosing with IMP, as long as patient consents to the optional collection. Only available at select sites in some countries.
n Archived samples 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.
o 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).
p Following randomization and during the treatment period - if spirometry is not performed at the scheduled visit it should be performed at the following visit during the treatment period.
q The EXACT, SGRQ and EQ-5D-5L are to be completed in the patient's electronic diary.

2 INTRODUCTION

SAR440340 (also known as REGN3500 or R3500) is a human monoclonal antibody (mAb) that targets IL-33 and is under development as a potential novel treatment for both asthma and COPD.

2.1 STUDY RATIONALE

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease worldwide that is associated with significant economic burden and for which available standard-of-care therapy shows insufficient efficacy on symptoms, lung function, exacerbations and long-term evolution of the disease. IL-33 is a pro-inflammatory cytokine that initiates and amplifies innate and adaptive inflammatory cascades in response to epithelial cell stress or damage due to exposure to airborne allergens, viruses, cigarette smoke, and air pollutants. The objective of the current study is to investigate the effects of 300 mg SAR440340 administered SC once every 2 weeks as compared to placebo on reducing the incidence of exacerbations in patients with moderate-to-severe COPD.

2.2 BACKGROUND

2.2.1 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a heterogeneous syndrome associated with an abnormal inflammatory immune response of the lung to noxious particles and gases (1). Chronic inflammation causes structural changes, 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. It results in progressive airflow obstruction that is only partly reversible or even irreversible. The inflammation component of COPD is thought to involve many cell types including structural cells, T lymphocytes, neutrophils, macrophages, and their biological products. In some patients, there may also be an increase of eosinophils, T-helper (Th) 2 or Group 2 Innate Lymphoid cells, especially where there is clinical overlap with asthma. The main cause of COPD is smoking tobacco, but other factors have been identified, such as air pollution, occupational exposure, and genetic susceptibility. The most common respiratory symptoms include chronic dyspnea, cough and/or sputum production. The disease is further aggravated by exacerbations, particularly for severe COPD. These are most often due to viral and bacterial infections of the lungs which trigger the inflammatory response, tissue destruction, and the resultant hypoxia. Exacerbations in COPD patients are associated with rapid disease progression (rate of lung function decline over time) and increased risk of mortality. 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.

Chronic obstructive pulmonary disease is a highly prevalent, serious and progressive disease resulting in significant morbidity, mortality, and economic burden (2, 3). 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. 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.

The standard of care for moderate COPD starts with bronchodilators (such as long-acting muscarinic antagonists [LAMA] or long-acting β2 agonists [LABA]), and as disease progresses bronchodilators are combined with other drugs such as inhaled corticosteroids (ICS), and phosphodiesterase type 4 (PDE-4) inhibitors (roflumilast) (4, 5, 6). The major limitations of the existing agents for COPD include modest efficacy and risk of respiratory infections (ICS). Oral or systemic corticosteroids are reserved for treatment of exacerbations given their unacceptable long-term safety profile in the COPD population. No approved therapeutic agent blocks the decline in forced expiratory volume in 1 second (FEV1) 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. The anti-interleukin (IL)-5 mAb mepolizumab shows a modest 18%-20% reduction of exacerbations in COPD patients with high blood eosinophils. The anti-IL-5 receptor mAb benralizumab is still in Phase 3 clinical trials, and preliminary data from Phase 2a trial suggest that the FEV1 improvement versus placebo averaging approximately 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 (7, 8).

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.

2.2.2 SAR440340 - Anti-IL-33 monoclonal antibody

SAR440340 is a human mAb that targets IL-33. IL-33 is a proinflammatory cytokine that initiates and amplifies innate and adaptive inflammatory cascades (9) in response to epithelial cell stress or damage (“alarmin”) due to exposure to airborne allergens, viruses, cigarette smoke, and air pollutants. Accumulating evidence from human studies and animal models suggests that IL-33 is potentially implicated in the pathogenesis of COPD, and provides the rationale for the use of SAR440340 in patients with COPD. Studies from the Regeneron Genetics Center provide evidence that genetic variation in the IL-33 and IL1RL1 genes are common risk factors for COPD. In humans, increased levels of IL-33 have been reported in bronchial cells of COPD patients (10, 11). It is also known that IL-33 protein expression in the lungs correlates with COPD severity and is a negatively correlated with FEV1 (11). A separate study has found that plasma IL-33 level in patients with stable COPD was related to eosinophil count and chronic bronchitis phenotype (12). Supporting data from a preclinical murine smoking model of COPD suggests a dual role for IL-33 in amplifying lung inflammation during viral exacerbations of COPD. Initially, smoke inhalation upregulates intracellular IL-33 in mice, as well as the proportion of epithelial cells expressing IL-33; secondly, viral infection leads to focal cellular necrosis, release of IL-33, and increased production of proinflammatory cytokines such as IL-6 and tumor necrosis factor-α

(TNF-α) in the lung (11). Therefore, it is hypothesized that blockade of IL-33 which is locally released in the airway in the setting of environmental triggers such as infection or toxic inhalants may be a novel therapeutic approach to prevent exacerbations.

2.3 BENEFIT/RISK ASSESSMENT

The Phase 1 study in healthy subjects suggests that SAR440340 is well-tolerated at doses up to 10 mg/kg administered IV as single dose. Unblinded safety data from the ongoing multiple ascending dose study (R3500-AS-1619, data as of February 23, 2018) in asthma patients have demonstrated that weekly doses of 75 mg and 150 SC are so far well tolerated. No SAEs or deaths have been reported in any of the Phase 1 studies. SAR440340 is expected to inhibit the proinflammatory activity of IL-33, which is elevated in COPD patients. Thus, the benefit/risk profile for SAR440340 in this study supports its evaluation as a potential agent for treatment of COPD.

There is a potential risk of infection associated with blocking of host defense pathways by SAR440340. The preliminary safety data from the first in human (FIH) study of SAR440340 have revealed no safety signals. Therefore, the anticipated safety of SAR440340 is considered reasonable, with close monitoring of adverse events (AEs) and laboratory results throughout the study and follow-up period. The safety data and other potential risks (systemic hypersensitivity, embryo-foetal toxicity, immunogenicity) for SAR440340 are summarized in the Investigator's Brochure (IB).

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To investigate effects of SAR440340 (anti-IL 33 mAb) compared with placebo, on the annualized rate of moderate-to-severe acute exacerbations of COPD (AECOPD) over up to 52 weeks of treatment.	- Annualized rate of moderate*-to-severe** AECOPD over the treatment period. *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, emergency medical care visit or resulting in death.
Secondary	
• To investigate effects of SAR440340 compared with placebo, on improving respiratory function, as assessed by pre bronchodilator FEV1 over 24 weeks.	• Average change from baseline to Week 16-24*** in FEV1 (pre-bronchodilator) *** Model-based averages across Weeks 16, 20 and 24 will be compared between the treatment groups
• To evaluate effects of SAR440340 compared with placebo, on Post-bronchodilator FEV1 over 24 weeks	• Change from baseline to Week 24 in FEV1 (post-bronchodilator****) **** Post-bronchodilator means 30 minutes after either 400 mcg of salbutamol/albuterol (4 puffs of 100 mcg each) or 80 mcg of ipratropium bromide (4 puffs of 20 mcg each).
• To evaluate effects of SAR440340 compared with placebo, on duration from baseline to first moderate or severe AECOPD event over up to 52 weeks	• Time to first moderate or severe AECOPD.
• To evaluate effects of SAR440340 compared with placebo, on safety and tolerability	• Treatment-emergent adverse events (TEAE) • Serious adverse events (SAE)
• **Tertiary/exploratory**	
• To evaluate the effects of SAR440340 compared with placebo, on patient reported symptoms and quality of life as documented by e-Diary and utilizing Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT), St. George's Respiratory Questionnaire (SGRQ) and Euroqol-5Dimension (EQ 5D) questionnaire - in all patients treated with SAR440340/placebo - in subpopulations with high blood eosinophil level (≥250 /mm^3) and low blood eosinophil level (<250 /mm^3)	• Change from baseline in the EXACT scores at Week 24 • Change from baseline in the SGRQ scores at Week 24 • Change from baseline in the EQ-5D scores at Week 24
• To evaluate the pharmacokinetic (PK) profile of SAR440340 in serum	• Serum functional SAR440340 concentrations
• To evaluate the effects of SAR440340 Antidrug antibodies (ADA)	• Antidrug antibodies (ADA) against SAR440340
• To evaluate the effects of SAR440340 compared with placebo, on FEV1, AECOPD, and other relevant endpoints - in subpopulations with high blood eosinophil level (≥250 /mm3) and low blood eosinophil level (<250 /mm3) - in subpopulations according to use/no use of ICS	• Change from baseline to Week 24 in FEV1 (pre-bronchodilator and post-bronchodilator) • Rate of moderate-to-severe AECOPD

Objectives	Endpoints
with bronchodilators as background therapy, fibrinogen levels, and smoking status.	
• To evaluate the effects of pharmacogenomics on SAR440340	• Future Assessment of DNA or RNA samples for the pharmacogenomics sub study to identify genomic associations with clinical or biomarker response, other clinical outcome measures and possible AEs
• To evaluate the effects of SAR440340 compared with placebo on other respiratory assessments (expanded AECOPD endpoint)	• Change from baseline to Week 16-24 in FVC (% predicted and absolute values in mL). • Time to the first moderate and severe exacerbations or time to study drug discontinuation (after Week 4) due to lack of efficacy, based on the investigator's judgement (expanded AECOPD endpoint)
• To evaluate the clinical symptoms of COPD in patients treated with SAR440340 versus placebo - in all patients treated with SAR440340/placebo - in subpopulations with high blood eosinophil level (≥250 /mm^3) and low blood eosinophil level (<250 /mm^3) - in subpopulations according to use/no use of ICS with bronchodilators as background therapy, fibrinogen levels, and smoking status	• Time to first Clinically Important Deterioration (CID) as defined by decrease of >100 mL from baseline in trough FEV1 and /or deterioration in SGRQ by 4 units and/or moderate-to-severe AECOPD up to Week 24 (and over the 52 week variable treatment period
• To evaluate the pharmacodynamics effects of SAR440340	• Blood eosinophil and neutrophil counts. • Levels of biomarkers of the interleukin (IL)-33 and/or Type 2 inflammation pathway - Total IL-33, sST2 levels - Calcitonin levels - PARC levels - Eotaxin-3 levels - Total IgE levels - Fibrinogen levels • Induced sputum for RNA expression (optional for patients at a subset of sites). • Optional: Messenger ribonucleic acid sequencing or whole transcriptome analysis. • Optional: DNA/RNA sample will be collected for pharmacogenomic effects.
• Optional actigraphy (sleep and activity) and home spirometry (available for patients in US and Canada only): To evaluate the effects of SAR440340 compared to placebo on parameters of sleep, activity, and at-home spirometry.	• Change from average measurement over baseline (2 weeks prior to randomization) to average measurements over Weeks 10-12 (2 weeks prior to Visit 8) and Weeks 22-24 (2 weeks prior to Visit 14) of sleep and activity parameters. - Sleep: Total sleep time, wake after sleep onset, overnight activity counts - Activity: Daytime activity counts, percent of time spent in sedentary activity, percent of time spent in moderate to vigorous physical activity - Spirometry: FEV1
• Optional actigraphy (sleep and activity) and home spirometry (available for patients in US and Canada only): To compare the utility of at-home spirometry against in-clinic spirometry	• FEV1 (Spirometry performed at home) • FEV1 (Spirometry performed at the clinic)

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 group (2 groups), Proof of Concept (PoC) study that is designed to assess the efficacy, safety, and tolerability of SAR440340 in patients with moderate-to-severe COPD on an established LABA, LAMA and/or ICS background therapy (double or triple therapy). Patients will be treated with SAR440340 or placebo for a minimum of 24 weeks and up to a maximum of 52 weeks*, and a 20-week safety follow-up period.

**This study employs a variable treatment duration from 24 to 52 weeks to maximize data for the primary endpoint (annualized rate of exacerbation) in a time-efficient manner. Patients enrolled in the trial will remain in the treatment period for up to a maximum of 52 weeks or until the last patient randomized completes a minimum treatment period of 24 weeks. Of note, the accrual and drop-out rates will be closely monitored. If the accrual rates are significantly lower than planned and/or the drop-out rates are higher than expected, the minimum treatment duration may be extended to achieve the desired amount of total exposure. The maximum treatment duration of 52 weeks will not be changed.*

The study duration is outlined below:

- Screening period (10 days to 4 weeks)
- Randomized IMP treatment period (24 to 52 weeks)
- Post IMP safety follow-up treatment period (20 weeks).

The randomization/baseline Visit is defined as Day 1. The visit schedule should be adhered to within ±3 days for the screening period and randomized IMP treatment period, and ±5 days for the 2 visits during the post IMP treatment period.

At screening, patients must be on Standard of Care background therapy, for 3 months prior to Visit 2/Randomization and at a stable dose for at least 1 month prior to the Screening Visit 1, including either:

- Double therapy: LABA + LAMA or ICS + LABA or ICS + LAMA.

  OR

- Triple therapy: ICS + LABA + LAMA.

Patients who satisfy the inclusion and exclusion criteria will be randomized (1:1) to:

- SAR440340 (300 mg) administered as 2 SC injections every 2 weeks (q2w) for 24 to 52 weeks
- Matching placebo for SAR440340 administered as 2 SC injections q2w for 24 to 52 weeks

It is planned to enroll approximately 50% of patients on ICS-containing background therapy (ICS + LABA; ICS + LAMA or ICS + LABA + LAMA).

Patients must be willing to stay on their established background medication for COPD throughout the duration of the study.

Treatment discontinuation follow-up:

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 visit (ETD) with all assessments normally planned for the EOT visit, to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment is available. In addition, and to allow assessment of patient outcomes over the stipulated study period, patients will be asked and encouraged to complete all remaining study treatment visits, and participate in all safety follow-up assessments according to the visit schedule with a +/-5 day window. For such patients the assessment schedule will be reduced (See study flowchart for patients after permanent treatment discontinuation in Section 1.3.2) and alternate visits during the planned treatment period may be conducted by phone (those with odd visit numbers, except for the planned EOT), as can visits F1 and F2.

Under exceptional circumstances when a patient cannot come to the site for a scheduled visit, a phone contact can be made. During the phone contact, at least information about AEs, concomitant medication and COPD exacerbation events should be collected.

Post IMP treatment follow-up:

Upon completing the 24-52 weeks randomized IMP treatment, patients will continue their established ICS/LABA/LAMA therapy and enter the 20-week safety follow-up period.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The first-in-human study (R3500-HV-1551) to investigate safety and pharmacokinetics (PK) of a single intravenous (IV) infusion of 0.3, 1, 3 or 10 mg/kg or a single subcutaneous (SC) injection of 150 mg of SAR440340 in normal healthy volunteers was completed. Treatment with SAR440340 was generally well-tolerated. No deaths and no serious adverse events (SAEs) were reported.

The first-in-patient study (R3500-AS-1619) to investigate safety, tolerability, PK, and pharmacodynamic (PD) effects of a repeated SC administration of SAR440340 at 2 dose levels (75 and 150 mg), every week for 4 weeks, in adult patients with moderate asthma is ongoing, with all patients in the postdosing follow-up period. Unblinded safety data (as of February 23, 2018) have demonstrated that SAR440340 is so far well tolerated. No SAE’s or deaths have been reported.

A PD study (R3500-AS-1633) to assess the effects of a single IV dose of 10 mg/kg SAR440340, 2 repeated SC doses of dupilumab (600 mg loading dose then 300 mg dose), and the coadministration of SAR440340 with dupilumab on markers of inflammation after Bronchial

Allergen Challenge in patients with mild allergic asthma is ongoing. At the time of writing this protocol, acceptable safety and tolerability was observed from the blinded assessments in this study.

A randomized, placebo-controlled study design where the effects of the IMP is 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 (7, 8). 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 dose regimen of SAR440340 selected for this study is 300 mg SC administered every 2 weeks (q2w). This dosage regimen is predicted to achieve single-dose exposure which falls well within the maximum exposure achieved by the single 10 mg/kg IV dose shown to be safe in the FIH (R3500-HV-1551) single-ascending dose study. Safety after repeated dose administration of SAR440340 can be inferred from the results of the chronic safety study in cynomolgus monkeys where doses as high as 100 mg/kg were administered weekly SC for 26 weeks. Based on systemic drug exposures (area under the concentration [AUC]-time curves) in the toxicology studies, the proposed SC dose of 300 mg q2w provides a safety margin (exposure multiple based on predicted human exposure) of 13.7-29.8 for a proposed 24-52 week study.

In addition to safety, PK-PD factors were considered. Based on modeling and simulation of SAR440340 HV-1551 FIH drug concentration, the 300 mg q2w regimen is expected to achieve a minimum concentration at steady state which is approximately 5-fold higher than the concentration of SAR440340 (17 mg/L) that showed efficacy consistently across all endpoints in an HDM-induced chronic lung inflammation mouse model. The higher-fold exposure of the 300 mg q2w regimen should conservatively ensure all patients are above this efficacy threshold when taking into account PK inter-individual variability, as well as the uncertainty in translating the PD of SAR440340 from the HDM mouse model to COPD in humans.

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. This study has a variable treatment period, therefore all participants who complete the planned treatment period of 24 to 52 weeks and all phases for the follow-up including the end of study visit are completers.

The end of this study is defined as completion of the last patient last visit which will occur at the end of a 20-week safety follow-up period for the final patient(s) who complete(s) the study as per protocol.

For patients who 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

Participant must be 40 to 75 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 01. Participants with a diagnosis of COPD for at least 1 year (based on Global Initiative for Chronic Obstructive Lung Disease [GOLD] definition, see (1).

I 02. Participants with moderate-to-severe COPD (post-bronchodilator FEV1/forced vital capacity [FVC] <70% and post-bronchodilator FEV1 % predicted <80%, but ≥30%) at Visits 1 and 2.

I 03. Participants with COPD Assessment Test (CAT) score ≥10 at Screening Visit 1 and Visit 2/Randomization.

I 04. Participants with reported history of signs and symptoms of chronic bronchitis (chronic productive cough for 3 months in the year up to screening in a patient in whom other causes of chronic cough [eg, gastroesophageal reflux, chronic rhinosinusitis, bronchiectasis] have been excluded).

I 05. Participants with a documented history (eg. medical record verification) of ≥2 moderate exacerbations or ≥1 severe exacerbation within the year prior to screening

- a moderate exacerbation is defined as an AECOPD requiring systemic corticosteroids (oral, intravenous, or intramuscular) and/or treatment with antibiotics (however, use of antibiotics alone does not qualify as a "moderate exacerbation" unless documentation is available that use of antibiotics was necessary for treatment of worsening symptoms of COPD)
- a severe exacerbation is defined as an AECOPD that required a hospitalization.

I 06. Participants with Standard of Care background therapy, for 3 months prior to Visit 2/Randomization and at a stable dose for at least 1 month prior to the screening, including either:

- Double therapy: LABA + LAMA or ICS + LABA or ICS + LAMA.

OR

Triple therapy: ICS + LABA + LAMA.

I 07. Current or former smokers with a smoking history of ≥10 packs-year.

Weight

I 08. Body mass index (BMI) ≥18.0 kg/m^2 (inclusive).

Sex

I 09. Male or Female

See E 28 for required contraceptive measures.

Informed Consent

I 10. 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:

Active comparator and/or mandatory background therapy

E 01. Clinically significant abnormal electrocardiogram (ECG) at Visit 1 that may affect the conduct of the study in the judgment of the Investigator.

E 02. Concomitant severe diseases or diseases for which the use of ICS (eg, active pulmonary tuberculosis [E 07]) or LABA are contraindicated (eg, diagnosis of a history of significant cardiovascular diseases, insulin-dependent diabetes mellitus, hyperthyroidism, thyrotoxicosis, pheochromocytoma, hypokalemia).

E 03. Use of injectable glucocorticosteroids or oral systemic glucocorticosteroids within 1 month prior to Visit 1/Screening or more than 4 courses of IV glucocorticosteroids within the 6 months prior to Visit 1.

E 04. Participants receiving medications or therapy that are prohibited as concomitant medications (see Section 6.5).

E 05. A participant with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. A specific example includes but is not limited to poorly controlled insulin-dependent diabetes.

E 06. Participants with Bronchial thermoplasty procedure (up to 3 years prior to Visit 1).

E 07. Exclusion related to tuberculosis (TB):

- Active TB or a history of incompletely treated TB.
- Confirmed Quantiferon-positive patients (no active disease) are excluded from the study unless the following conditions are met:
  - Patients with a history of prior documented completed chemoprophylaxis for latent tuberculosis infection (with a treatment regimen as per local guidelines) or treatment of active TB infection, and
  - Has obtained consultation with a specialist to rule out or treat active TB infection.
- Suspected extrapulmonary TB infection.
- Patients at high risk of contracting TB, such as close contact with individuals with active or latent TB.

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E 08. The exclusion criterion was deleted (Amended Protocol 01).

E 09. A current diagnosis of asthma according to the Global Initiative for Asthma (GINA) guidelines (13).

E 10. Significant pulmonary disease other than COPD (eg, lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, bronchiectasis, eosinophilic granulomatosis with polyangiitis, significant sleep apnea on Bilevel Positive Airway Pressure, etc) or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts.

E 11. Diagnosis of α-1 anti-trypsin deficiency.

E 12. Advanced COPD with need for chronic (>15 hours/day) oxygen support.

E 13. Participant with a moderate or severe AECOPD event (for definition, see Table 1, primary objective) within 4 weeks prior to screening.

E 14. A participant who has experienced an upper or lower respiratory tract infection within 4 weeks prior to Screening/Visit 1 or during the screening period.

E 15. Prior history of or planned pneumonectomy or lung volume reduction surgery.

E 16. Participants with a history of a systemic hypersensitivity reaction to a mAb drug.

E 17. Anti-IgE therapy (eg, omalizumab [Xolair®]) within 130 days prior to Visit 1 or any other biologic therapy (including anti-IL5 mAb, e.g. benralizumab [Fasenra®] or mepolizumab [Nucala®]) for asthma or systemic immunosuppressant (e.g., methotrexate) to treat other inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) and other diseases, within 2 months or 5 half-lives prior to Visit 1, whichever is longer.

E 18. Current history of substance and/or alcohol abuse.

E 19. Inability to follow the procedures of the study (eg, due to language problems, psychological disorders) or unable to read, understand and fill a questionnaire or use an electronic diary without any help.

E 20. Exposure to another investigative drug (small molecules as well as mAbs, including dupilumab) within a time period prior to Visit 1 that is <5 PK half-lives of the antibody. In case the half-life is not known, then the minimum interval since the exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (nonantibody) investigative study medication is 30 days prior to Visit 1.

E 21. Patients who are participating in the acute phase of a pulmonary rehabilitation program, i.e. who started rehabilitation <4 weeks prior to screening (Note: patients in the maintenance phase of a rehabilitation program can be included).

E 22. Clinically relevant (based on study Investigator's judgment) abnormal laboratory values suggesting an unknown disease and requiring further evaluation.

E 23. Participants previously treated in any clinical trial of SAR440340.

E 24. Participant is the Investigator, or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.

E 25. Prisoners and participants who are legally institutionalized.

Current knowledge of Sanofi compounds

E 26. Known allergy to doxycycline or related compounds, or known allergy to SAR440340 excipients.

E 27. Females who are lactating, breastfeeding or who are pregnant.

E 28. <u>For Women in the study</u>

Women of childbearing potential (premenopausal female biologically capable of becoming pregnant) who

Do not have:

- A confirmed negative serum β-human chorionic gonadotropin (β-hCG) test at Visit 1.
- Negative urine pregnancy test prior to Visit 2/Randomization.

Who are not protected by one of the acceptable forms of effective contraception (Appendix 4: Contraceptive guidance and collection of pregnancy information, see Section 10.4) (during the protocol-defined time frame from the signing of the ICF until the end of study visit).

Postmenopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception.

For men in the study:

Male participants with female partners of childbearing potential are not eligible to participate unless they agree to ONE of the following (during the protocol-defined time frame [Appendix 4, Section 10.4])

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year (Appendix 4, see Section 10.4) when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration (during the protocol-defined time frame from the signing of the ICF until the end of study visit).

E 29. 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 30. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology.

E 31. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, TB, histoplasmosis, listeriosis, coccidioidomycosis, penumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per Investigator's judgment.

E 32. Live, attenuated vaccinations within 12 weeks prior to Visit 1 or planned live, attenuated vaccinations during the study (see Appendix 7: List of prohibited live, attenuated vaccines, Section 10.7).

E 33. Patients with autoimmune disease or patients using systemic immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) or patients with high titer autoantibodies at screening who are suspected of having high risk for developing autoimmune disease at the discretion of the Investigator or the Sponsor.

E 34. Patients with cardiovascular diseases/conditions:

- Unstable ischemic heart disease, including acute myocardial infarction within past 1 year or unstable angina in the last 6 months.

- 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 β 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.
- Cardiomyopathy, as defined by stage III-IV (New York Heart Association) cardiac failure, or other relevant cardiovascular disorder that in Investigator's judgment may put the patient at risk or negatively affect the study outcome
- Uncontrolled hypertension (i.e. systolic blood pressure [BP] >180 mm Hg or diastolic BP >110 mm Hg despite use of anti-hypertensive therapy).

E 35. Hepatitis B and/or C serologies indicative of active or chronic infection.

E 36. Any prior history of malignancy or active malignancy, including lymphoproliferative diseases (except successfully-treated carcinoma in-situ of the cervix, nonmetastatic squamous cell or basal cell carcinoma of the skin) within 5 years prior to Visit 2.

E 37. Clinically significant laboratory tests at Screening/Visit 1:

- Alanine transaminase (ALT) or aspartate transaminase (AST) >3 times upper limit of normal range (ULN).
- Hemoglobin <10 g/dL for male and <9 g/dL for female.
- Neutrophils <1.5 K/mm^3 (<1 K/mm^3 for those of African descent).
- Platelets <100 K/mm^3.
- Creatinine ≥150 µmol/L.

E 38. Patients on macrolide (eg, azithromycin) therapy, unless on stable therapy for >1 year.

E 39. Patients on PDE-4 inhibitors (roflumilast) or leukotriene blockers (montelukast; Singulair etc).

E 40. Despite screening of the patient, enrollment/randomization is stopped at the study level.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

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, reason for screen failure, eligibility criteria, and any serious adverse event (SAE).

Patients can be rescreened if they do not meet an exclusion criterion. Patients may be rescreened one time if they do not meet the eligibility criteria (I 02) at the Screening Visit (Visit 1) or Randomization Visit (Visit 2) due to a spirometry equipment malfunction, or because the patient is unable to provide sufficient reproducible efforts. Up to 3 total attempts during the screening visit (V1) are allowed for the reasons mentioned above.

Patients who meet eligibility criteria (either meet an exclusion criterion, or who do not meet ([I 02]) may be rescreened only once during the open screening period of the study; a different patient identification number will be issued. Rescreening is not permitted if the patient fails to meet inclusion criteria, except for I 02 (see Section 6.3.1). 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 and all Visit 1 procedures must be repeated.

6 STUDY INTERVENTION

The IMP includes SAR440340 and placebo for SC injection during the course of the study.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of Investigational Medicinal Products administered

Investigational Medicinal Product name	SAR440340	Placebo
Dosage formulation	Sterile SAR440340 will be provided in one 20 mL vial containing 287 mg of lyophilisate drug product. One vial of lyophilisate drug product (287 mg) is reconstituted by an unmasked site pharmacist or designee (not involved in any study related assessments/activities except preparation of IMP) with 2.5 mL of sterile water for injection resulting in 2.9 mL of 100 mg/mL SAR440340. A volume of 1.5 mL per injection will be withdrawn from the vial. Patients will receive 2 injections per dose.	Sterile placebo will be provided in one 20 mL vial containing lyophilisate placebo. One vial of lyophilisate is reconstituted by an unmasked site pharmacist or designee (not involved in any study related assessments/activities except preparation of IMP) with 2.5 mL of sterile water for injection resulting in 2.9 mL IMP. A volume of 1.5 mL per injection will be withdrawn from the vial. Patients will receive 2 injections per dose.
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 visits	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 visits
Dosing instructions	14±3 days (q2w)	14±3 days (q2w)
Packaging and labeling	SAR440340 will be supplied in a glass vial packed in a kit box. Each kit box will be labeled as required per country requirement.	Matched placebo will be supplied in a glass vial packed in a kit box. Each kit 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).

Investigational medicinal product (IMP) will be administered by the Investigator or designee following clinic procedures and blood collection. Patients should be monitored by site personnel 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. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs.

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 visits.

6.1.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Background therapy

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

Route(s) of administration: Oral inhalation

Dose regimen: As prescribed.

At Screening Visit 1, all patients must be on Standard of Care background therapy, for 3 months prior to Visit 2/Randomization and at a stable dose for at least 1 month prior to the Screening/Visit 1, including either:

- Double therapy: LABA + LAMA or ICS + LABA or ICS + LAMA.

  OR
- Triple therapy: ICS + LABA + LAMA.

Throughout the study, patients should continue their established background therapy for COPD.

Patients must be willing to stay on their established background medication for COPD throughout the duration of the study. After successful management of an acute exacerbation of COPD (e.g. 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.

Reliever Medication

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

Route(s) of administration: Oral inhalation

Dose regimen: As prescribed.

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

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

Study personnel will convert salbutamol/albuterol nebulizer, levosalbutamol/levalbuterol nebulizer or ipratropium or ipratropium/short-acting β agonists [SABA] combination 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/short-acting β agonists [SABA] nebulizer-to-puff conversion: Patient received 3 ipratropium or ipratropium/short-acting β agonists [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/non-investigational 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 and in the instruction leaflet.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.
2. Only participants enrolled in the study may receive IMP and only authorized site staff may supply or administer IMP. All IMP 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 IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused IMPs are provided in a Pharmacy manual.

Preparation of IMP

SAR440340 or matching placebo lyophilisate will be reconstituted by an unmasked site pharmacist or designee (not involved in any study related assessments/activities except preparation of IMP) as per instruction provided in study pharmacy manual.

Administration will be performed by blinded nurse or designee as per instruction provided in study pharmacy manual.

Responsibilities

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

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

Any quality issue noticed with the receipt or use of an IMP/NIMP/device (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 8.3.8).

A potential defect in the quality of IMP/NIMP/device 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/device and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP/device to a third party, 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. The investigational product (SAR440340 or matching placebo) will be packaged in accordance with the list. The Sanofi Clinical Supplies team will provide the randomized treatment kit number list to the centralized treatment allocation system (Interactive Voice Response System [IVRS]/Interactive Web Response System [IWRS]). This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the treatments to the patients. Patients who meet the entry criteria will be randomized to receive either SAR440340 or matching

placebo. 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:

- SAR440340 300 mg q2w
- Matching placebo for SAR440340.

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

Returned IMP should not be re-dispensed to the participants.

Patients can be rescreened if they do not meet an exclusion criterion. Patients may be rescreened one time if they do not meet the eligibility criteria (I 02) at the Screening Visit (Visit 1) or Randomization Visit (Visit 2) due to a spirometry equipment malfunction, or because the patient is unable to provide sufficient reproducible efforts. Up to 3 total attempts during the screening visit (V1) are allowed for the reasons mentioned above.

Patients who meet exclusion criteria or who do not meet I 02 as specified above, may be rescreened only once during the open screening period of the study. Rescreening is not permitted if the patient fails to meet inclusion criteria (except for I 02, as described above). For rescreening, see Section 5.4.

Randomization will be stratified by Screening/Visit 1 eosinophil count (see below) and by country.

To ensure scientific validity, alerts will be built into the IVRS/IWRS to control the number of patients enrolled into each stratification group, as follows:

1. Eosinophil <250 /mm^3: approximately 50% (170) patients
2. Eosinophil ≥250 /mm^3: approximately 50% (170) patients

6.3.2 Methods of blinding

SAR440340 and matching placebo will be provided in treatment kits indistinguishable in appearance and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

In accordance with the double-blind design, study patients, Investigators, and study site personnel (except the personnel who conduct the reconstitution of the IMP and preparation of syringes for injection) will remain blinded to study treatment and will not have access to the randomization (randomized treatment kit number) except under circumstances described in Section 6.3.3.

To maintain blinding, the personnel involved with dose preparation will be required to agree not to reveal to other study personnel the type of IMP solution (SAR440340 versus placebo) in the vials/syringes.

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 interactive response technology (IRT) 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 dispensed, used, and unused. The product accountability and inventory form is to be updated each time investigational product is dispensed. The study monitor will periodically check the supplies of the IMP held by the Investigator or pharmacist to verify accountability.

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

All used, partially used, or unused treatments will be destroyed according to the standard practice at the site or per local regulations. A detailed treatment log of the IMP will be established with the Investigator or other personnel designated by the Investigator, and countersigned by the Investigator and the Monitoring Team. Confirmation of destruction will be provided to the Sponsor.

For NIMP not provided by the Sponsor, tracking, reconciliation and destruction will be managed according to local regulation.

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 treatments are not permitted during the screening or treatment phases:

- Systemic steroids (except when used to treat exacerbations)

  Note: one short-term course of systemic corticosteroids (up to 6 days) is permitted in 24 weeks, when medically necessary for reasons not related to AECOPD, eg. in the case of severe poison ivy exposure.
- PDE-4 inhibitor such as roflumilast
- Methylxanthines (theophylline, aminophyllines)
- Leukotriene receptor antagonists or leukotriene synthesis inhibitors
- Lipoxygenase inhibitors
- Anti-IL5 mAb (eg, benralizumab; mepolizumab)
- Anti-IgE therapy (eg, omalizumab)
- Anti-IL4R mAb (eg, dupilumab)
- Systemic immunosuppressants (eg, methotrexate, any anti-TNF mAbs, B and/or T cell targeted immunosuppressive therapies)
- Bronchial thermoplasty
- Intravenous immunoglobulin (IVIG) therapy
- Live Attenuated Vaccines: refer to Appendix 7: List of Prohibited Live Attenuated Vaccines, Section 10.7.
- β-adrenergic receptor blockers (except for a selective β-1 adrenergic receptor blocker used with dose stable 1 month prior to Visit 1)
- COPD relievers other than salbutamol/albuterol, levosalbutamol/levalbuterol or ipratropium: their use is not recommended during the study period. In case of use in exceptional circumstances (eg, prescribed by a physician not participating in the study), their use will be documented in the patient's file and reported in the eCRF.
- Other investigational drugs

Note: The following is a list of permitted concomitant medications during the study:

- Antihistamines are permitted as concomitant medication
- Ocular, intranasal, and topical corticosteroids are permitted during the study.

6.6 DOSE MODIFICATION

Not applicable for this study.

6.7 INTERVENTION AFTER THE END OF THE STUDY

Not applicable

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 CRF or eCRF. In any case, the patient should remain in the study as long as possible.

7.1.1 Permanent discontinuation

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 treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator’s decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

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

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Pregnancy.
- Anaphylactic reaction or systemic allergic reactions or acute allergic reactions that are related to IMP and require immediate treatment (Appendix 14: Definition of anaphylaxis, see Section 10.15).

- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any situation that meets permanent discontinuation rule as outlined in Appendix 6: Liver and other safety: suggested actions and follow-up assessments (Appendix 6, Section 10.6).
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (Appendix 15: List of Opportunistic Infections, See Section 10.16).
- Serum ALT >3 ULN and total bilirubin >2 ULN (Appendix 6, see Section 10.6).
- Serum ALT >5 ULN if baseline ALT ≤2 ULN or ALT >8 ULN if baseline ALT >2 ULN (Appendix 6, see Section 10.6).

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 intervention discontinuation

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 visit (ETD) with all assessments normally planned for the EOT visit, to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment is available. In addition, and to allow assessment of patient outcomes over the stipulated study period, patients will be asked and encouraged to complete all remaining study treatment visits, and participate in all safety follow-up assessments according to the visit schedule with a +/-5 day window. For such patients the assessment schedule will be reduced (See study flowchart for patients after permanent treatment discontinuation in Section 1.3.2) and alternate visits during the planned treatment period may be conducted by phone (those with odd visit numbers, except for the planned EOT), as can visits F1 and F2.

Under exceptional circumstances when a patient cannot come to the site for a scheduled visit, a phone contact can be made. During the phone contact, at least information about AEs, concomitant medication and COPD exacerbation events should be collected.

Participants 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.

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

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs.

If patient is unable to return to clinic for a given visit within the specified visit window, patient should follow-up with all visit procedures planned for the subsequent visit (excluding randomization and EOT). Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2). For all temporary treatment discontinuations, duration must be recorded by the Investigator in the CRF or eCRF.

Following a temporary interruption or a missed dose, the IMP treatment should be reinitiated at the next scheduled visit, maintaining the original dosing schedule.

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. The investigator should also inform the Sponsor that appropriate actions are taken regarding these samples.
- 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 treatment visits (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 CRF or e-CRF 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 stop participating 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 re-randomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

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 IMP.
- 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).

8.1 EFFICACY ASSESSMENTS

8.1.1 Disease-specific efficacy measures

8.1.1.1 COPD exacerbation

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, emergency medical care visit or resulting in death.

All other exacerbations will be classified as "mild".

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 (e.g. 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 page. These events should not be reported as AEs unless they fulfill a seriousness criterion. Any course of systemic steroids/antibiotics started <7 days of finishing a previous course should be considered as treatment for a single exacerbation.

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 (14) and prior to administration of investigational product.

For pre-bronchodilator measured parameters, including FEV1, peak expiratory flow (PEF), 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 other 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.

8.1.1.3 Optional Fractional exhaled nitric oxide (FeNO)

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

FeNO will be measured at sites only with access to FeNO equipment.

8.1.1.4 Disease-specific, daily efficacy assessments

See Patient Reported Outcomes (Section 8.1.2)

8.1.1.5 Optional actigraphy and home spirometry assessments

Optional assessments of actigraphy (sleep and activity) and home spirometry will be available for patients in the US and Canada only. Patient will be issued an actigraphic wristband and asked to wear it continuously (including at night) throughout three monitoring periods defined in study flowchart (Section 1.3) on the nondominant hand, including at night. The actigraphic data is used to measure sleep parameters and daytime activity. The actigraph will be worn during the screening period as well as two monitoring periods during the treatment phase. Data from the device will be uploaded to a computer at each clinic visit following a monitoring period.

Patients will receive documented in-clinic training for use of ambulatory at-home spirometry during screening. During the study patients will be required to use at-home spirometry with electronic data storage to measure FEV1. Patients will be instructed to perform expiratory flow maneuvers as described in the study manual at least twice daily between 06:00 and 12:00 hour and between 18:00 and 24:00 hour during the screening period and for 2 week intervals during the treatment and follow-up period as indicated in the study flowchart.

8.1.1.6 Optional Sputum Collection

A subset of study sites will be selected to perform evaluations of induced sputum, and patients at these selected sites will have the option to participate in this assessment. Sputum induction is a relatively noninvasive method to obtain sputum for cell or fluid phase inflammatory indices, culture or cytology. It is performed with an aerosol of normal or hypertonic saline generated by an ultrasonic nebulizer. As this aerosol is a potential bronchoconstrictive stimulus, it is made safe by pretreatment with salbutamol and inhalation in a dose response manner. Collection will be performed according to protocol flowchart.

Further details will be provided in the site procedure manual.

8.1.2 Patient reported outcomes questionnaires

At screening (Visit 1), patients will be issued an electronic diary. Patients will be instructed 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 uses an electronic diary to:

- Respond to the COPD symptom scale questions of the EXACT tool
- Record the daily use of COPD reliever medication
- Record use of systemic corticosteroids and/or antibiotics taken for COPD exacerbation.

The electronic diary will be used for patient reported outcome questionnaires.

In the Post IMP Treatment Period, the patient's response in the electronic diary will not be recorded daily; questionnaires will only be administered at on-site visits. When completed at study site, PRO assessments should be completed as part of the visit (per SoA, Section 1.3) but prior to any meaningful communication with a health care professional or any other study procedures.

8.1.2.1 COPD Assessment Test (CAT)

The CAT (15) is a new questionnaire that is designed for patients with COPD to measure the effects of the disease on their quality of lives. The CAT™ is an 8-item self-administered questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD (see Appendix 10: COPD Assessment Test, Section 10.11).

The CAT™ score ranges from 0 to 40, a higher score indicating a higher impact on health status. The test is about cough, phlegm, chest tightness, dyspnea, activity limitation, confidence, sleep and energy (16). Patients scored questions from 1-5 according to their own feelings about the disease (1 = I am very happy; 5 = I am very sad).

8.1.2.2 St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire (SGRQ [(17), (18)]) is a 50-item questionnaire designed to measure and quantify health-related 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 11: St. George's Respiratory Questionnaire, Section 10.12).

The first part ("Symptoms") evaluates symptomatology, including frequency 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 activities that cause breathlessness or are limited because of breathlessness. The "Impacts" section covers a range of factors including influence on employment, being in control of health, panic, stigmatization, the need for medication, side effects of prescribed therapies, expectations for health and disturbances of daily life. 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.

8.1.2.3 Exacerbations of chronic obstructive pulmonary disease tool (EXACT)

The EXACT Total Score measures symptoms of acute bacterial exacerbations of chronic bronchitis-COPD (ABECB-COPD), ie, an acute, sustained, and worsening of signs and symptoms beyond day-to-day variability (see Appendix 12: Exacerbations of Chronic obstructive pulmonary disease tool [EXACT], Section 10.13). The instrument's total score is made up of a total of 14 items representing the following domains:

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

The EXACT is a daily diary, completed each evening before bedtime. The instrument was developed with e-diary administration in mind, with cognitive interviews performed with paper pen booklet and personal digital assistant (PDA) to document respondent understanding in either mode and user acceptance of the PDA.

8.1.2.4 Euro Quality of Life-5 Dimension questionnaire (EQ-5D)

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 (19). EQ-5D is designed for self-completion by patients, (Appendix 13: Euroquol Questionnaire, see Section 10.14).

8.2 SAFETY ASSESSMENTS

The same safety assessments will be applied across all 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 examinations 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 BP (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.

Vital signs will be measured in the sitting position using the same arm (preferably), at each visit detailed in the SoA (Section 1.3), and will be measured prior to receiving investigational product at the clinic visits.

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. 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: Clinical Laboratory Tests (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) 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 22 weeks after the last dose of IMP 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 16: 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 (see 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 Section 8.3.2, even if not fulfilling a seriousness criterion, using the screens in the eCRF.

Anaphylactic reactions, systemic allergic reactions that require treatment (refer to Section 10.15 for definition of anaphylaxis).

- Anaphylactic reactions, systemic allergic reactions that require treatment (refer to Section 10.15 for definition of anaphylaxis).
- Severe injection site reactions (ISR) that last longer than 24 hours

  Note: A severe ISR (for AE reporting) is any event that meets one of the following criteria:

  - With a diameter of at least 10 cm.
  - Impacting daily activities.
  - With ulceration or necrosis.
  - For which operative intervention is required.
- Any infection meeting at least one of the following criteria:
  - Any serious infection (SAE).
  - Requires parenteral (IV, intramuscular, SC) antimicrobial therapy
    Note: Antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.
  - Requires oral antimicrobial therapy for longer than 14 days.
  - Is a parasitic infection.
  - Is an opportunistic infection (see Appendix 15: List of Opportunistic Infections, Section 10.16).
- Significant ALT elevation.
  - ALT >3 x the upper limit of normal (ULN) associated with Total Bilirubin >2 x ULN; or
  - ALT >5 x ULN in patients with baseline ALT ≤2 x ULN; or
  - ALT >8 x ULN if baseline ALT >2 x ULN.
- Malignancy
- Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient 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 (Appendix 4: Contraceptive guidance and collection of pregnancy Information, see 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/noninvestigational medicinal product (NIMP)
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose during an interval of <8 days. "The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form".
  - 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".
  - Of note, asymptomatic overdose has to be reported as an AE.

Table 6 - Safety instructions for Adverse Events of Special Interest

AESI	Description
Hypersensitivity	Allergic reaction is a potential risk associated with the administration of most therapeutic mAbs. Acute allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Anaphylaxis may represent the most severe form of allergic reaction, but these events may also occur via non-IgE mediated mechanisms (eg, anaphylactoid reactions), or may occur via other immune-mediated mechanisms (eg, cytokine-mediated). Allergic reactions may begin within a few hours and persist up to 24 hours post dosing. Refer to Section 10.15 "Definition of Anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis. Delayed onset or late phase hypersensitivity reactions (ie, Type 1 hypersensitivity reaction) may manifest between 10 and 12 hours post dosing. Patients should be monitored for at least 30 minutes after IMP dose administration for any signs or symptoms of a hypersensitivity reaction throughout the study. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Anaphylactic reactions, systemic allergic reactions that require treatment must be reported as an AESI with immediate notification (for further details, see Table 7). If an anaphylactic reaction, systemic allergic reaction requiring treatment occurs and is considered related to IMP by the investigator the study treatment should be permanently discontinued. Anti-drug antibodies and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.
Severe injection site reactions	Based on the SC mode of administration of high doses of protein ISRs are considered as a potential risk for SAR440340. Patients who experience an ISR must be closely monitored for the possibility of a more intense ISR with a future injection. Any severe ISR that lasts over 24 hours will be reported as an AESI with immediate

	notification (for further details please see Table 7). Anti-drug antibodies and PK samples will be collected near the onset and resolution of the AESI for any additional analysis If there is any consideration being given to premedicating before the next dose (for preceding an injection site reaction, please contact Sponsor prior to dosing patients).
Infections, including opportunistic infections	Some biologic therapies have been associated with an increased risk of infection, including opportunistic infection. IL-33 is a proinflammatory cytokine released by damaged epithelial cells in response to insults such as allergens, viruses, or bacteria. IL-33 signaling initiates and amplifies multiple downstream inflammatory pathways resulting in effects characteristic of both type 1 and type 2 immune inflammations. Although blockade or knockout of IL-33 signaling in mice did not reveal any unique role for IL-33 in mounting an acute immune response to viral challenge and did not lead to worsening of symptoms or outcome, patients will be monitored for signs or symptoms of infection. SAR440340 inhibits the T-helper 2 (Th2) cytokines production. Infections with a diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte responses. The Th2 response is characterized by production of IL4, IL13, and IL5, subsequently generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a number of helminthic parasitic diseases. The eosinophilic response to helminths is determined both by the host's immune response and by the parasite, including its distribution, migration, and development within the infected host. Therefore, patients treated with SAR440340 may potentially have an increased risk of parasitic infection. To minimize the risk, patients with certain type of infections are not allowed to participate in the study (eg, patients with active opportunistic or parasitic infections or at high risk of developing the infections, patients with medical history of invasive opportunistic infections, patients with HIV infection or HIV seropositivity, patients with positive screening for hepatitis B and C). As a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness. During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue and hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/or residence in endemic areas, especially when conditions are conducive to infection (eg, extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc). Subsequent medical assessments (eg, stool exam, blood tests, etc) must be performed in order to rule out parasitic infection/infestation. Infections defined in Section 8.3.1 should be reported as AESIs with immediate notification. A complete diagnostic work-up should be performed (ie, cultures, histopathological or cytological evaluation, antigen detection and serum antibody titers). Patients should be referred to an infectious disease specialist if deemed necessary for diagnostic work up and appropriate treatment. Infections or infestations that do not respond to medical treatment should have study drug discontinued until the infection is resolved. For any opportunistic infection, such as TB, or other infections whose nature or course may suggest an immunocompromised status (see Section 10.16), patients must be permanently discontinued from study medication.
Elevated liver function tests	No preclinical and clinical data has suggested any hepatic toxicity of SAR440340; however, as a general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity. In order to closely follow liver function tests (LFT), assessment of total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing. Guidance for the investigation of elevated LFTs as well as concurrent management of IMP is provided in Section 10.6.

	ALT elevations defined in Section 8.3.1 should be reported as AESIs with immediate notification.
Malignancy	In toxicology studies on SAR440340-mediated IL-33 blockade, the effect of SAR440340 administration has not demonstrated the development of malignancy. Long term use has not been studied. The investigator should carefully monitor for any signs or symptoms of malignancy. Malignancy should be reported as AESI with immediate notification.
Pregnancy	In case of positive urinary test, the study treatment will be withheld and a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. Pregnancy will lead to definitive treatment discontinuation in all cases. Refer to Section 1.3 for the schedule of pregnancy tests performed throughout this study.

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 up to the end of study 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 and AESI 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 IMP 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).

Adverse event (SAE and AESI) reporting is summarized in Table 7.

Table 7 – Adverse event reporting

Adverse event/laboratory abnormality		Reporting timeframe
Serious adverse event		Within 24 hours
Pregnancy		Within 24 hours
Overdose	Symptomatic	Within 24 hours
	Asymptomatic	Routine
ALT elevation		
	ALT >3 x ULN and associated with total bilirubin >2 x ULN	Within 24 hours
	ALT >5 ULN if baseline ALT is ≤2 ULN	Within 24 hours
	ALT >8 ULN if baseline ALT is >2 ULN	Within 24 hours
Anaphylactic or systemic allergic reactions that require treatment.		Within 24 hours

Adverse event/laboratory abnormality	Reporting timeframe
Severe injection site reactions that last longer than 24 hours.	Within 24 hours
Infections as defined in Table 6	Within 24 hours
Malignancy	Within 24 hours

ALT: alanine aminotransaminase; ULN: upper limit of normal.

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 an IMP 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 an IMP 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 (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators.
- 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 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 and thus will not be considered unexpected. 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).

Any other AE not listed as an expected event in the IB or in this protocol will be considered unexpected.

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

Any defect in the IMP/NIMP/device 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 of IMP is an AESI (defined in Section 8.3.1). No antidote is available for SAR440340.

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.
3. Obtain a serum sample for PK analysis as soon as possible, from the date of the last dose of IMP 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.

8.5 PHARMACOKINETICS

Blood samples will be collected for determination of functional SAR440340 in serum as specified in the SoA (Section 1.3). Samples may be collected at additional time points during the study if warranted (see Appendix 6, Section 10.6). Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. The actual date and time (24-hour clock time) of each sample will be recorded.

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 16, see Section 10.17).

Table 8 - Summary of handling procedures for pharmacokinetic (PK) samples

Sample type	PK (SAR440340)
Matrix	Serum
Blood sample volume	5 mL
Anticoagulant	None
Blood handling procedures	See Operational Manual
Serum aliquot split	2 aliquots
Serum shipment condition	In dry ice

PK = pharmacokinetics.

The bioanalytical methods for pharmacokinetics are summarized in Table 9.

Table 9 - Summary of bioanalytical methods for pharmacokinetics samples

Analyte	PK (SAR440340)
Matrix	Serum
Analytical technique	ELISA
Site of bioanalysis	Regeneron

ELISA: enzyme-linked immunosorbent assay; PK: pharmacokinetics.

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: If an SAE or AESI (anaphylaxis, hypersensitivities, ISR, or certain laboratory abnormalities [see appendix 6, Section 10.6]) occur in a patient, blood samples should be collected for determination of functional SAR440340 concentration, and ADA assessment at or near the onset and completion of the occurrence of the event, if possible. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled systemic drug concentration page in the eCRF must be completed as well. If necessary for safety monitoring, additional ADA samples may be collected after the EOS Visit until resolution of AE.

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

- Blood eosinophil and neutrophil counts.
- Induced sputum for RNA expression (optional for patients at a subset of sites).
- Selected biomarkers of the IL-33 and/or Type 2 inflammation pathway
  - Total IL-33, soluble IL-33 receptor (sST2),
  - Calcitonin
  - PARC
  - Eotaxin-3
  - Total IgE.
  - Fibrinogen
- Optional: Messenger ribonucleic acid sequencing or whole transcriptome analysis.
- Optional: DNA/RNA sample will be collected for pharmacogenomic effects (Section 8.7).

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 phramcodynamics will be provided in a lab manual.

8.6.2 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 (see Section 1.3).

8.6.3 Plasma/serum biomarkers

Total IL-33, sST2, PARC will be assayed using a validated enzyme immunoassay.

Calcitonin assay: (development of assay method ongoing).

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.

8.7 PHARMACOGENOMICS

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

For those patients who consent to the optional pharmacogenomic sample collection section of the ICF, blood samples for exploratory genetic analysis of DNA or RNA (See Appendix 5: Pharmacogenomics, Section 10.5) will be collected at the study visit as specified in the SoA (Section 1.3), and these samples will be stored for future analysis(Appendix 16: Future use of samples, see Section 10.17). Specific procedures for collection, storage and shipping of 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 (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 pharmacogenomic biomarkers are described in Section 8.6 and Section 8.7, respectively.

8.8.1 Immunogenicity assessments

Blood samples will be collected for determination of antibodies to SAR440340 in serum as specified in the SoA (Section 1.3). Blood samples should be collected at the final visit from participants who discontinued IMP or were withdrawn from the study. Samples may be collected at additional time points during the study if warranted (see Appendix 6, Section 10.6). Special procedures for the collection and handling of samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Table 10 - Summary of handling procedures for antidrug antibody (ADA) samples

Sample type	ADA (SAR440340)
Matrix	Serum
Blood sample volume	5 mL
Anticoagulant	None
Blood handling procedures	See Operational Manual
Serum aliquot split	2 aliquots
Serum shipment condition	In dry ice

ADA = antidrug antibodies

The bioanalytical method for antidrug antibody is summarized in Table 11. In a patient with treatment-emergent ADA response, if the sample at week 12 is positive in the ADA assay, then ADA assessments may be performed on PK samples collected at Week 4.

Table 11 - Summary of bioanalytical methods antidrug antibody

Analyte	ADA (SAR440340)
Matrix	Serum
Analytical technique	ELISA/Electrochemiluminescence
Site of bioanalysis	Regeneron

ADA = antidrug antibodies; ELISA: enzyme-linked immunosorbent assay

Note: If an SAE or AESI (anaphylaxis, hypersensitivity, or an ISR lasting more than 24 hours) occurs in a patient, blood samples should be collected for 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 page in the eCRF must be completed as well. If necessary for safety monitoring, additional ADA labs may be drawn after the EOS Visit until resolution of AE.

8.9 HEALTH ECONOMICS

Health economics and patient related outcome (Section 8.1.2]) data, associated with medical encounters, will be collected in the PRO questionnaires (see Section 8.1.2) by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded from the PRO questionnaires.

When completed at study site, PRO assessments should be completed as part of the visit (per study flow chart) but prior to any meaningful communication with a health care professional or any other study procedures.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The statistical hypothesis for the primary efficacy endpoint of annualized rate of moderate-to-severe AECOPD is to test that SAR440340 is superior to placebo at the two-sided 5% alpha level:

> H0: Rate ratio of SAR440340 versus placebo ≥1 versus Ha: Rate ratio of SAR440340 versus placebo <1.

The statistical hypothesis for the key secondary efficacy endpoint, the change from baseline to Week 16-24 in pre-bronchodilator FEV, is to test that SAR440340 is superior to placebo at the two-sided 5% alpha level:

> H0: The change in the SAR440340 group is not larger than that in the placebo group versus Ha: The change in the SAR440340 group is larger than that in the placebo group.

9.2 SAMPLE SIZE DETERMINATION

To assess the power of the primary efficacy endpoint the annualized rate of moderate-to-severe AECOPD, we assume

- Average of 1.0 to 1.5 AECOPD per year in the placebo group of this study population enriched for severity and high risk of AECOPD.
- The number of AECOPD follows a negative binomial distribution with dispersion parameter 1.5 (8) for all the groups.
- A Wald-test is used to test whether the risk ratio is 1 with 2-sided 5% significance level.
- Patients will be treated with a minimum of 24 weeks and a maximum of 52 weeks depending on their study entry times. The monthly cumulative patient accruals are assumed to be 1, 5, 10, 25, 50, 90, 150, 210, 270, 335 and 340 for an eleven (11)-month accrual period.
- Cumulatively, 9%, 15% and 20% of patients drop out of the study due to discontinuation or other reasons by 12, 24 and 52 weeks after study entry.
- Patients are randomized to the treatment group and the placebo group with a 1:1 ratio.

With these assumptions and 170 patients per group (340 patients in total), the study will yield 81.6% to 88.8% powers with risk reduction equal to 45% and the placebo rate ranging from 1.0 to 1.5 per year. To obtain at least 80% power, the minimum risk reduction is from 44.2% to 40.6%. The minimum detectable risk reduction (i.e. with 50% power) is from 32.7% to 30.0%. See the table below for more details.

Table 12 - Power calculation for various event rates in the placebo group

	Power for certain Risk Reduction (RR)			Minimum RR for certain power	
Placebo rate	RR=40%	RR=45%	RR=50%	Power=80%	Power=50%
1.0	69.9%	81.6%	90.3%	44.2%	32.7%
1.2	74.1%	85.2%	92.9%	42.5%	31.4%
1.5	78.5%	88.8%	95.2%	40.6%	30.0%

RR: risk reduction

Based on the accrual and drop-out assumptions, the mean exposure time is 35.5 (±12.8) weeks. Since we use variable follow-up times for patients entering at different times, the power will depend on the actual accrual rates and the drop-out rates. We will closely monitor these rates. If the accrual rates are significantly lower than planned and/or the drop-out rates are higher than expected, the minimum treatment period may be extended to achieve the desired amount of total exposure. The maximum treatment period of 52 weeks will not be changed.

To assess the key secondary efficacy endpoint the change from baseline to Week 24 in post-bronchodilator FEV1, we assume that:

- A common standard deviation of 0.3 L in each of the two groups is assumed, which is a consensus value based on the review of historical data from COPD trials.
- A difference of 0.12 L between the treatment group and the placebo group.
- A 2-sided t-test with 5% significance level.
- Fifteen percent (15%) of patients with missing data at Week 24 due to discontinuation or other reasons.
- Patients are randomized to the treatment group and the placebo group with a 1:1 ratio.

With these assumptions and 170 patients per group (340 patients in total), we will have 92.6% power to detect the difference of 0.12 L between the treatment group and the placebo group. The least significant difference between groups will be 0.07 L.

Randomization will be stratified by Screening/Visit 1 eosinophil count (see below) and by country.

To ensure scientific validity, alerts will be built into the interactive voice/web response system (IVRS/IWRS) to control the number of patients enrolled into each stratification groups, as follows:

1. Eosinophil <250 /mm^3: approximately 50% (170) patients
2. Eosinophil ≥250 /mm^3: approximately 50% (170) patients.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 13):

Table 13 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF
Randomized	Randomized patients consist of all patients with a treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used or not. These patients form the randomized population. Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population. Data from these patients will be summarized separately. For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.
Modified Intent-to-treat (mITT)	The analysis population for the efficacy endpoints will be the modified intent-to-treat (mITT) population: all randomized patients who received at least 1 dose of IMP, analyzed according to the treatment group allocated by randomization. Randomized patients for whom it is unclear whether they took the study medication will be included in the mITT population according to treatment they are randomized.
Safety	The safety population will include all randomized patients who received at least 1 injection of IMP. For safety analyses, patients will be analyzed in the treatment group for which they received the majority of injections.
Pharmacokinetic (PK)	The PK population will consist of all patients in the mITT population with at least 1 postdose, nonmissing SAR440340 serum concentration.
Antidrug antibody (ADA)	The ADA population will consist of all patients in the mITT population with at least one qualified result in the anti-SAR440340 assay following the first dose of study medication. Patients will be analyzed according to the treatment actually received.

ICF: informed consent; mITT: modified intent-to-treat; PK:pharmacokinetic; ADA: antidrug antibody.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock 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

All efficacy analyses will be performed on the mITT population, unless otherwise specified.

Table 14 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary Rate of moderate-to-severe AECOPD over 52 weeks.	For the primary efficacy endpoint, the annualized exacerbation rate, a negative binomial regression model will be used to assess treatment differences. The model will include the total number of events occurring during the observation period (up to Week 52) as response variable, and the treatment group, the baseline eosinophil strata and region (pooled countries) as covariates. Log-transformed observation duration will be the offset variable. Parameters will be estimated using the maximum likelihood method with the Newton-Raphson algorithm. The annualized event rate for each of the treatment groups and the ratio between the treatment and placebo along with its 95% confidence interval will be estimated from the model. In the case of premature discontinuation of study drug, a secondary analysis will include events up to 14 days after the last dose. Using the same method, subgroup analyses will be performed separately by the baseline eosinophil levels (≥250 /mm^3 versus <250 /mm^3).
Secondary	
Key Secondary • Change from baseline in FEV1 to Week 16-24 (pre-bronchodilator*)	Key Secondary Endpoint The key secondary efficacy endpoint, the average change from baseline to Week 16-24 in pre-bronchodilator FEV1 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. Model-based averages across Weeks 16, 20 and 24 will be compared between the treatment groups. The dependent variable is the change from baseline in pre-bronchodilator FEV1 at each time points. The model will include baseline FEV1 value, treatment group, visit, and treatment-by-visit interaction, the baseline eosinophil strata, and region (pooled countries), as covariates. An unstructured correlation matrix will be used to model the within-patient correlations. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Additional covariates such as the background medications, age, height, gender, race and smoking status will be considered for inclusion in the analysis model based on evaluation of blinded data and the final analysis model documented in the statistical analysis plan (SAP). Comparison between the treatment group and the placebo group will be made within this model and the least square mean difference and their 95% confidence intervals will be estimated. In the case of premature discontinuation of study drug the primary analysis will include data up to 14 days after the last dose. Subgroup analyses will be performed using the same method by baseline eosinophil levels (≥250 /mm^3 versus <250 /mm^3)
Other Secondary • Change from baseline in FEV1 to Week 24 (post-bronchodilator*) • Time to first moderate or severe AECOPD	Other secondary endpoints Change from baseline to Week 24 in FEV1 post-bronchodilator will be analyzed in the same way as the key secondary efficacy endpoint. Similar analytic method will be applied to analyze change from baseline to time points past Week 24 in FEV1 (both pre-bronchodilator and post-bronchodilator). Time to first moderate or severe AECOPD will be analyzed using a Cox regression model with treatment, baseline eosinophil strata, and region (pooled country) as covariates. The Kaplan-Meier (K-M) method will be used to estimate the probabilities of first AECOPD at specific time points for each group. Additional covariates will be considered based on evaluation of blinded data and the final analysis model documented in the SAP.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2 Safety analyses

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

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

Table 15 - Safety analyses

Endpoint	Statistical Analysis Methods
AE, SAE, AE leading to 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, serious TEAE, and TEAE leading to discontinuation of the study will be tabulated by treatment group. In addition TEAEs will be described according to maximum intensity and relation to the study drug. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.
AESI	The following summaries will be generated: 1. Incidence of each AESI will be tabulated by treatment group. 2. The time-to-first event analyzed using K-M methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used. 3. An overview summary of the number (%) of patients with - any TEAE - any serious AE (regardless of treatment-emergent status) - any treatment-emergent SAE - any AE leading to death - any TEAE leading to permanent study drug discontinuation - any TEAE by maximum intensity, corrective treatment, and final outcome - cumulative incidence at specified time points (K-M estimates at Week 1, 4, 12, 24, 52 and 72) Definitions of AESIs and the method to identify AESIs 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) and reasons for death 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.
PCSA	The following definitions will be applied to laboratory parameters, vital signs, and ECG. - The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG. - The 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.
Laboratory parameters, vital signs, and ECG	The following definitions will be applied to laboratory parameters, vital signs, and ECG. - Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. - The proportion of patients who had at least one incidence of PCSA at any time during the TEAE period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

AE: adverse event; SAE: serious adverse event; SOC: system organ class; HGLT: high-level group term; HLT: high level term; PT: preferred term; n: number; AESI: adverse event of special interest; K-M: Kaplan-Meier; SAP: statistical analysis plan; PCSA: potentially clinically significant abnormality; ECG: electrocardiogram.

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

9.4.3 Other analyses

PK, pharmacodynamic, and biomarker exploratory analyses are described here briefly and will be detailed in the statistical analysis plan finalized before database lock.

The population PK analysis and pharmacodynamic analyses be presented separately from the main clinical study report (CSR).

Table 16 - Other analyses

Endpoint	Statistical Analysis Methods
Pharmacokinetics (PK)	Concentrations of functional SAR440340 will be summarized using arithmetic and geometric means, standard deviation, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by treatment per visit.
Anti-drug antibodies (ADA)	The incidence of positive ADA response for SAR440340 will be assessed as absolute occurrence (n) and percent of patients (%), presented by treatment groups. Listing of ADA titer levels will be provided for patients positive in the ADA assay. The ADA analysis will be detailed in the SAP.
Pharmacodynamics	The values to be used as baseline will be those collected on Day 1 (predose assessments). If any of the scheduled assessments on Day 1 are technically disqualified (eg, insufficient sample), then values determined at Screening can be used as baseline. For all parameters, raw data, absolute changes from baseline, and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point. Summary plots (mean ± standard error of the mean) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment group.
Patient Reported Outcomes (health-related quality of life/health economics variables)	Change from baseline in the following variables: EXACT, SGRQ, and EQ-5D will be analyzed with an MMRM approach described previously for the continuous efficacy variables. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 95% CI's, and the p-values will be provided for comparison between the active treatment groups and the placebo group.

9.5 INTERIM ANALYSES

No formal interim analysis is planned.

Analyses of study data will be performed on an ongoing basis and provided to an internal DMC for internal decision making. No formal stopping rules or adjustment for multiplicity will be applied.

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (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 to an Institutional Review Board (IRB) /Independent Ethics Committee (IECs) by the Investigator and reviewed and approved by the IRB/IEC 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

- 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.

10.1.4 Committees Structure

The study data will be reviewed by an internal DMC.

10.1.4.1 Data Monitoring Committee (DMC)

An internal DMC will be comprised of individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC members are independent of the project/study teams and are not involved in the study conduct. The primary responsibilities of the DMC are to review and evaluate the study data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to project/study team.

The DMC procedures and data to be reviewed by the DMC are described in the DMC charter.

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 clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. 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: clinicalstudydatarequest.com.

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.
- 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 15 years after study completion 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 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 the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- 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 recruitment of participants by the Investigator
- Discontinuation of further IMP development.

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 17 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 IMP administration and/or response evaluation. Additionally, if the local laboratory results are used to make either an IMP decision or response evaluation, the results and normal ranges 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 17 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Hematology	To include hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with 5-part differential count, and total red blood cell count. Neutrophil and eosinophil counts (study biomarkers) will be evaluated as a part of hematology testing, and are also evaluated at additional timepoints (see SoA Section 1.3).
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 nonconjugated bilirubin), ALT, AST, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase.
Routine urinalysis	To 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. Cotinine will be tested using the urine sample collected.
Other tests	• Clinical laboratory testing at Screening Visit 1 will include hepatitis screen covering HBs Ag, hepatitis B surface antibody (HBs Ab), HBc Ab, hepatitis C virus antibodies (HCV Ab), 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 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). • Clinical laboratory testing at Screening Visit 1 will also include Quantiferon gold testing for all patients. If the result is confirmed positive, the patient should be referred to an Infectious Disease specialist. Please refer to the central laboratory manual for additional details.

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 IMP, whether or not considered related to the IMP.
- 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 IMP.

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, Section 8.3.7).
- 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 IMP 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 IMP 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

- 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 (see Section 8.3.7).
- 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 even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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.

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

- Intensive treatment in an emergency room or at home for:
  - Anaphylaxis (refer to Section 10.10 for the definition of anaphylaxis)
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc).

- Convulsions (seizures, epilepsy, epileptic fit, etc)
- Development of drug dependence or drug abuse
- ALT >3 x the upper limit of normal (ULN) + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study
- Chronic neurodegenerative diseases (newly diagnosed).

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 IMP 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 IMP 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 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.
- 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 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.

CONTRACEPTION GUIDANCE

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 18 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant
- In addition male participants must refrain from donating sperm for the duration of the study and for 22 months after the last dose of study intervention.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame (from the signing of the ICF until the end of study visit).

Female participants

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 18.

Table 18 - 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]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
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 for for subsequent visits.

Additional pregnancy testing should be performed 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:

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 IMP.
- 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.

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

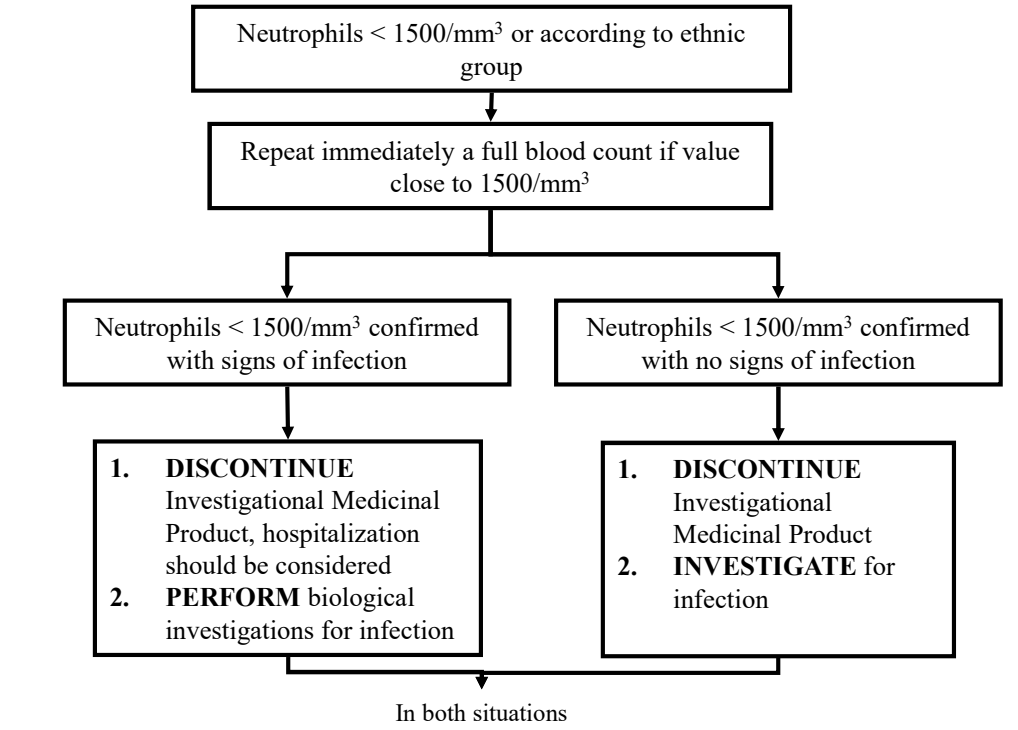
10.5 APPENDIX 5: PHARMACOGENOMICS

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

NEUTROPENIA

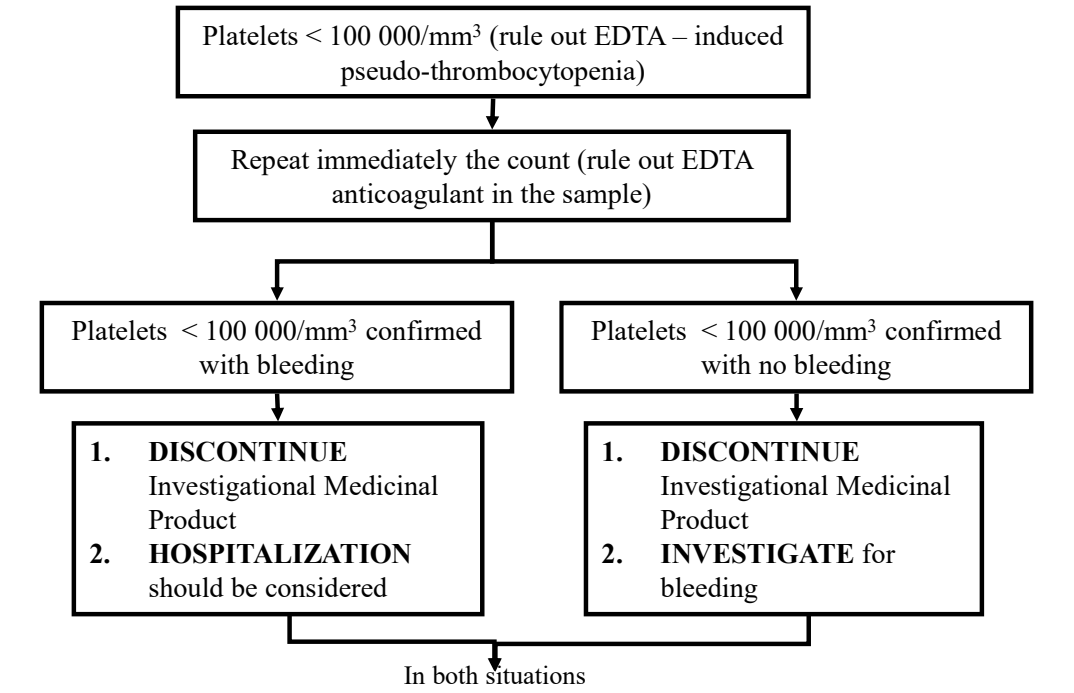


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

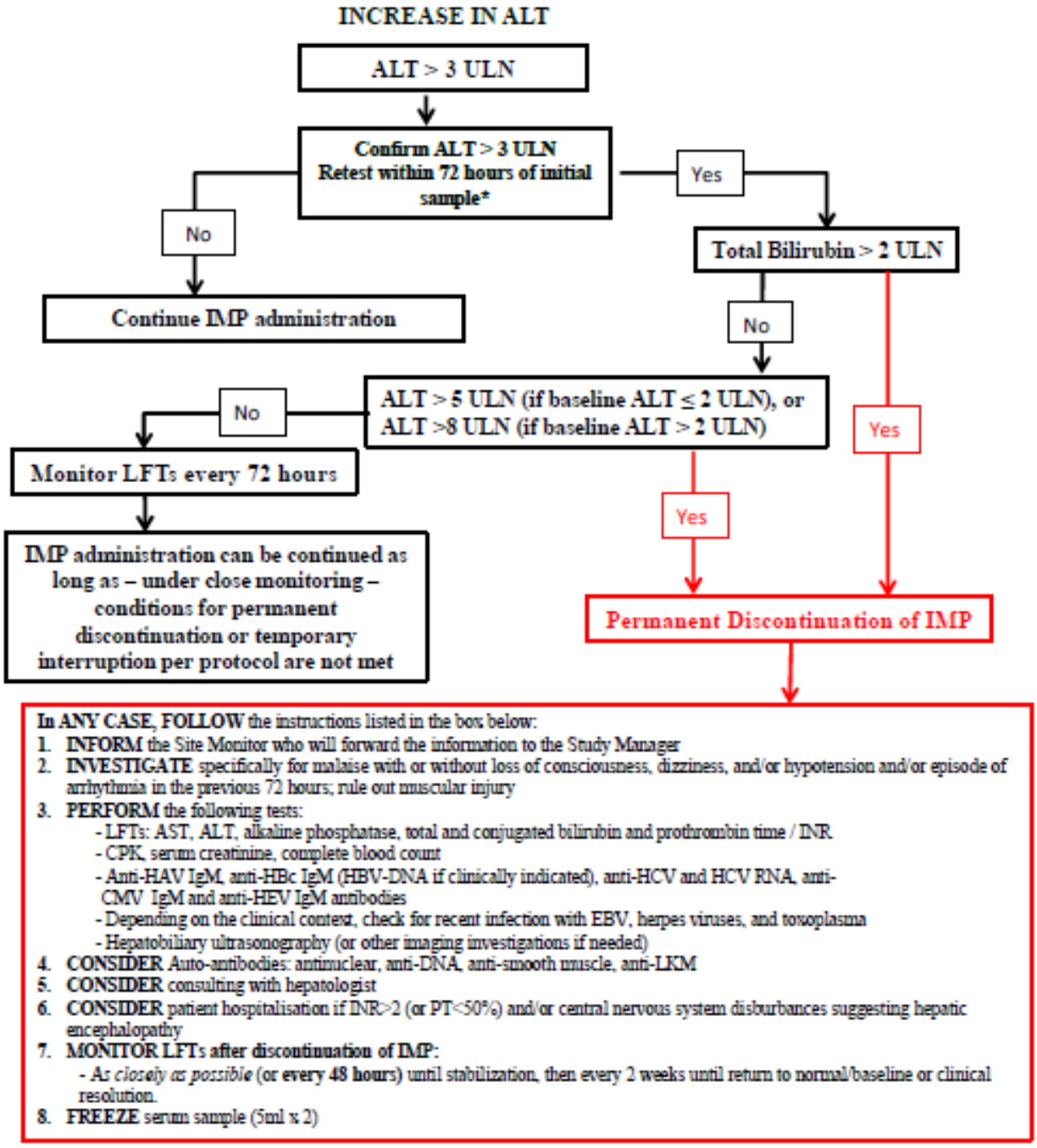
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

THROMBOCYTOPENIA



Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

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

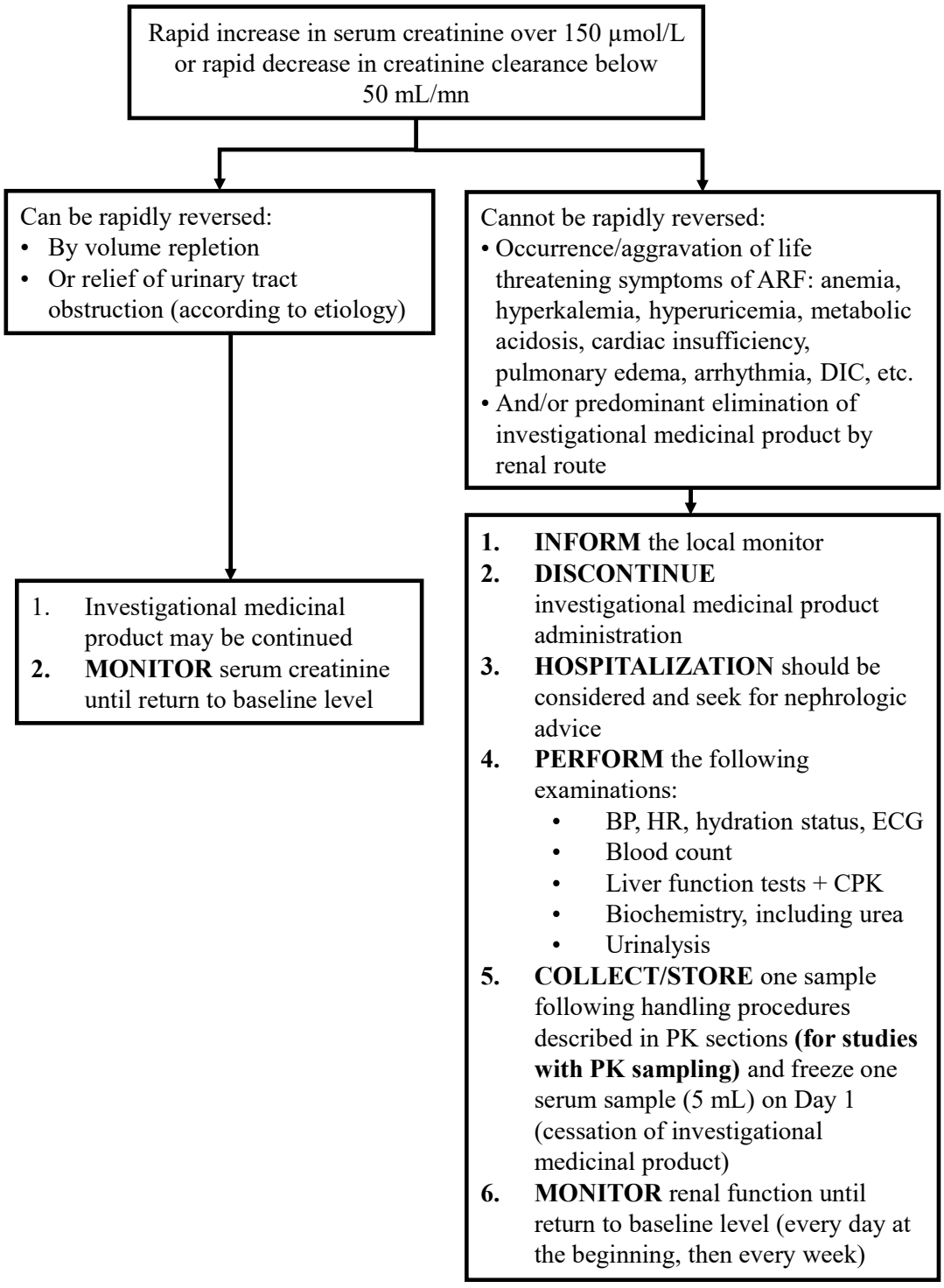


*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

- "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 and Table 7 for guidance on safety reporting.
- Normalization is defined as ≤ ULN or baseline value, if baseline value is >ULN.

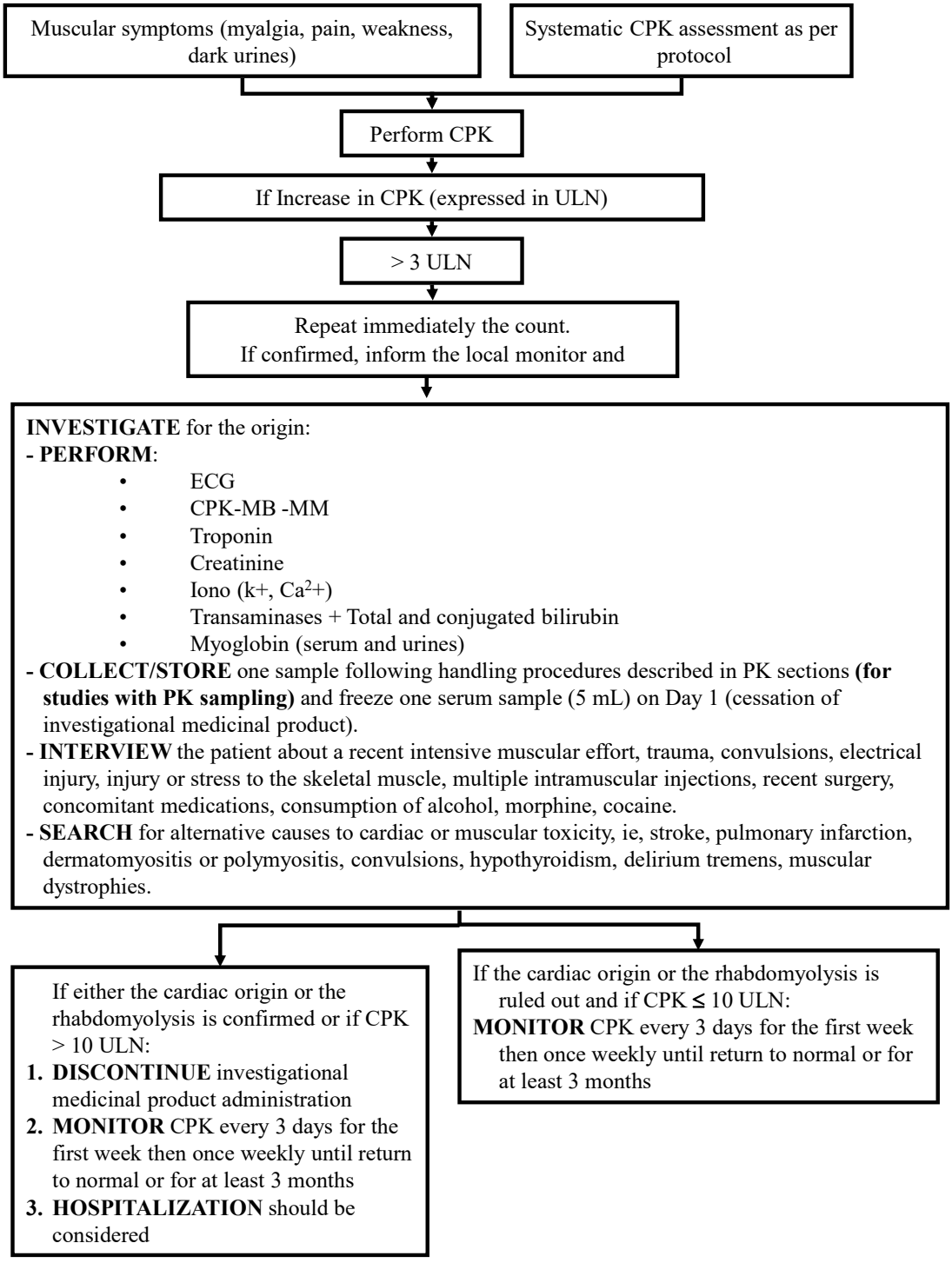
Note: In case of SUSPICION of GILBERT Syndrome, a DNA diagnostic test should be done.

INCREASE IN SERUM CREATININE



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

INCREASE IN CPK SUSPECTED TO BE 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

ABECB:	acute bacterial exacerbations of chronic bronchitis
AEs:	Adverse events
AESI:	Adverse events of special interest
ALT:	Alanine transaminase
AST:	Aspartate transaminase
BMI:	body mass index
BP:	blood pressure
CAT:	COPD Assessment Test
CID:	Clinically Important Deterioration
COPD:	Chronic obstructive pulmonary disease
DMC:	Data monitoring committee
ECG:	Electrocardiogram
eCRF:	electronic Case Report Form

EQ-5D:	Euroqol-5Dimension
EXACT:	Exacerbations of Chronic Obstructive Pulmonary Disease Tool
FEV1:	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
GSO:	Global Safety Officer
HIV:	Human immunodeficiency virus
ICF:	Informed consent form
ICH:	International Council for Harmonisation
ICS:	Inhaled corticosteroids
IEC:	Independent Ethics Committee
IL:	Interleukin
IL-33:	Interleukin-33
IMP:	investigational medicinal product
IRB:	Institutional Review Board
ISR:	injection site reactions(s)
IV:	Intravenous
IVRS:	Interactive Voice Response System
IWRS:	Interactive Web Response System
LABA:	Long-acting β2 adrenergic agonists
LAMA:	Long-acting muscarinic antagonist
mAb:	Monoclonal antibody
miTT:	Modified Intent-to-treat
MMRM:	Mixed-effect model with repeated measures
NIMP:	noninvestigational medicinal product
PCSA:	Potentially clinically significant abnormality
PD:	Pharmacodynamics
PK:	Pharmacokinetics
q2w:	Once in every 2 weeks
QoL:	Quality of life
SABA:	Short-acting β agonists
SAEs:	Serious adverse events
SAP:	Statistical analysis plan
SC:	Subcutaneous
TB:	Tuberculosis
ULN:	Upper limit of normal range

10.10 APPENDIX 10: PROTOCOL AMENDMENT HISTORY

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

10.11 APPENDIX 11: COPD ASSESSMENT TEST

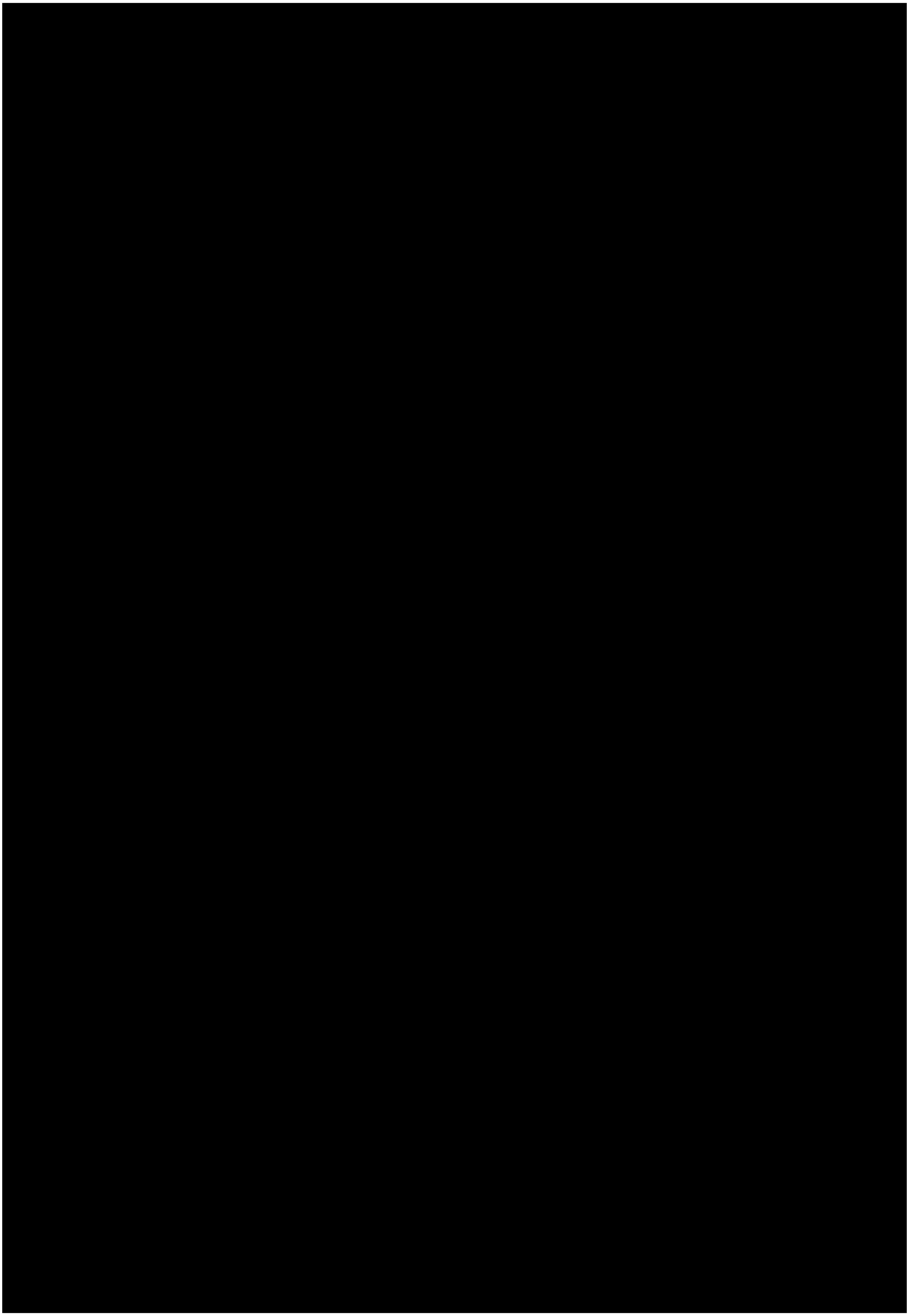
[redacted]

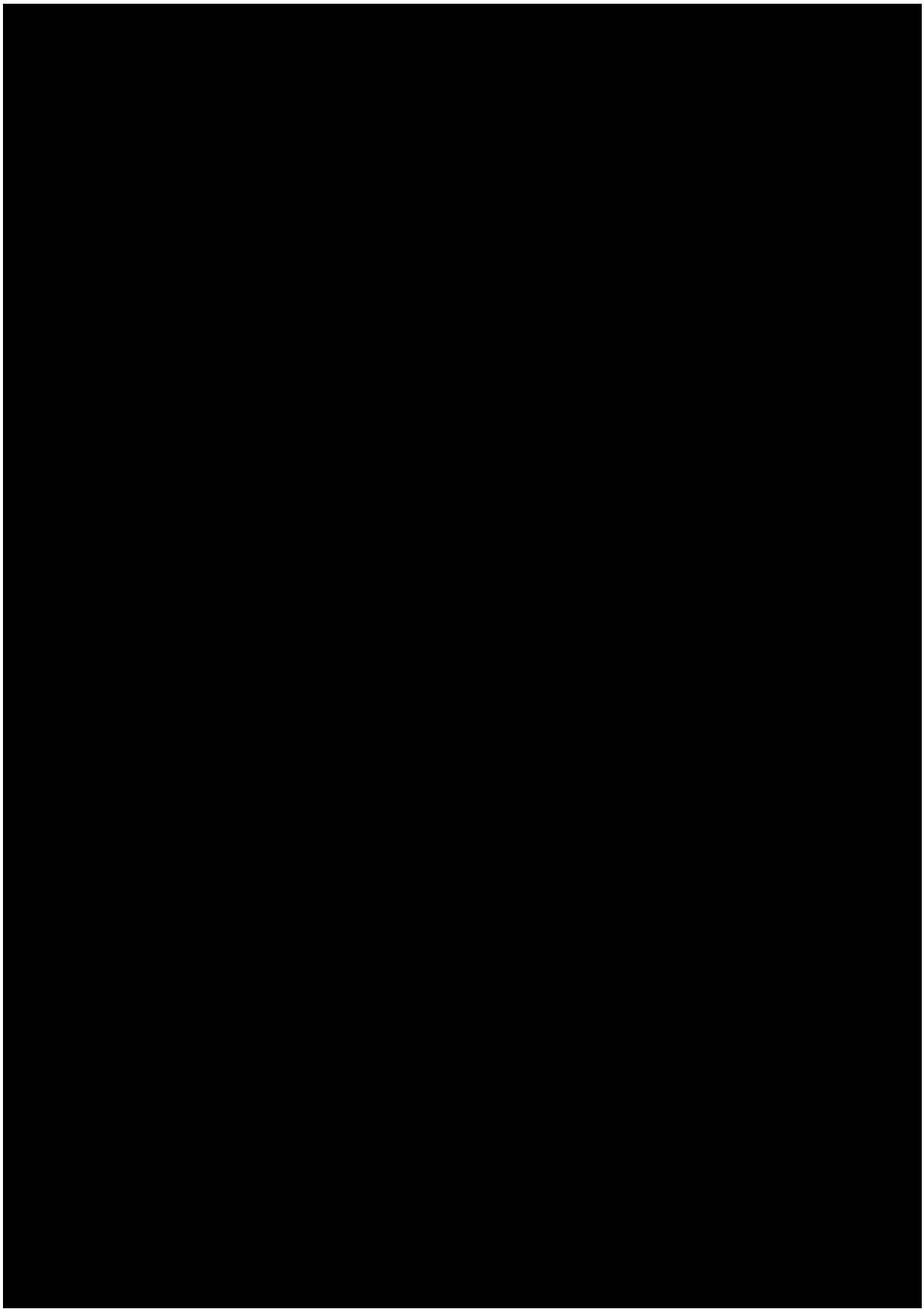
10.12 APPENDIX 12: ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

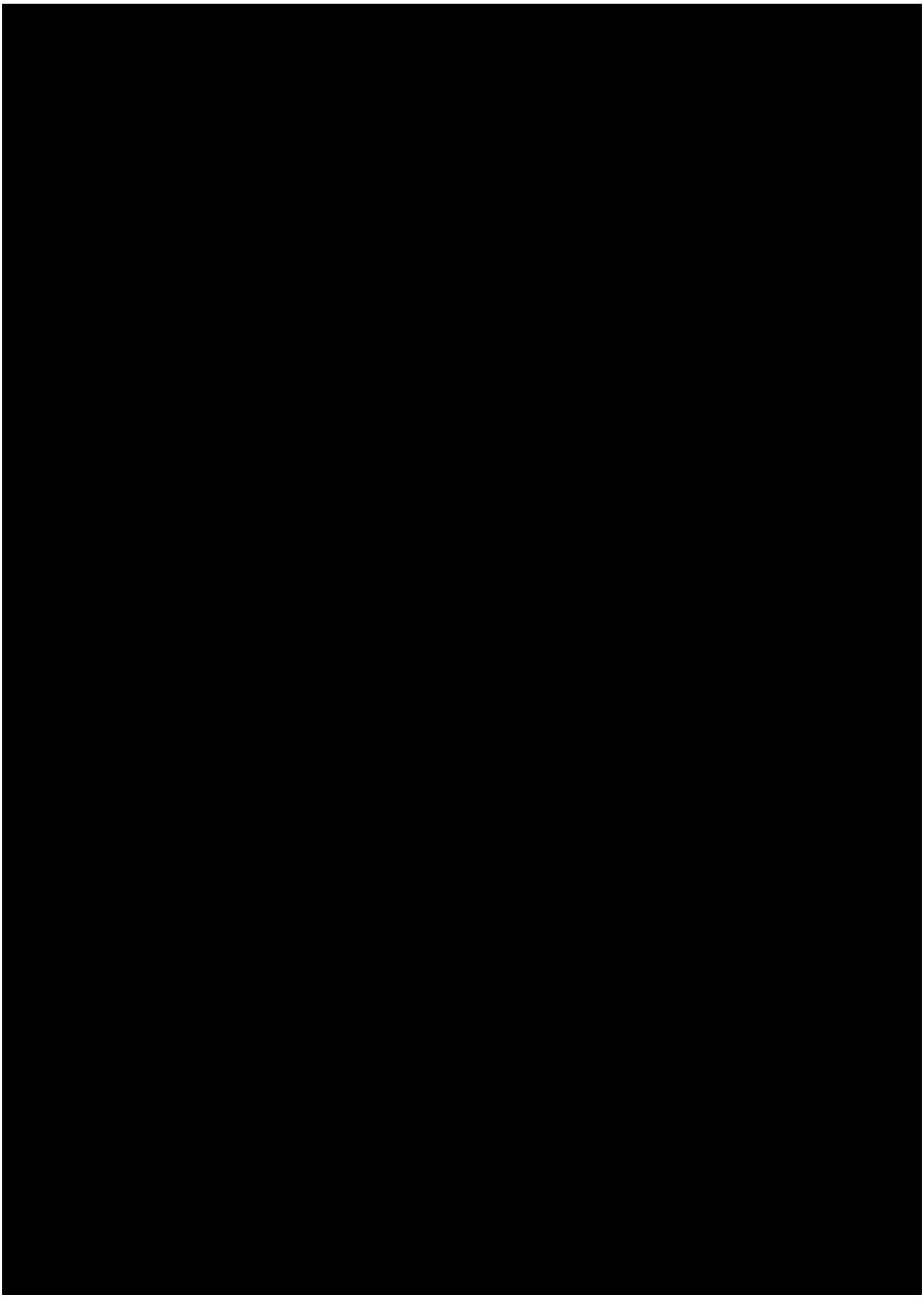
[redacted]

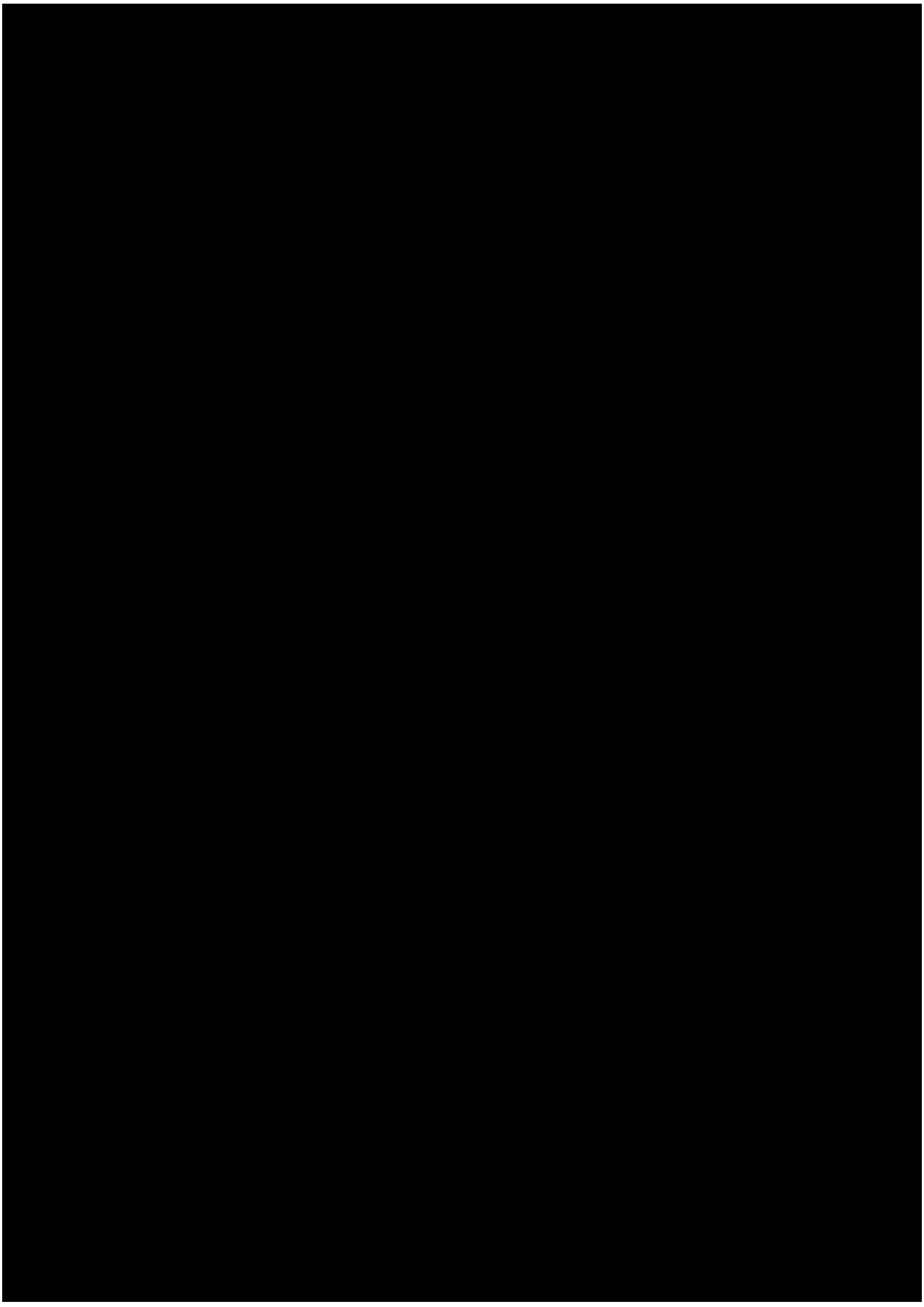
P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,

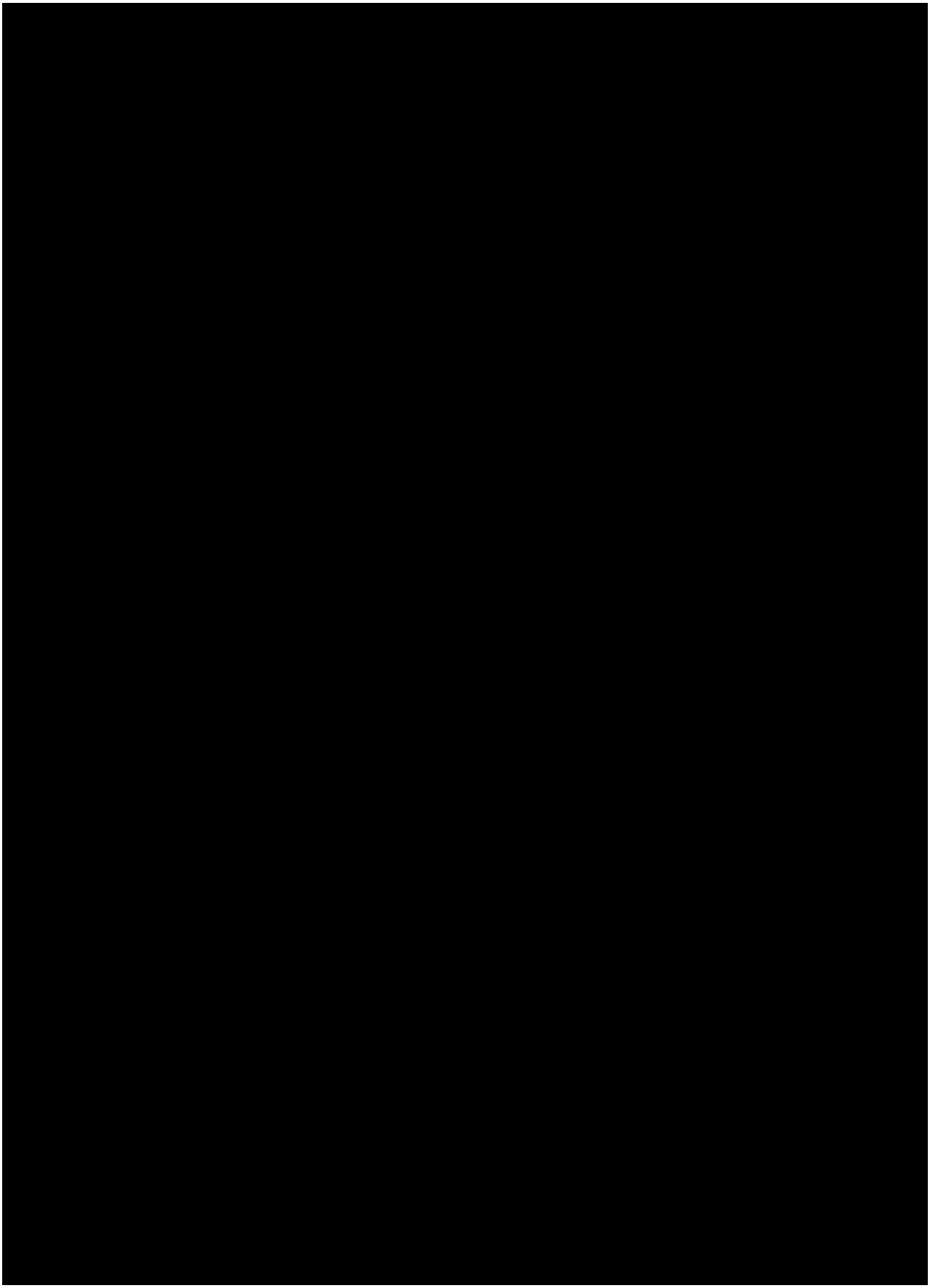
[redacted]











10.13 APPENDIX 13: EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE TOOL (EXACT)

[redacted]

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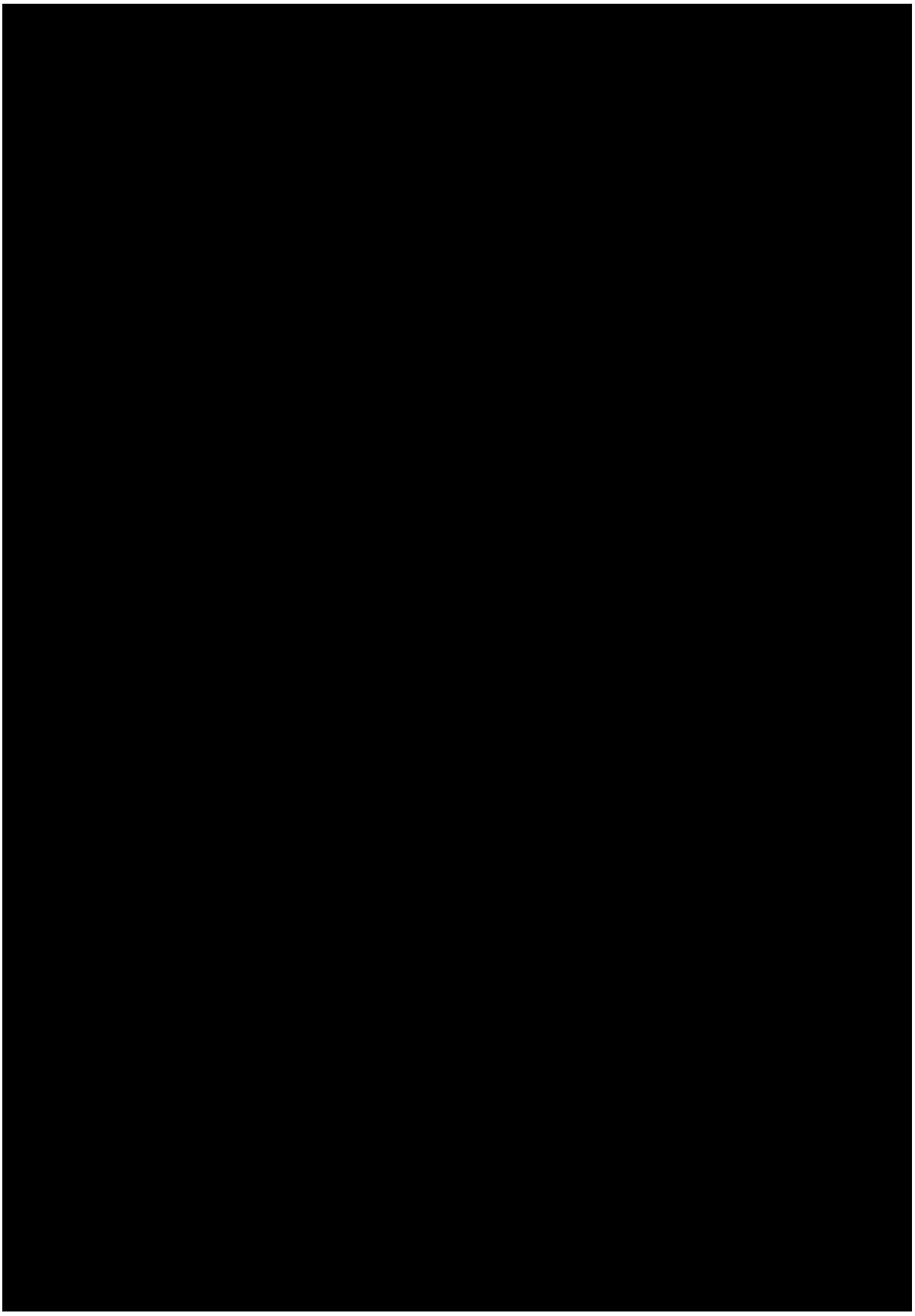
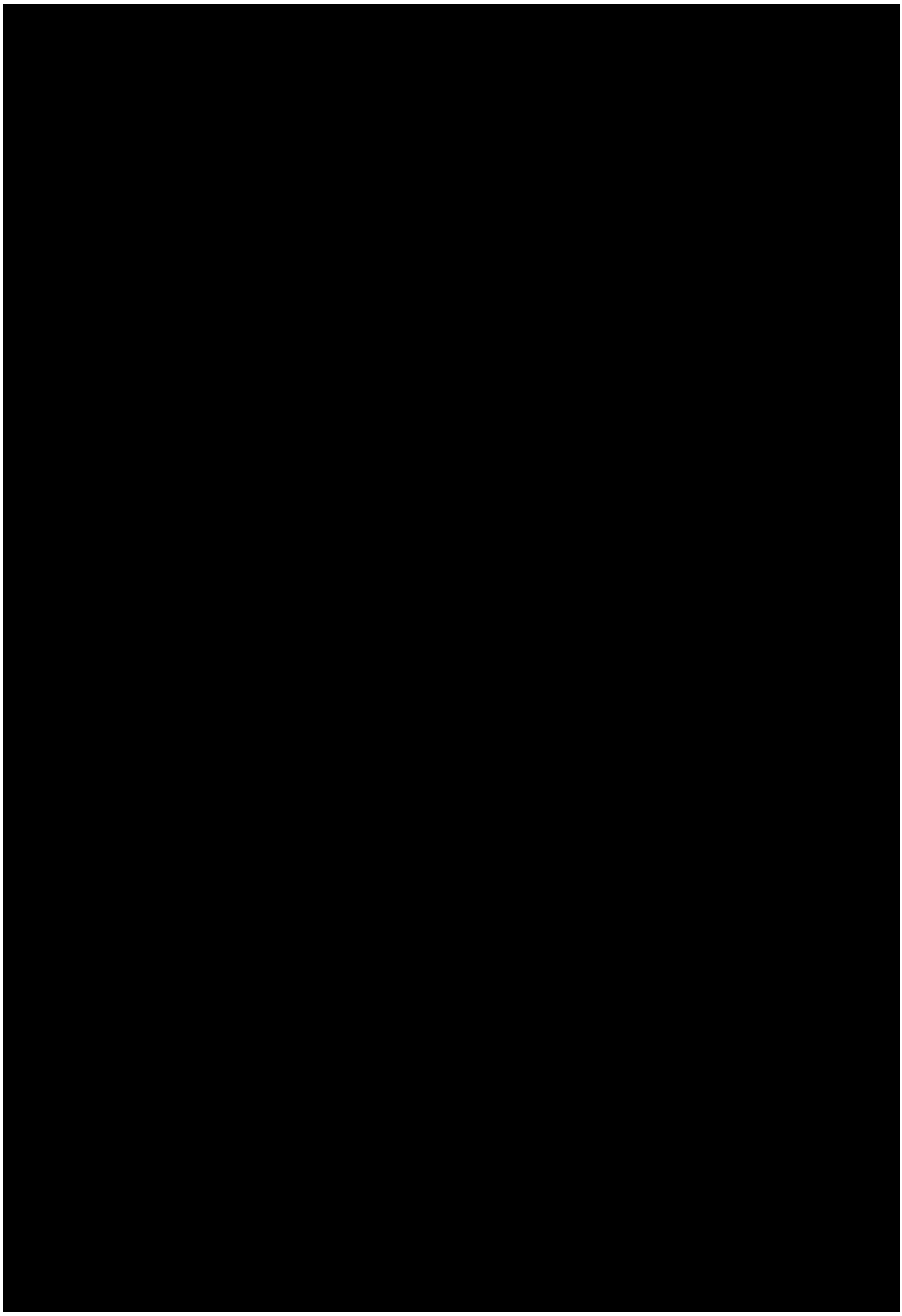
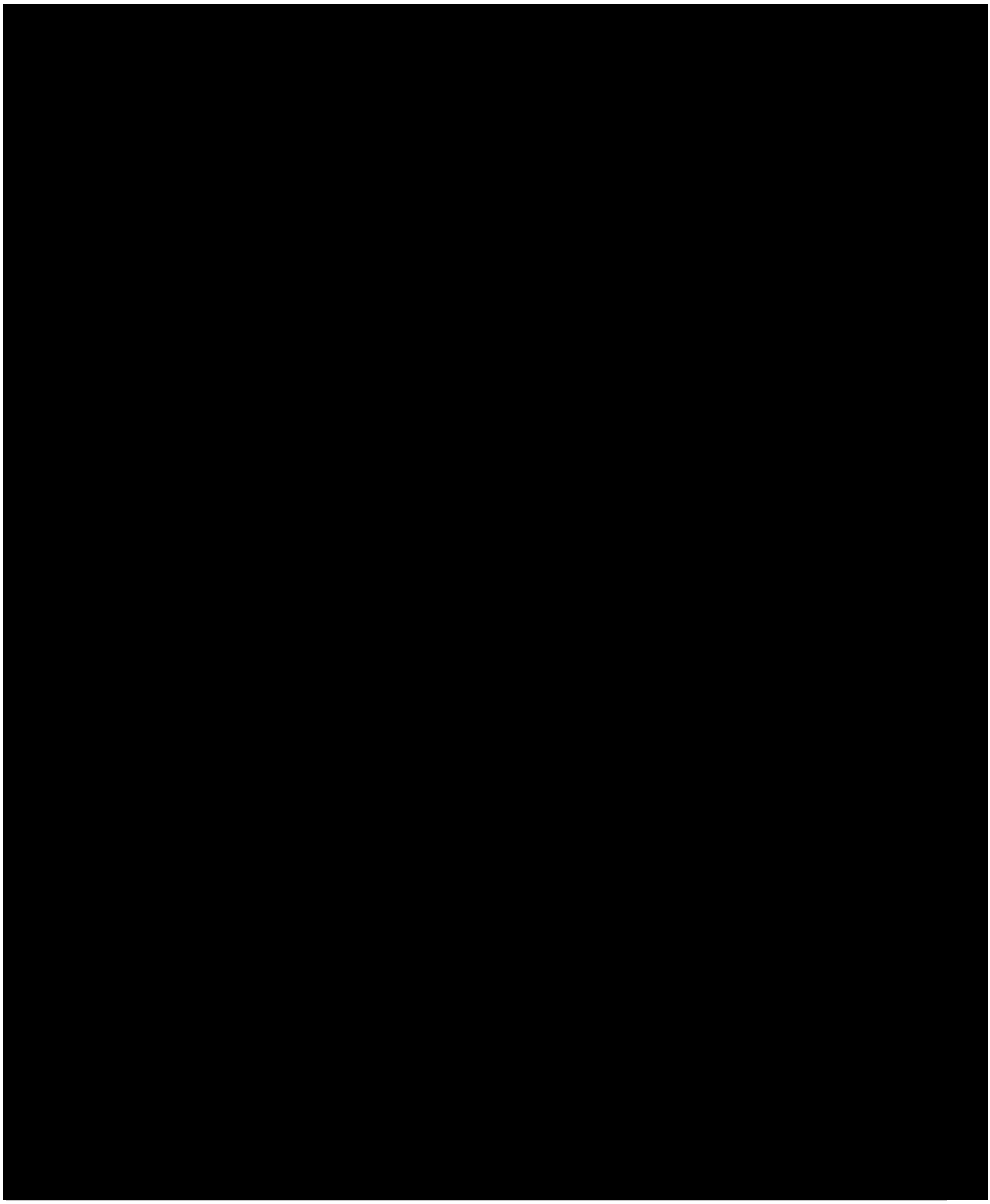
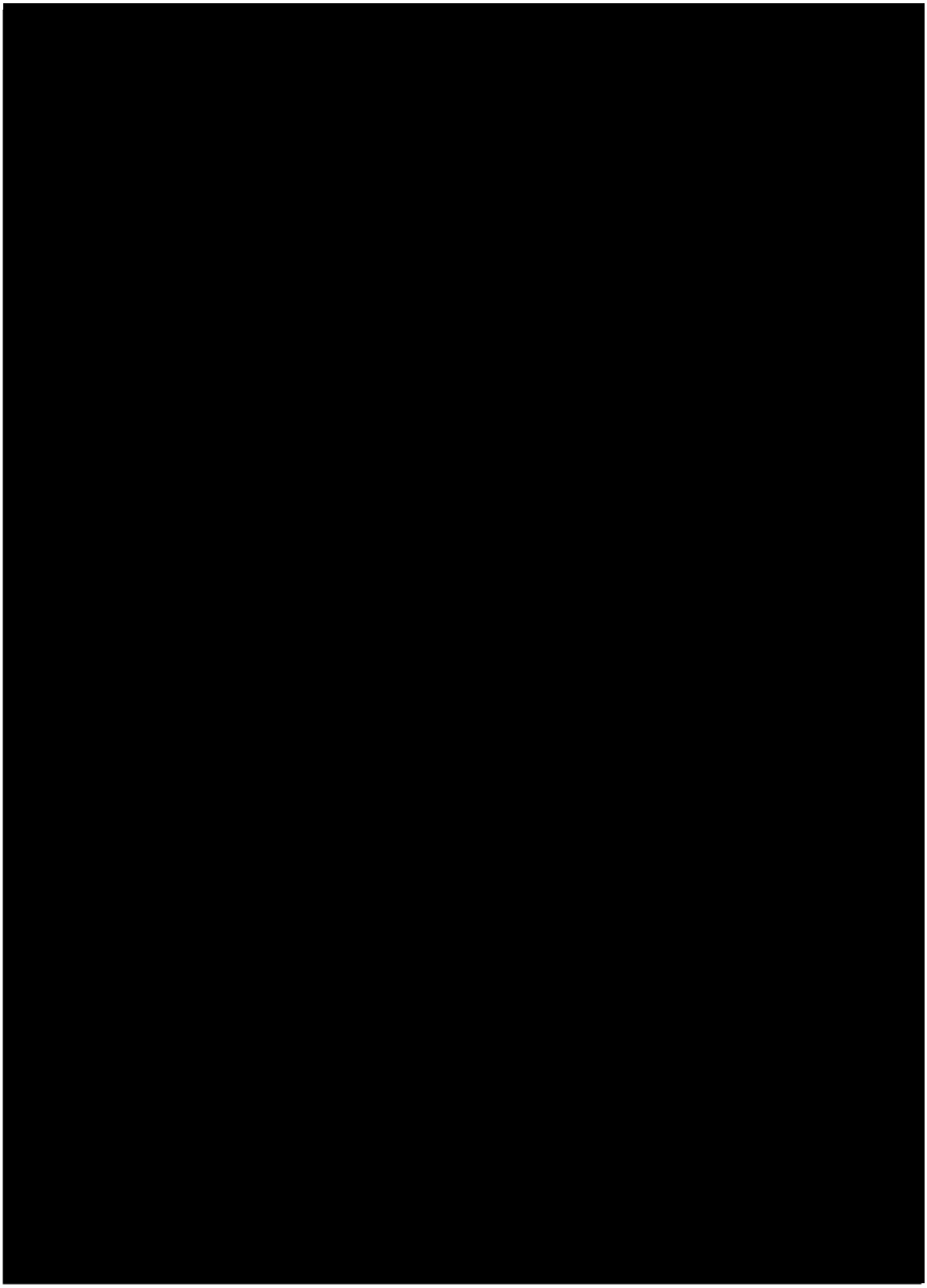
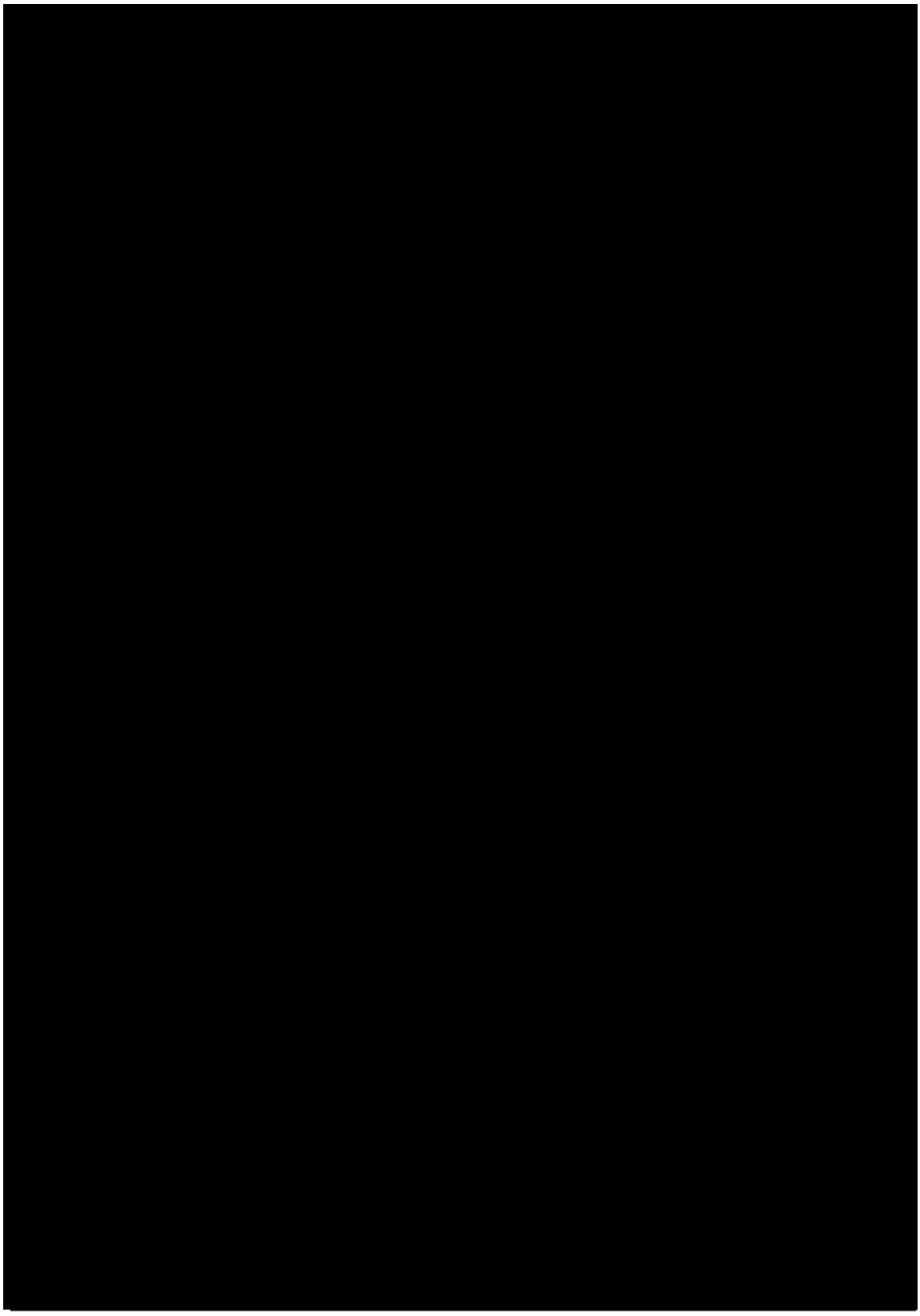




10.14 APPENDIX 14: EUROQOL QUESTIONNAIRE (EQ-5D-5L)







10.15 APPENDIX 15: DEFINITION OF ANAPHYLAXIS

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

(Adapted from *Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA , Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117: 391-7)*

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, extensive mucosal or cutaneous candidiasis.
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (severe/disseminated)
- Herpes Zoster
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)
- Tuberculosis (TB)

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 subjects 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).

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ACT15104 16.1.1 Amended Protocol 01

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
[redacted]	Clinical Approval	[redacted]