STATISTICAL ANALYSIS PLAN

A randomized, double-blind, placebo-controlled, parallel-group, Proof-of-Concept (PoC) study to assess the efficacy, safety and tolerability of SAR440340/REGN3500, in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

SAR440340-ACT15104

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	Anti-drug antiboy
AESI:	Adverse event of special interest
ANA:	Anti-nuclear antibody
ATC:	Anatomic therapeutic class
BD:	Bronchodilator
BMI:	Body mass index
HBc Ab:	Hepatitis B core antibody
HBs Ab:	Hepatitis B surface antibody
HBs Ag:	Hepatitis B surface antigen
HCV Ab:	Hepatitis C virus antibody
HIV:	Human immunodeficiency virus
HLGT:	High-level group term
HLT:	High-level term
IL33:	Interleukin-33
LLOQ:	Lower limit of quantification
LLT:	Lower-level term
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	Modified intent-to-treat
MMRM:	Mixed-effect model with repeated measures
PARC:	Pulmonary and activation-regulated chemokine
PCSA:	Potentially clinically significant abnormality
PT:	Preferred term
SD:	Standard deviation
SOC:	System organ class
sST2:	Soluble IL33 receptor
WBC:	White blood cell
WHO-DD:	World Health Organization - Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multinational, randomized, double-blind, placebo controlled, parallel group (2 groups), Proof of Concept (PoC) study assessing the efficacy, safety, and tolerability of SAR440340 (also referred to as REGN3500) in patients with moderate-to-severe COPD on a combination of long-

acting β2 adrenergic agonist (LABA), long-acting muscarinic antagonist (LAMA), and/or inhaled corticosteroid (ICS) background therapy (as double or triple therapy of any combination). Patients will be treated with SAR440340 or placebo for a minimum of 24 weeks and up to a maximum of 52 weeks, followed by a 20-week post treatment 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 maximally 52 weeks or minimally until 24 weeks after the last patient is randomized, whichever is earlier.

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 period (20 weeks).

Patients must be on Standard of Care background therapy for at least 3 months prior to Visit 2 (Randomization) and on a stable dose for at least 1 month prior to Visit 1 (Screening), 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

Upon completing the 24-52 weeks randomized IMP treatment or early permanent treatment discontinuation, patients will continue their established background therapy and enter the 20-week post treatment follow-up period.

Approximately 340 patients will be randomized in this study (170 patients per arm). Randomization will be stratified by blood eosinophil count at Visit 1 (Screening) (<250 /mm^3 vs ≥ 250 /mm^3) and country. Alerts will be built into an interactive response technology (IRT) system to balance the number of patients enrolled in the two eosinophil strata:

- Eosinophil<250 /mm^3: approximately 50% (170) patients
- Eosinophil≥250 /mm3: approximately 50% (170) patients

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is 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.

1.2.2 Secondary objectives

- To investigate effects of SAR440340 compared with placebo, on improving respiratory function, as assessed by pre‑ bronchodilator FEV1 over 24 weeks.
- To evaluate effects of SAR440340 compared with placebo, on post-bronchodilator FEV1 over 24 weeks.
- To evaluate effects of SAR440340 compared with placebo, on duration from baseline to first moderate or severe AECOPD event over up to 52 weeks of treatment.
- To evaluate effects of SAR440340 compared with placebo, on safety and tolerability.

1.3 DETERMINATION OF SAMPLE SIZE

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 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% in rate of AECOPD 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 1 - Power calculation for various AECOPD 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 pre-bronchodilator FEV1, we assume that:

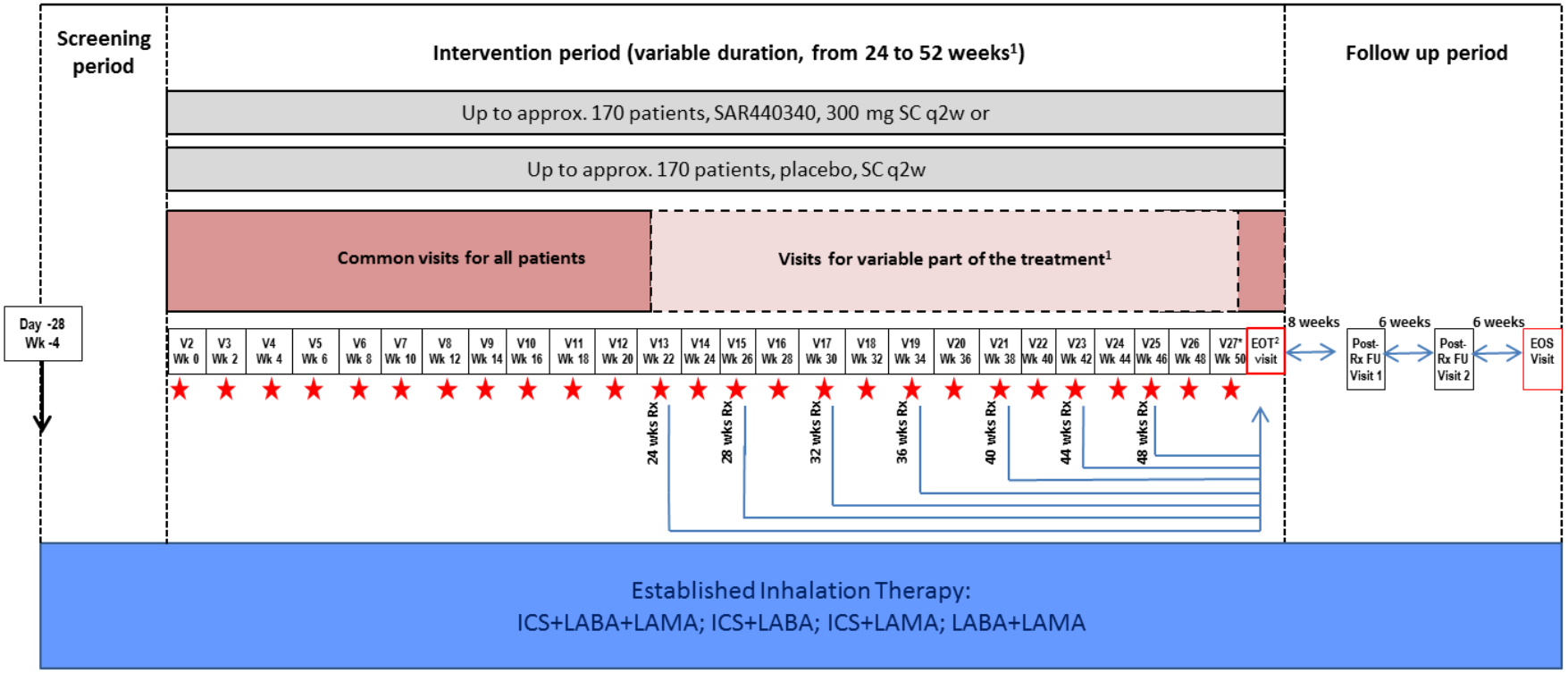
- A common standard deviation of 0.3 L in each of the two groups, which is a consensus value based on the review of historical data from COPD trials.
- A difference of 0.12 L between the treatment group and the placebo group.
- A 2-sided t-test with 5% significance level.
- Fifteen percent (15%) of patients 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, 170 patients per group (340 patients in total) will provide >90% power to detect a 0.12 L difference in FEV1 between the treatment group and the placebo group. The least significant difference between groups will be 0.07 L.

1.4 STUDY PLAN

Please refer to Section 1.2 of the study protocol for study flow chart. The graphical study design is provided in Figure 1

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

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

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

A secondary efficacy population is added in the SAP. This secondary population includes all patients in the mITT population (the primary efficacy population) with baseline eosinophil values $\geq 250/mm^3$.

A tertiary endpoint, proportion of SGRQ responders at Week 24, is added. The SGRQ responders are patients whose Week-24 SGRQ total scores decrease 4 points or more from baseline. The corresponding efficacy analysis for this endpoint is logistic regression detailed in Section 2.4.4.3.2.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value prior to the first dose of IMP. For patients randomized but not treated, the baseline value is the last available value up to randomization.

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

Demographic characteristics

The following demographic characteristics will be summarized separately by treatment and overall:

- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Island, White, Multiple, Unknown, Not Reported)
- Age (years)
- Age groups (<60, ≥60-<65, ≥65-<70, ≥70-≤75 years)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino, Unknown, Not Reported)
- Region (East Europe: Poland, Russia, Turkey and Ukraine; Latin America: Argentina and Chile; Western Countries: USA, Canada, Australia and Germany)
- Body weight (kg)
- Body weight group (<70, ≥70-<90, ≥90 kg)
- Body mass index (BMI, kg/m^2)
- BMI group (<25, ≥25-<30, ≥30-<35, ≥35 kg/m^2)

Alcohol use will also be included in this summary as alcohol drinking frequency (Never, Occasional, At least daily, At least weekly, At least monthly) and number of standard alcohol drinks on a typical day when drinking (1 or 2, >2).

Medical or surgical history

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

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

COPD and allergic comorbidity medical history will be summarized separately, including:

- Hospitalization because of severe respiratory infection (Yes, No)
- Long stay in neonatal intensive care unit (Yes, No)
- Diagnosed with bronchopulmonary dysplasia (Yes, No)
- Family history of COPD (Yes, No)
- Exposed to occupational/environmental pollutants (Yes, No), if Yes, summarize years of exposure.
- Comorbidities (Yes, Ongoing for each): Asthma, Bronchiectasis, Nasal polyps, Chronic sinusitis, Atopic dermatitis, Allergic conjunctivitis, Allergic rhinitis, Food allergy, Hives, Eosinophilic esophagitis, Hypersensitivity to aspirin, Hypersensitivity to NSAD, Atopic disease (Nasal Polyps or Chronic sinusitis or Atopic dermatitis), Allergies (Allergic conjunctivitis or Allergic rhinitis or Food allergy), Hypersensitivity (Hypersensitivity to NSAID or Hypersensitivity to Aspirin)

Disease characteristics at baseline

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

- Age at diagnosis of COPD (years)
- Time since diagnosis of COPD at randomization (years)
- Time since last COPD exacerbation at randomization (months)
- Number of moderate or severe COPD exacerbations experienced in the past one year before screening visit (quantitative variable and qualitative variable: 0, 1, 2, 3, ≥4)
- Number of moderate COPD exacerbations experienced within 1 year before screening visit (Among the moderate COPD exacerbations, how many required use of (1) systemic corticosteroids and antibiotics, (2) only systemic corticosteroids, (3) only antibiotics. And if systemic corticosteroids were used to treat the moderate COPD exacerbations, the total number of treatment days in the past one year, which will be further broken down to the treatment days using oral, intravenous and intramuscular systemic corticosteroids)
- Number of severe COPD exacerbations experienced within 1 year before screening visit (Among the severe COPD exacerbations, how many required use of (1) systemic corticosteroids and antibiotics, (2) only systemic corticosteroids, (3) only antibiotics. And if systemic corticosteroids were used to treat the severe COPD exacerbations, the total number of treatment days in the past one year, which will be further broken down to the treatment days using oral, intravenous and intramuscular systemic corticosteroids)

- Smoking history (Former, Current), time since cessation of smoking (years) and smoking quantity in pack-years
- Baseline spirometry data including pre-bronchodilator (pre-BD) FEV1 (L), post-bronchodilator (post-BD) FEV1 (L), pre-BD and post-BD FEV1 percent predicted (%), pre-BD and post-BD FEV1/FVC (%), pre-BD and post-BD FVC (L) and pre-BD and post-BD FVC percent predicted (%)
- Baseline COPD Assessment Test (CAT) score
- Baseline Euroqol Questionnaire (EQ-5D-5L) score
- Baseline St. George's Respiratory Questionnaire (SGRQ) score
- Baseline Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) score
- Baseline blood eosinophil count (< 250 /mm^3 and ≥250 /mm^3)
- Eosinophil count for stratification (< 250 /mm^3 and ≥250 /mm^3)
- Background therapy containing ICS (Yes/No); if ICS were used, dose of ICS (quantitative variable and qualitative variable: medium, high*)
  **Medium: total daily dose of fluticasone = 500 or 460 mcg; high: total daily dose of fluticasone = 1000 or 920 mcg*
- Type of background therapy (Double therapy: LABA + LAMA, ICS + LABA, or ICS + LAMA; Triple therapy: ICS + LABA + LAMA)

Baseline biomarkers

Baseline values of biomarkers, including eosinophils, neutrophils, total IL33, sST2, calcitonin, PARC, eotaxin-3, total IgE, fibrinogen, and FeNO (optional, both pre-BD and post-BD), will be summarized. Eosinophils will be further summarized as

- Baseline blood eosinophil count (quantitative in < 250 /mm^3 and in ≥250 /mm^3)
- Eosinophil count for stratification (quantitative in < 250 /mm^3 and in ≥250 /mm^3)
- Baseline blood eosinophil count (quantitative and qualitative < 150, 150-300, ≥300 /mm^3)

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

2.1.2 Prior or concomitant medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving from 3 months prior to screening visit to the end of study will be recorded in the electronic case report form (eCRF).

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

- Prior medications are those the patient used prior to first IMP injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the first administration of IMP to the last administration of IMP + 154 days.
- If applicable, post-treatment medications are those the patient took in the period from the last administration of IMP + 155 days to the end of the study.

A given medication can be classified in more than one category. Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.2.1 Background therapy

Requirements for background therapy prior to screening and during the study are described in Section 1.1.

2.1.2.2 Reliever medication

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method. Usage of reliever medication will be recorded in the electronic diary.

Salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use recorded in the electronic diary will be converted to number of puffs as shown on the following tables:

Table 2 - Salbutamol/Albuterol Nebulizer dose conversion

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 dose = 7.5 mg or 12 puffs.

Table 3 - Levosalbutamol/Levalbuterol Nebulizer dose conversion

Levosalbutamol/Levalbuterol Nebulizer Solution Total Daily Dose (mg)	Number of Puffs*
0.63	2
1.25/1.26	4
1.89	6
2.5/2.52	8
3.15	10
3.75/3.78	12
4.41	14
5/5.04	16
5.67	18
6.25/6.30	20
6.93	22
7.50/7.56	24

*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 dose = 3.75 mg or 12 puffs.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint is the annualized rate of moderate-to-severe AECOPD over the treatment period.

Moderate exacerbations are recorded by the Investigator and defined as AECOPD that requires 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.

2.1.3.2 Secondary efficacy endpoint(s)

The key secondary efficacy endpoint is the average change from baseline to Weeks 16, 20 and 24 in pre-bronchodilator FEV1.

The other secondary efficacy endpoint is the change from baseline to Week 24 in post-bronchodilator FEV1.

The third secondary efficacy endpoint is time to first moderate or severe AECOPD up to week 52.

2.1.3.3 Tertiary efficacy endpoint(s)

- Change from baseline at Week 24 in the patient-reported outcome including EXACT domain and total scores, EQ-5D-5L index score and Visual Analogue Scale (VAS) and SGRQ domain and total scores.
- Proportion of patients with a decrease from baseline of 4 points or more in the SGRQ total score (i.e. change from baseline ≤-4) at Week 24.
- Average change from baseline to Week 16-24 in FVC (% predicted and absolute values in mL)
- Time to the first expanded AECOPD endpoint (moderate or severe AECOPD or study drug discontinuation [after week 4] due to lack of efficacy) up to week 52
- Time to first Clinically Important Deterioration (CID) as defined by decrease of >100mL from baseline in trough pre-BD FEV1 and/or deterioration in SGRQ by 4 units and/or moderate-to-severe AECOPD over the treatment period

2.1.3.3.1 Patient-reported outcomes

COPD Assessment Test (CAT)

The CAT is a short, validated, patient-completed questionnaire to assess the impact of COPD on health status (see Appendix C). It comprises 8 questions that cover a broad range of effects of COPD on patients' health. Each question is scored in a range between 0 (I am very happy) and 5 (I am very sad), with the higher end indicating a higher impact of COPD on the patient's wellbeing. The CAT total score, the sum of the 8 individual question scores, ranges from 0 (best) to 40 (worst). This score is collected only at screening and baseline to assess patient eligibility.

St. George's respiratory questionnaire (SGRQ)

St. George's Respiratory Questionnaire (SGRQ) is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (see Appendix E). The questionnaire is divided into two parts: part one consists of eight items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part two consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition.

The SGRQ yields a total score and three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment; 100 represents the worst possible health status and 0 indicates the best possible health status (minimal clinically important difference: −4 units). Likewise, the domain scores range from 0–100, with greater scores indicative of greater impairment. See Appendix F for the scoring algorithm.

This questionnaire is assessed at baseline and at weeks 4, 8, 12, 24, 36, 52, 60 and 72.

Exacerbations of chronic obstructive pulmonary disease tool (EXACT)

The EXACT is a 14-item daily diary designed to provide a direct measure of patient-reported symptoms of COPD exacerbation (see Appendix B) and covers 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).

It is completed each evening before bedtime.

The EXACT total score is an interval-level scale ranging from 0 to 100, where higher scores indicate a more severe condition.

Additional information can be obtained through 3 domain scores: Breathlessness (items 7, 8, 9, 10 and 11), Cough & Sputum (items 2 and 3), and Chest Symptoms (items 1, 5, and 6). These scores also range from 0 to 100, with higher scores indicating more severe symptoms. Note that items 4, 12, 13 and 14 do not correspond to a domain score.

Additional information related to computing scores and frequency, severity, and duration of events can be found in the *The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Patient-Reported Outcome (PRO) User Manual- Scoring guide* (Version 7.0), October 2014.

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

EQ-5D-5L

EQ-5D-5L is a standardized questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (1). EQ-5D is designed for self-completion by patients.

The EQ-5D consists of 2 pages - the EQ-5D descriptive system and the EQ VAS (see Appendix D). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems/unable. EQ-5D-5L health status will be converted into a single index value by using EQ-5D-5L crosswalk value sets based on UK population (2).

The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

This questionnaire is assessed at baseline and weeks 24, 52, 60 and 72.

2.1.3.4 Exploratory efficacy endpoint(s)

- Change from the average of measurements over baseline to the average of measurements over Weeks 10-12 and over Weeks 22-24 in sleep parameters (total sleep time, wake after sleep onset, overnight activity counts), for patients in US and Canada only
- Change from the average of measurements over baseline to the average of measurements over Weeks 10-12 and over Weeks 22-24 in activity parameters (daytime activity counts, percent of time spent in sedentary activity, percent of time spent in moderate to vigorous physical activity), for patients in US and Canada only
- Change from the average of measurements over baseline to the average of measurements over Weeks 10-12 and over Weeks 22-24 in FEV1 measured at home, for patients in US and Canada only

The daily/nightly actigraphy (activity, sleep) and daily home spirometry data will be first averaged in the designated analysis windows and the resulted averages are used to calculate the change from baseline.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, electrocardiogram (ECG), etc.

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the first administration of the IMP.
- The **treatment** epoch is defined as the time from the first administration of the IMP to the last administration of the IMP + 14 days.
- The **residual treatment** epoch is defined as the time from the last administration of the IMP + 15 days to the last administration of the IMP + 154 days.
- If applicable, the **post-treatment** epoch is defined as the time from the last administration of the IMP + 155 days to the patient's end of study (defined as last protocol-planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

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

The on-study observation period is defined as the time from the first administration of the IMP to the end of the study.

2.1.4.1 Adverse events variables

Adverse event observation period

- Pre-treatment adverse events are adverse events that developed or worsened or became serious during the screening epoch.
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period.
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment epoch.

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

***Adverse event of special interest (AESI*) and other selected AE groupings** will be searched based on criteria in Table 4:

Table 4 - Criteria for adverse events of special interest and other selected AE groupings

AE Grouping	Criteria
AESI	
Anaphylactic reaction (medically reviewed)	Anaphylactic reaction algorithmic approach (*Introductory Guide for Standardised MedDRA Queries (SMQs) Version 20.0*): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of anaphylactic reaction or not.
Hypersensitivity (medically reviewed)	SMQ hypersensitivity (20000214) narrow search or Preferred terms of pruritus or pruritus generalized and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic events

AE Grouping	Criteria
Injection site reactions (serious/severe and lasting 24 hours or longer)	HLT = 'Injection site reaction' and either with serious status or non-serious events with (AE end date/time-AE start date/time)≥ 24 hours or ongoing and at least one of the following checked on the Injection Site Reaction Complementary Form: - Diameter of at least 10cm - Prevents daily activities - Presence of ulceration or necrosis - Operative intervention required
Infection	Primary SOC = 'Infections and infestations' and meeting at least one of the following criteria – Serious status – 'Have any parental treatment (IV, Intramuscular, SC) been given for this event?' is answered Yes on eCRF Infection Event Form – 'Did this event require Prolonged Medication (greater than 14 Days)?' is answered Yes on eCRF Infection Event Form
Parasitic infection	Infection Type 'Parasitic' selected on eCRF Infection Event Form
Opportunistic infection	'Has the AE been assessed as opportunistic infection?' is answered Yes on eCRF Infection Event Form
Potential drug-related hepatic disorder	Drug-related hepatic disorders-Comprehensive search narrow SMQ (20000006)
Malignancy	Sub-SMQ (20000091)-Malignant or unspecified tumors
Pregnancy	'Pregnancy' or 'Partner Pregnancy' ticked on the Pregnancy eCRF.
Symptomatic overdose with IMP	'Overdose of IMP' and 'Symptomatic Overdose' are both ticked Yes on the Overdose eCRF
Symptomatic overdose with NIMP	'Overdose of NIMP' and 'Symptomatic Overdose' are both ticked Yes on the Overdose eCRF
Other selected AE grouping	
Injection site reaction	HLT = 'Injection site reaction'

2.1.4.2 Deaths

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

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period
- Death post-study: deaths occurring after the end of the study and recorded in the clinical database

2.1.4.3 Laboratory safety variables

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

Blood samples for clinical laboratories will be taken at Visits 1, 2, 6, 10, 14, 20, EOT, EOS and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, total red blood cell count, platelet count
  - **White blood cells:** total white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism**: glucose, total cholesterol, total protein, creatine phosphokinase, albumin
  - **Electrolytes**: sodium, potassium, chloride, bicarbonate
  - **Renal function**: creatinine, estimated creatinine clearance (Cockcroft's formula in Section 2.5.1), blood urea nitrogen, uric acid
  - **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin)
  - **Pregnancy test**: serum beta-human chorionic gonadotropin (β-hCG) will be performed at Visit 1 in women of childbearing potential
  - **Hepatitis screen:** clinical laboratory testing at 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), and hepatitis C virus antibody (HCV Ab).
  - **QuantiFERON-TB Gold / Plus** will be tested at Visit 1
  - **Human immunodeficiency virus (HIV) screen**: anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1

- **Anti-nuclear antibody (ANA)** will be tested at Visit 1

  Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

Urine samples will be collected:

- **Urinalysis** will be performed at Visit 1, 2, 6, 10, 14, 20, EOT and EOS for 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.
- **Urine dipstick pregnancy test** will be performed at Visits 2 (prior to randomization), 4, 6,8,10,12,14,16,18,20,22,24,26,EOT and EOS in women of child bearing potential.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (°C) will be measured at all visits. Body weight (kg) will be measured at Visit 1, EOT and EOS. Height (cm) will be measured at Visit 1 only.

2.1.4.5 Electrocardiogram variables

Recording of a standard 12-lead ECG will be centrally collected and read for Visits 1, 2, 8, 14, 20, EOT and EOS. 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 for each ECG. All ECG recordings will be centrally read by independent experts.

2.1.4.6 Physical Examination

Physical examinations will be performed at Visits 1, 2, 8, 14, 20, EOT and EOS including an assessment of skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. All deviations from normal will be recorded in eCRF, including those attributable to the patient's disease.

2.1.5 Pharmacokinetic (PK) variables

Pre-dose concentrations of SAR440340 in serum at Visits 2, 3, 4, 6, 8, 10, 14, 20 and EOT will be analyzed. Follow-up concentrations will be collected at Visit F1 and EOS. In addition PK will be collected if an SAE or AESI (anaphylaxis, hypersensitivities, ISR, or certain laboratory abnormalities) occur in a patient.

2.1.6 Anti-drug antibody (ADA) variables

The ADA variables are ADA status and titer over time. ADA against SAR440340 samples will be performed at Visits 2, 8, 14, EOT and EOS. If an SAE or AESI (anaphylaxis, hypersensitivities, ISR, or certain laboratory abnormalities) occur in a patient, blood samples will be collected for ADA assessment at or near the onset and completion of the occurrence of the event, if possible.

Patients who discontinue early from treatment may be asked to return to the clinic to have additional PK/ADA samples collected for up to 20 weeks after treatment discontinuation.

2.1.7 Pharmacodynamic (PD)/genomics endpoints

PD endpoints include:

- **Whole blood biomarkers:** blood eosinophil and neutrophil count measured at Visits 1, 2, 4, 6, 8, 14, 20, EOT, F1 and EOS.
- **Serum biomarkers:** total interleukin-33 (IL33), soluble IL33 receptor (sST2) and calcitonin assayed at Visits 1, 2, 4, 6, 8, 14, EOT, F1 and EOS; Total IgE measured at Visits 1, 2, 4, 8, 14 and EOT; pulmonary and activation-regulated chemokine (PARC) measured at Visits 1, 2, 4, 8, 14, 20 and EOT.
- **Plasma biomarkers:** Eotaxin-3 measured at Visits 1, 2, 4, 8, 14, 20 and EOT.
- **Fibrinogen** measured at Visits 1, 2, 14 and EOT.
- Optional PD endpoints (for patients who provide a separate consent for each individual test) include:
  - Pre- and post-bronchodilator FeNO (Fractional exhaled nitric oxide) at Visits 2, 4, 6, 8, 14, 20.
  - Induced sputum for RNA expression at Visits 2, 14 and EOT.
  - RNA samples collected at Visits 1, 2, 4, 14 and EOT.
  - Archived blood samples collected at Visits 1, 2, 4, 8, 14, 20 and EOT.

2.2 DISPOSITION OF PATIENTS

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

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

Randomized patients are any patient who has signed informed consent and has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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

- Screened patients
- Screen failure patients and reasons for screen failure
- Non-randomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who did not complete the treatment as per protocol
- Patients who discontinued the treatment by main reason for permanent treatment discontinuation
- Patients who withdraw from the study
- Patients who withdraw from the study by main reason for study discontinuation
- Status at last study contact (Alive, Deceased)

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

Additionally, the analysis populations for safety, efficacy, PK and ADA will be summarized in a table by number of patients on the randomized population.

2.2.1 Protocol deviations

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

2.3 ANALYSIS POPULATIONS

The randomized population includes any patient who has signed informed consent and has been allocated to a randomized treatment regardless of whether the treatment kit was used or not.

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

2.3.1 Efficacy populations

The primary efficacy analysis population will be the modified intent-to-treat (mITT) population which includes all randomized patients who have received at least one dose of IMP. Randomized patients will be 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 allocated by randomization.

A second efficacy analysis population will be the high eosinophil population which includes all patients in the mITT population with baseline eosinophil count ≥250 /mm^3.

2.3.2 Safety population

The safety population includes all patients exposed to IMP, regardless of the amount of exposure. Patients will be analyzed according to the treatment actually received. Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population in the group to which they are randomized. Randomized patients who took at least one SAR440340 dose will be included in the SAR440340 group.

2.3.3 Pharmacokinetic analysis population

The PK population will consist of all patients in the safety population with at least one post-dose, non-missing SAR440340 serum concentration. Patients will be analyzed according to the treatment actually received.

2.3.4 Anti-drug antibody population

The ADA population will consist of all patients in the safety population with at least one non-missing result in the anti-SAR440340 assay following the first dose of IMP. Patients will be analyzed according to the treatment actually received.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum, Q1 and Q3 for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Summaries of demographics, baseline disease characteristics and baseline biomarkers will also be provided for the subset of patients with baseline eosinophil count ≥ 250 /mm^3. Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment group using descriptive statistics.

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

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

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

2.4.2 Prior or concomitant medications

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

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

The table for prior medications will be sorted by decreasing frequency of anatomic class followed by decreasing frequency of therapeutic class within anatomic class based on the incidence in the overall group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medications will be summarized for the treatment epoch and treatment emergent period separately. The tables for concomitant medications will be sorted by decreasing frequency of anatomic class followed by decreasing frequency of therapeutic class within anatomic class based on the incidence in the SAR440340 group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

2.4.2.1 Background therapy

Pre-screening background therapy will be summarized by treatment group as LABA + LAMA, ICS + LABA, ICS + LAMA and ICS + LABA + LAMA.

2.4.3 Extent of investigational medicinal product exposure and compliance

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

2.4.3.1 Extent of investigational medicinal product exposure

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

Duration of IMP exposure is defined as last dose date – first dose date + 14 day, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, standard deviation [SD], median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

>0 and ≤8 weeks

>8 and ≤16 weeks

>16 and ≤24 weeks

>24 and ≤32 weeks

>32 and ≤40 weeks

>40 and ≤48 weeks

>48 and <52 weeks - 3 days

≥52 weeks - 3 days

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

2.4.3.2 Compliance

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

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations that the patient was planned to take during the treatment epoch defined in Section 2.1.4.

Treatment compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, Q1, Q3, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized. In addition, numbers and percentages of patients with the wrong dose or an overdose will be summarized.

Cases of overdose (defined as at least twice the intended dose during an interval of less than 8 days) will be listed as such.

2.4.4 Analyses of efficacy endpoints

All efficacy endpoints will be analyzed using the mITT population, unless otherwise specified. In the following and throughout the rest of the SAP, baseline eosinophil strata are defined based on the actual eosinophil count at baseline, which could vary from the stratification grouping used for randomization based on the eosinophil count at screening.

2.4.4.1 Analysis of primary efficacy endpoint(s)

Main statistical model and adjustment of covariates

The primary endpoint is the annualized rate of moderate-to-severe AECOPD.

The primary analysis is a modified intention-to-treat analysis. Off-treatment measurements up to the planned treatment durations for patients who prematurely discontinue treatment will be included for the analysis. The planned treatment duration for a patient is from randomization to the earlier of 52 weeks or 24 weeks after the last patient randomized, ie, patients are treated for a minimum of 24 weeks and a maximum of 52.

The observation duration is equal to the planned treatment duration, except when a patient withdraws early from the study, in which case, the observation duration is from randomization to the last contact of the patient within the planned treatment duration. In the primary analysis, all the exacerbation events that happen in the observation duration will be included, regardless if the patient is on treatment or not.

The primary endpoint of the annualized exacerbation rate will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the observation period as response variable, and the treatment group, the baseline eosinophil strata and region (pooled countries), number of severe COPD exacerbations experienced in previous year (0 vs. 1+) at baseline, smoking history (current vs. former smoker), post-BD FEV1 percent predicted (<50% vs. ≥50%) at baseline 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 the two groups and the relative risk ratio for SAR440340 versus placebo with its 95% confidence interval will be estimated from the model.

Sample SAS code is provided below:

```
proc glimmix data=event;
class eosblgpn trt01pn cntygr1n nscopd csmoker ppredFev1;
model numevents=trt01pn eosblgpn cntygr1n nscopd csmoker ppredFev1
/offset=logdur dist=negbin link=log solution;
run;
```

If the model fails to achieve convergence, different estimation algorithms will be applied in the order: default→LAPLACE→QUAD. If the issue still exists, other handling may be considered. The adjustment will be added to the footnote of the corresponding outputs. The gross estimates of the annualized event rates will also be presented by treatment group. Mean cumulative function plot will be provided for descriptive purposes.

Similar analysis will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

Estimated clinical efficacy of SAR440340 versus placebo

An analysis to assess the efficacy of SAR440340 if patients adhere to the treatment as directed will also be conducted. In this approach, off-treatment measurements of exacerbation events from patients who prematurely discontinue treatment will be excluded from the analysis. Negative binomial model with the same set of covariates as specified in the primary analysis will be used. The offset will be log-transformed on-treatment duration, which is defined as the duration from the first dose to the last dose +14 days within the observation duration. This approach defines the estimand of the efficacy of SAR440340 with treatment adherence. Similar analysis will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

Missing data handling

If patients withdraw from the study before completing the planned treatment durations, exacerbation events that may occur after study discontinuation will not be observed. These patients are considered as patients with missing data on exacerbation. Number of patients with missing data, reasons and timing of study withdrawals will be summarized by treatment groups. Summary statistics of selected demographic and baseline disease characteristics will be provided for patients with missing data and patients with complete data separately. Graphical summaries of the dropout patterns such as Kaplan-Meier plots of time to study discontinuation with different reasons of discontinuation may be provided to examine if there is any different missing data pattern between treatment groups. In addition, the following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model.

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

For each patient with missing data of exacerbation events, the number of events that could occur in the period from study discontinuation to the end of planned treatment duration will be estimated based on a negative binomial regression model using observed data with adjustment of the treatment group, region (pooled country), baseline eosinophil strata, number of severe exacerbation events within 1 year prior to the study, smoking history (current vs. former smoker) and post-BD FEV1 percent predicted (<50% vs. ≥50%) at baseline. The period from study discontinuation to the end of planned treatment duration will be the exposure time. Once the number of events in the period is imputed, the total number of events in the planned treatment duration will enter the negative binomial regression model as described in the primary analysis with the offset equal to the log-transformed planned treatment duration.

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

For each patient with missing data of exacerbation events, the number of events that could occur in the period from study discontinuation to the end of planned treatment duration will be estimated based on the same negative binomial regression model mentioned in the previous bullet point,

except the imputation will be based on the estimate of the control group only. Once the number of events in the residual treatment duration is imputed, similar model as in the PMM-MI will be used.

- ***Tipping point analysis***

For each patient with missing data of exacerbation events, the number of events that could occur in the residual treatment duration will be estimated in a similar fashion as PMM-MI, based on various event rates. If the patient is on SAR440340, the event rate will be increased and if the patient is on placebo, the event rate will not be changed. The adjusted rate will then be used to impute the number of events that would occur in the period with missing data. A sequence of increasing event rates will be used to generate different imputed datasets.

Similar analyses will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

Technical details on missing data handling are provided in Appendix J.

Subgroup analysis

To assess the consistency of treatment effects across the subgroup levels, subgroup analyses will be performed for the groups listed below. Within each subgroup, descriptive statistics including number of patients, number of moderate to severe AECOPD, treatment exposure time, annualized rate of moderate to severe AECOPD will be provided by treatment group using the same model as for the primary analysis. Risk ratio between treatment and control and the corresponding 95% CI will be provided within each subgroup. Treatment-by-subgroup interaction and its p-value will be derived by a negative binomial regression model. The model will include treatment, baseline eosinophil strata, region, number of severe COPD exacerbations experienced in previous year (0 vs. 1+) at baseline, smoking history (current vs. former smoker), post-BD FEV1 percent predicted (<50% vs. ≥50%) at baseline, subgroup (if different from the aforementioned covariates) and subgroup-by-treatment interaction.

- Blood eosinophil groups (≥150 /mm^3 versus <150 /mm^3, ≥250 /mm^3 versus <250 /mm^3, ≥300 /mm^3 versus <300 /mm^3) defined by actual lab values
- Blood eosinophil groups (≥250 /mm^3 versus <250 /mm^3) from randomization strata.
- Baseline PARC group (<baseline median versus ≥ baseline median)
- Baseline Fibrinogen group (<baseline median versus ≥ baseline median)
- Age groups (<65 versus ≥65 years)
- Sex (Male, Female)
- Region (East Europe: Poland, Russia, Turkey and Ukraine; Latin America: Argentina and Chile; Western countries: USA, Canada, Australia and Germany)
- Race (White, Non-white)
- Background ICS dose level at randomization (none/low, medium, high)
- Baseline CAT score (below median, equal to or above median)

- Baseline post-BD FEV1 percent predicted (<50% vs. ≥50%)
- Baseline weight (<70, ≥70-<90, ≥90 kg)
- BMI (<25, ≥25-<30, ≥30 kg/m^2)
- Smoking history (Current, Former)
- Background therapy (triple versus double)

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Average change from baseline to Week 16-24 in pre-bronchodilator FEV1

Main statistical model and adjustment of covariates

The key secondary efficacy endpoint, the average change from baseline to Week 16-24 in the pre-bronchodilator FEV1 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. Model-based average 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 point. The model will include sex, baseline height, smoking history (current vs. former smoker), baseline FEV1 value, treatment group, visit and treatment-by-visit interaction, baseline FEV1-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. No imputation will be performed on missing FEV1 measurements.

Descriptive statistics including number of patients, mean, standard error, and least squares (LS) means will be provided for each treatment group. Difference in LS means and the corresponding two-sided 95% CI and p-value will be provided for the comparison. Sample SAS code can be found below:

```
proc mixed data=fev1data method=reml;
  class usubjid sex csmoker trt01pn cntygr1 eosbgp1n avisitn;
  model chg = sex height csmoker trt01pn trt01pn *avisitn FEV1bl
FEV1bl* avisitn cntygr1 eosbgp1n avisitn
              trt01pn*avisitn /ddfm=kr residual;
  repeated avisitn / subject=usubjid type=un;
  lsmestimate trt01pn*avisitn 'Tx wks 16-24 avg minus pbo wks 16-24 avg' 0 0
1 1 1 0 0 -1 -1 -1/ divisor=3;
  lsmeans trt01pn*avisitn / pdiff cl e;
  ods output LSMeans=LSMeans Diffs=Diffs LSMEstimates=LSMEstimates;
run;
```

If the above model fails to converge, the specification may be changed as follows: 1) use maximum likelihood estimation instead of restricted maximum likelihood method; 2) specify a different covariance structure to reduce the number of unknown parameters to be estimated, the path will be UN→TOEPH→TOEP→AR(1).

MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time points measured. Differences in LS means, the corresponding 95% CI, and the p-value will be provided for comparison of SAR440340 versus placebo, along with descriptive statistics.

Similar analysis will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

Sensitivity analyses

The following sensitivity analyses will be conducted to assess the robustness of the main model:

Analyses without imputation of the missing FEV1 data: these analyses will use the same MMRM model and estimation methods as specified above and include

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

Analyses with imputation of the missing FEV1 data: these analyses will use the same MMRM model and estimation methods as specified above after missing data being imputed using the following methods

- Pattern-mixture multiple imputations: Missing pre-BD FEV1 values will be imputed multiple times using a regression model. The covariates to be included are sex, baseline height, smoking history (current vs. former smoker), baseline FEV1 value, treatment group, visit and treatment-by-visit interaction, baseline FEV1-by-visit interaction, the baseline eosinophil strata, and region (pooled countries). Forty imputations will be performed. For each imputation, the average change from baseline in pre-BD FEV1 to Weeks 16 to 24 will be analyzed. Statistical inference obtained from all imputed data will be combined using Rubin's rule.
- Control-based multiple imputations: Missing values will be imputed sequentially for each assessment time point using a regression model. Only estimate of the placebo group will be used to fit the MI models.

Similar analyses with imputation of the missing FEV1 data will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

Technical details on the analyses with imputation of the missing FEV1 data are provided in Appendix J.

Subgroup analysis

Subgroup analyses of the average change from baseline to Week 16-24 in pre-BD FEV1 will be conducted in the same subgroups as for the primary endpoint based on the primary MMRM model for pre-BD FEV1 described above. Within each subgroup, descriptive statistics including number of patients, mean, SD, and LS means will be provided for each treatment group. Difference in LS means and the corresponding two-sided 95% CI will be provided for the comparison of

SAR440340 and placebo within each subgroup. Treatment-by-subgroup interaction and its p-value will be derived from a MMRM model. The model covariates will include sex, baseline height, smoking history (current vs. former smoker), baseline FEV1 value, treatment group, visit, treatment-by-visit interaction, baseline FEV1-by-visit interaction, the baseline eosinophil strata, region, subgroup (if different from the aforementioned covariates), subgroup-by-treatment interaction, and subgroup-by-treatment-by visit interaction.

2.4.4.2.2 Change from baseline to Week 24 in post-bronchodilator FEV1

The analysis method for this endpoint is identical to the analysis of the key secondary efficacy endpoint, the average change from baseline to Week 16-24 in pre-BD FEV1, except that here we only have the value at Week 24, not at Weeks 16 and 20. Similar analysis will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

2.4.4.2.3 Time to first moderate or severe AECOPD

Time to first moderate or severe AECOPD that occurs from randomization up to week 52 will be analyzed using a Cox regression model with treatment, baseline eosinophil strata and region (pooled countries), number of severe COPD exacerbations experienced in previous year (0 vs. 1+) at baseline, smoking history (current vs. former smoker) and post-BD FEV1 percent predicted (<50% vs. ≥50%) at baseline as covariates. The hazard ratio (HR) between SAR440340 and placebo along with its 95% confidence interval will be estimated by the Cox model. The Kaplan-Meier (K-M) method will be used to estimate the probabilities of first AECOPD at specific time points for each group. P-value from the log-rank test stratified by baseline eosinophil strata and region will be provided.

Time to first moderate or severe AECOPD is defined as (onset date of the first moderate or severe AECOPD-randomization date+1). If the patient did not experience any moderate to severe AECOPD events, the event time will be considered as censored at date of EOT or the last contact date within the planned treatment duration. Below is sample SAS code for the Cox regression model:

```
proc phreg data=ttevent;
class trt01pn eosbgp1n cntygr1 nscopd csmoker ppredFev1/ param = glm;
model aval*cnsr(1) = trt01pn eosbgp1n cntygr1 nscopd csmoker ppredFev1;
estimate "SAR440340 vs Placebo"          trt01pn -1 1 / exp;
ods output Estimates = Estimates;

run;
```

Similar analysis will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

2.4.4.3 Additional efficacy analysis(es)

2.4.4.3.1 Change from baseline analysis in other continuous endpoints

Change from baseline in FVC (% predicted and absolute) to Week 16-24 will be analyzed using the similar MMRM main statistical analysis model as for the key secondary endpoint, pre-BD FEV1, except that baseline FVC will replace baseline FEV1. Sex and baseline height will be excluded in the model for FVC % predicted as its value has been corrected for sex and height.

Changes from baseline in EXACT domain and total scores, EQ-5D-5L index score and VAS and SGRQ domain and total scores to Week 24 will be analyzed using the MMRM approach described for the analysis of the post-BD FEV1. The covariates will be treatment, baseline eosinophil strata, region, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction. No imputation will be performed on missing values.

MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time points measured. Differences in LS means, the corresponding 95% CI, and the p-value will be provided for comparison of SAR440340 versus placebo, along with descriptive statistics. Similar analysis will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

2.4.4.3.2 Analyses of the proportion of SGRQ responders

A logistic regression model will be used to compare percentage of SGRQ responder patients in SAR440340 and placebo at Week 24 (using the 4-point decrease from baseline as threshold). The model will include treatment, baseline eosinophil strata, region, baseline SGRQ total score value as covariates. Odds ratio of being a responder comparing SAR440340 to placebo will be provided along with the corresponding 95% CI and p-value. Descriptive statistics including number and percentage of responders will also be provided.

Similar analysis will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

2.4.4.3.3 Analyses of the other time-to-event endpoints

Time to the expanded AECOPD endpoint and time to first Clinically Important Deterioration (CID) up to week 52 will be analyzed using the same approach as the analysis of the time to first moderate or severe AECOPD. Similar analysis will be performed for the secondary efficacy population (high EOS group), without the baseline eosinophil strata in the model.

2.4.4.3.4 Analyses of actigraphy and home spirometry data (for patients in US and Canada only)

Change from the average of measurements over baseline and the average of measurements over Weeks 10-12 and over Weeks 22-24 in sleep parameters (total sleep time, wake after sleep onset, overnight activity counts) will be summarized (using mean, standard error, min, Q1, median, Q3 and max) in a table.

Similarly, change from the average of measurements over baseline and the average of measurements over Weeks 10-12 and over Weeks 22-24 in activity parameters (daytime activity counts, percent of time spent in sedentary activity, percent of time spent in moderate to vigorous physical activity) will be summarized (using mean, standard error, min, Q1, median, Q3 and max) in a table.

Change from the average of measurements over baseline and the average of measurements over Weeks 10-12 and over Weeks 22-24 in FEV1 (L) measured at home, will be summarized (using mean, standard error, min, Q1, median, Q3 and max) in a table, which will also include the summary of FEV1 (L) values from the in-clinic visits for the same group of patients.

Additional exploratory analyses may be conducted depending on data availability.

2.4.4.4 Multiplicity issues

No adjustments for multiplicity are planned for this Phase 2a study. More specifically, no adjustments will be made in comparing the two treatment groups based on the secondary efficacy endpoints and no adjustments will be made for the subgroup analyses. All reported p-values will be nominal.

2.4.5 Analyses of safety data

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

General common rules

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

- Safety data in patients who do not belong to the safety population will be listed separately.
- The baseline value is defined as the last available value prior to the first dose of the IMP.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated May 2014, see Appendix A).
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE period by treatment group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the endpoint value. The endpoint value

is commonly defined as the value collected at or just prior to the last dose date +14 days, or at the end of treatment visit, whichever comes later. If this value is missing, this endpoint value will be the closest value prior to the last dose intake. The worst value is defined as the nadir and/or the peak post-baseline (up to last administration of IMP) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.

- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

All safety values including unscheduled measurements will be assigned to the appropriate safety analysis visit window defined in Section 2.5.4.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on TEAEs. Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an event by treatment group. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Sorting will be based on results for the SAR440340 group by the following orders:

- Tables presented by SOC: sorted by internationally agreed SOC order
- Tables presented by PT: sorted by decreasing frequency of PT
- Tables presented by SOC and PT: sorted by internationally agreed SOC order and decreasing frequency of PT within SOC

Analysis of all TEAEs

The following TEAE summaries will be generated for the safety population.

- Overview of TEAE, summarizing number (%) of patients with any
  - TEAE
  - Severe TEAE

  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
- All TEAEs by primary SOC
- All TEAEs by PT
- All TEAEs by primary SOC and PT
- All TEAEs related to SAR440340 or matching placebo by primary SOC and PT
- All TEAEs by maximal severity, presented by primary SOC and PT
- Listing of all TEAEs

Analysis of all treatment emergent SAEs

- All treatment-emergent SAEs by primary SOC and PT
- All treatment-emergent SAEs by PT
- All treatment-emergent SAEs related to SAR440340 or matching placebo by primary SOC and PT
- Listing of all treatment-emergent SAEs

Analysis of all TEAEs leading to permanent treatment discontinuation

- All TEAEs leading to permanent treatment discontinuation by primary SOC and PT
- All TEAEs leading to permanent treatment discontinuation by PT
- Listing of all AEs leading to permanent treatment discontinuation

Analysis of AESI

A summary of number of patients with any TEAE by AESI category (defined by the search criteria in Section 2.1.4.1) will be generated. In addition, for each AESI category the following will be provided:

- All TEAEs by PT
- Overview summary including
  - Number (%) of patients with any TEAE
  - Number (%) of patients with any SAE (regardless of treatment emergent status)
  - Number (%) of patients with any treatment-emergent SAE
  - Number (%) of patients with any AE leading to death
  - Number (%) of patients with any TEAE leading to permanent treatment discontinuation
  - Number (%) of patients with any TEAE related to IMP reported by investigator

- Number (%) of patients with any TEAE by maximum intensity, corrective treatment, and final outcome
- Number of TEAE adjusted by the exposure duration

For categories with at least 5 events in at least one treatment group, K-M plots of time to first event will be provided to depict the course of onset over time.

Analysis of pre-treatment and post-treatment adverse events

Listings will be provided for all pre- and post-treatment AEs. The following summaries may be generated if the number of events is large enough:

- All pre-treatment AEs by primary SOC and PT
- All pre-treatment SAEs by primary SOC and PT
- All pre-treatment AEs leading to treatment discontinuation by primary SOC and PT
- All pre-treatment AEs leading to death by primary SOC and PT
- All post-treatment AEs by primary SOC and PT
- All post-treatment SAEs by primary SOC and PT
- All post-treatment AEs leading to death by primary SOC and PT

2.4.5.2 Deaths

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

- Number (%) of patients who died by study period (on-study, on-treatment, post-study)
- TEAEs leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC and PT
- Listing of all AEs leading to death

In addition, summary of deaths in non-randomized patients or randomized but not treated patients may be generated.

2.4.5.3 Analyses of laboratory variables

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

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

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

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

Laboratory measurements obtained at either scheduled or unscheduled visits will be used in analyses of PCSA. In addition, both centralized and local test results will be used. Centralized data will be used preferentially to the local measures in the analysis when several measurements are performed on the same date and at the same time for a given laboratory test.

Listings will be provided with flags indicating the out of range values as well as the PCSA values.

Potential drug-induced liver injury

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

A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listing of selected laboratory parameters for possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) will be provided.

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

Change in Blood Eosinophil

Absolute and percent mean (median) change from baseline in eosinophil count will be summarized and plotted over time in each treatment group for patients with baseline blood eosinophil <0.25 Giga/L and patients with baseline blood eosinophil ≥0.25 Giga/L.

2.4.5.4 Analyses of vital sign variables

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

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

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

Listings will be provided with flags indicating the PCSA values.

2.4.5.5 Analyses of electrocardiogram variables

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

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

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

Listings will be provided with flags indicating the PCSA values.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

2.4.6.1 Analyses of serum concentrations

Concentrations of SAR440340 will be analyzed in the PK population. Concentrations of SAR440340 will be summarized in SAR440340-treated patients.

Arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time will be provided. If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. Concentrations below the lower limit of quantification (LLOQ) will be set to zero for pre-dose samples (Week 0). Other concentrations below LLOQ will be replaced by LLOQ/2. Values will be expressed in the tables with no more than three significant figures.

2.4.6.2 Pharmacodynamics/genomics analyses

PD biomarkers will be analyzed in the safety population. Baseline values will be the last value collected prior to the first IMP.

For each biomarker, biomarker value, absolute change from baseline and percent change from baseline will be summarized descriptively (number, arithmetic and geometric means, SD, SEM, CV, median, minimum and maximum) by treatment group and time point. Values reported as below the LLOQ will be imputed as LLOQ/2.

Summary plots by visit for each biomarker by treatment group will be provided as:

- mean +/- standard error of the biomarker value
- mean +/- standard error of the absolute change from baseline
- mean +/- standard error of the percent change from baseline
- median(IQR) of the percent change from baseline

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

2.4.7 Analyses of ADA variables

2.4.7.1 Analysis of ADA bioanalytical data

Analyses described in this section will be performed for ADA against SAR440340.

ADA response categories and titer categories are defined as follows:

ADA response categories

- **Pre-existing immunoreactivity:** defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.

- **Treatment-emergent response:** defined as a positive response in the ADA assay post first dose when baseline results are negative or missing. A treatment-emergent response is further classified as persistent, indeterminate or transient:
  - **Persistent response:** treatment-emergent ADA response detected at 2 or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time) with no ADA negative samples in between.
  - **Indeterminate response:** treatment-emergent response when only the last collected sample is positive.
  - **Transient response:** a treatment-emergent response that is not persistent or indeterminate.

- **Treatment-boosted response:** defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive.

Patients will be classified as ADA positive patients and ADA negative patients. ADA positive patients are the patients with treatment-emergent or treatment-boosted response, and ADA negative patients are patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.

Maximum Titer categories

- **Low** (Titer<1000)
- **Moderate** (1000≤Titer≤10000)
- **High** (Titer>10000)

The following summaries will be provided based on ADA population:

Baseline summary:

- Number (%) of patients with a positive response in the ADA assay at baseline
  - Summary statistics (including number, median, Q1, Q3, minimum and maximum) of titer for patients with a positive response
- Number (%) of patients with a negative response in the ADA assay at baseline

Post-baseline summary:

- Number (%) of patients with pre-existing immunoreactivity
- Number (%) of patients with treatment-emergent ADA response
  - Number (%) of patients with persistent response
  - Number (%) of patients with indeterminate response
  - Number (%) of patients with transient response
- Number (%) of patients with treatment-boosted ADA response
- Number (%) of ADA positive patients
- Number (%) of ADA negative patients

Listing of all ADA titer levels will be provided for patients with treatment-emergent and treatment-boosted responses.

2.4.7.2 Association of immunogenicity with exposure, safety and efficacy

The potential association between key ADA variables (ADA positive, persistent ADA and titer) and exposure will be explored. Association between ADA and safety/efficacy may be explored depending on the number of patients positive in the ADA assay.

Association between ADA and impact on drug concentration profile

Association between key ADA variables and systemic exposure to study drug will be explored. Descriptive summary of functional SAR440340 concentrations will be provided by anti-SAR440340 antibody patient classification in SAR440340-treated patients at each visit. In addition, plots of drug concentration may be provided for analyzing the potential impact of ADA on PK.

Association between ADA and safety

Association of safety versus key ADA variables may be explored. The safety assessment may focus on the following events:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity reactions
- Anaphylactic reactions

Number (%) of patients with these events may be summarized by ADA patient classifications.

Association between ADA and efficacy

Association between the key ADA variables and key efficacy endpoints may be explored. The following efficacy endpoints may be analyzed by ADA patient classifications:

- Annualized rate of moderate or severe AECOPD
- Mean change from baseline in pre-BD FEV1 to Weeks 16-24

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

Demographic formulas

- Age of onset of COPD is calculated as:

  Year of diagnosis of COPD –Year of birth

- Time since first diagnosis of COPD (years) is calculated as:

  (Year of randomization -Year of first diagnosis of COPD) + (month of randomization - month of first diagnosis of COPD)/12

- Time since cessation of smoking (years) is calculated as:

  (Year of randomization - Year of cessation) + (month of randomization -month of cessation)/12

- Time since last COPD exacerbation (months) is calculated as:

  (Year of randomization - Year of last COPD exacerbation)×12 + (month of randomization - month of last COPD exacerbation)

- BMI is calculated as:

  Weight in kg / (height^2 in meters)

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

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

Renal function formulas

Creatinine clearance (CrCl) value will be derived using the equation of Cockroft and Gault:

CLcr (ml/min) = (140 – age) × weight (kg) × (1 – 0.15 × sex (0-M, 1-F))/

(0.814 × creatinine (µmol/l))

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

Integer part of (Lab sampling date – Date of screening visit)/365.25 + Age at screening visit

2.5.2 Data handling conventions for other efficacy variables

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations per day is the number of inhalations recorded in one diary day including the evening diary and the following day's morning diary.

For the daily efficacy endpoints (eDiary, home spirometry, actigraphy), the time period used to calculate the periodical average at each study visit day is fourteen (14) days before the visit.

Table 8 summarizes the time periods corresponding to each study day and week.

Table 5 - Periodical average of daily efficacy assessment

Time point Day/Week	eDiary data, Actigraphy (daily activity), home spirometry	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol
Day 1/Randomization	Screening-Day -1	Screening-Day -1
Day 15/Visit 3	1-14	Diary Day 1-14
Day 29/Visit 4	15-28	Diary Day 15-28
Day 43/Visit 5	29-42	Diary Day 29-42
Day 57/Visit 6	43-56	Diary Day 43-56
…	…	…
Day 141/Visit 10	127-140	Diary Day 127-140
…	…	…
Day 365/Visit EOT	351 - 364	Diary Day 351 - 364

2.5.3 Missing data

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

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

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

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

Handling of medication missing/partial dates

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

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

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

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

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

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

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

Handling of missing severity of adverse events

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

Handling of potentially clinically significant abnormalities

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

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

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

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

2.5.4 Windows for time points

Visit windows based on days relative to the first IMP administration will be used to map the efficacy parameters (Table 6), selected safety variables (Table 7) and PK/PD variables (Table 8) to each scheduled visit. Date of randomization will be used as the reference date for patients not treated. The following rules will be applied:

1. For efficacy parameters, only scheduled measurements will be considered. If a patient has more than one measurement for the same parameter at different dates within the same visit window, the one that is closest to the target date will be used (or the latest in case of tie).
2. Only values from the central laboratory will be considered for laboratory variables.
3. For the same laboratory/vital sign/ECG/PK/PD parameter, if a patient has more than one measurement at different dates within the same visit window, the measurement that is closest to the target date will be used (or the latest in case of tie).
4. When a patient has more than one measurement on the same laboratory/vital sign/ECG/PK/PD parameter on the same date, then the one with the later/largest sample ID will be used.
5. For procedures planned on Visit 2, if it is done on the same date as the first IMP but the performance time is missing, it will be assigned to the Visit 2 time window.

Table 6 – Time window for efficacy endpoints

Visit	Target Day	Pre-BD spirometry	Post-BD spirometry
Visit 1 (Wk-4 to Wk-1)	-28±3	-28±3	-28±3
Visit 2 (Week 0)	1	≤1	≤1
Visit 3 (Week 2)	15	2-21	2-21
Visit 4 (Week 4)	29	22-42	22-42
Visit 6 (Week 8)	57	43-70	43-70
Visit 8 (Week 12)	85	71-98	71-126
Visit 10 (Week 16)	113	99-126	
Visit 12 (Week 20)	141	127-154	
Visit 14 (Week 24)	169	155-182	127-266
Visit 16 (Week 28)	197	183-210	
Visit 18 (Week 32)	225	211-238	
Visit 20 (Week 36)	253	239-266	
Visit 22 (Week 40)	281	267-294	
Visit 24 (Week 44)	309	295-322	
Visit 26 (Week 48)	337	323-343	
Visit 27 (Week 50)	351	344-357	
EOT (Week 52)	365	358-392	267-392
F1 (Week 60)	421	393-462	393-462
EOS (Week 72)	505	≥463	≥463

Table 7 – Time window for safety endpoints

Visit	Target Day	Vital signs	ECG	Hematology, biochemistry, urinalysis	Heptitis and HIV serology tests, quantiferon gold testing, serum pregnancy test	Urine pregnancy test
Visit 1 (Week -4 - 0)	-28±3	< -7	<-7	<-7	≤1	
Visit 2 (Week 0)	1	-7-1	-7-1	-7-1		≤1
Visit 3 (Week 2)	15	2-21				
Visit 4 (Week 4)	29	22-35				2-42
Visit 5 (Week 6)	43	36-49				
Visit 6 (Week 8)	57	50-63		2-84		43-70
Visit 7 (Week 10)	71	64-77				
Visit 8 (Week 12)	85	78-91	2-126			71-98
Visit 9 (Week 14)	99	92-105				
Visit 10 (Week 16)	113	106-119		85-140		99-126
Visit 11 (Week 18)	127	120-133				
Visit 12 (Week 20)	141	134-147				127-154
Visit 13 (Week 22)	155	148-161				
Visit 14 (Week 24)	169	162-175	127-210	141-210		155-182
Visit 15 (Week 26)	183	176-189				
Visit 16 (Week 28)	197	190-203				183-210
Visit 17 (Week 30)	211	204-217				
Visit 18 (Week 32)	225	218-231				211-238
Visit 19 (Week 34)	239	232-245				
Visit 20 (Week 36)	253	246-259	211-308	211-308		239-266
Visit 21 (Week 38)	267	260-273				
Visit 22 (Week 40)	281	274-287				267-294
Visit 23 (Week 42)	295	288-301				
Visit 24 (Week 44)	309	302-315				295-322
Visit 25 (Week 46)	323	316-329				

Visit 26 (Week 48)	337	330-343			323-350
Visit 27 (Week 50)	351	344-357			
EOT (Week 52)	365	358-392	309-434	309-434	351-434
F1 (Week 60)	421	393-462			
EOS (Week 72)	505	≥463	≥435	≥435	≥435

Table 8 – Time window for PK/PD endpoints

Visit	Target Day	Serum SAR440340 concentration	Anti-drug antibody	Blood eosinophil /neutrophil	FeNO	Total IL33, sST2, calcitonin	PARC, eotaxin-3	Total IgE	Fibrinogen
Visit 1 (Week -4 - 0)	-28±3			<-7		<-7	<-7	<-7	<-7
Visit 2 (Week 0)	1	≤1	≤1	-7 – 1	≤1	-7 – 1	-7 – 1	-7 – 1	-7 – 1
Visit 3 (Week 2)	15	2-21							
Visit 4 (Week 4)	29	22-42		2-42	2-42	2-42	2-42	2-42	
Visit 6 (Week 8)	57	43-70		43-70	43-70	43-70			
Visit 8 (Week 12)	85	71-98	2-126	71-126	71-126	71-126	43-126	43-126	
Visit 10 (Week 16)	113	99-140							
Visit 14 (Week 24)	169	141-210	127-266	127-210	127-210	127-266	127-210	127-266	2-266
Visit 20 (Week 36)	253	211-308		211-308	≥211		211-308		
EOT (Week 52)	365	309-392	267-434	309-392		267-392	≥309	≥267	≥267
F1 (Week 60)	421	393-462		393-462		393-462			
EOS (Week 72)	505	≥463	≥435	≥463		≥463			

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

Due to small sample size in some countries, the countries will be pooled into regions as defined below for the analyses:

- East Europe: Poland, Russia, Turkey and Ukraine
- Latin America: Argentina and Chile
- Western countries: USA, Canada, Australia and Germany

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No formal interim analysis is planned. Analyses will be performed for safety/efficacy monitoring and internal decision making. The analyses will be conducted by individuals independent of the study and the development program and reviewed by an independent Data Monitoring Committee (DMC). No formal stopping rules or adjustment for multiplicity will be applied. Full details on DMC procedures and data to be reviewed are described in the DMC charter.

4 DATABASE LOCK

A core database lock is planned to occur approximately 4 weeks after the last EOT visit. The final database is planned to be locked 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

1. EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208

2. van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012 Jul-Aug;15(5):708-15.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT)

Appendix C: COPD Assessment Test (CAT)

Appendix D: Euroqol Questionnaire (EQ-5D-5L)

Appendix E: St. George's Respiratory Questionnaire (SGRQ)

Appendix F: SGRQ Scoring Algorithm

Appendix G: List of opportunistic infections

Appendix H: Definition of anaphylaxis

Appendix I: Low, medium and high dose of inhaled corticosteroids

Appendix J: Handling of missing data

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

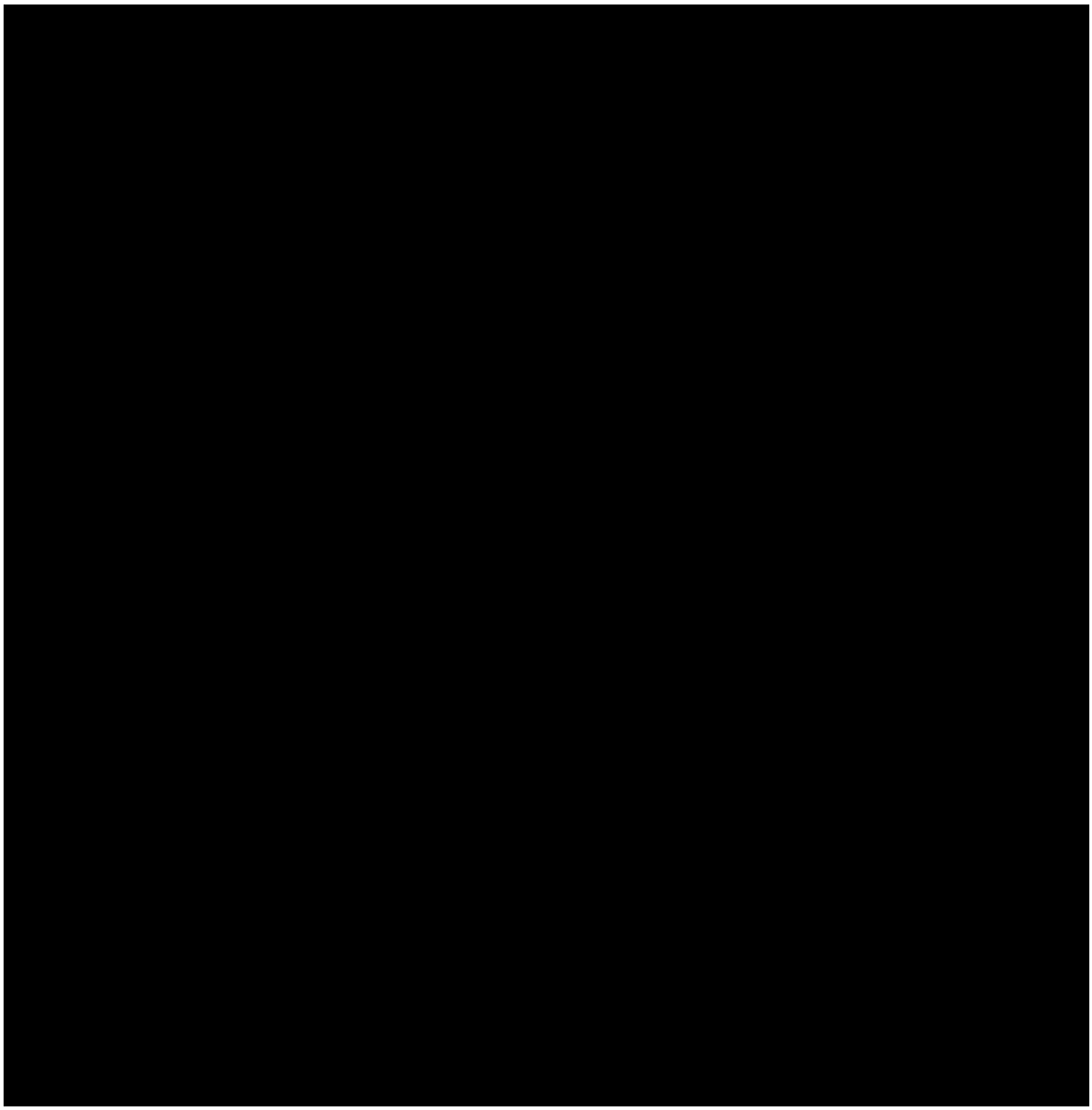
CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 "Analysis and reporting of safety data from clinical trials through the Clinical Study Report" Version 3, 21-MAY-2014)

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

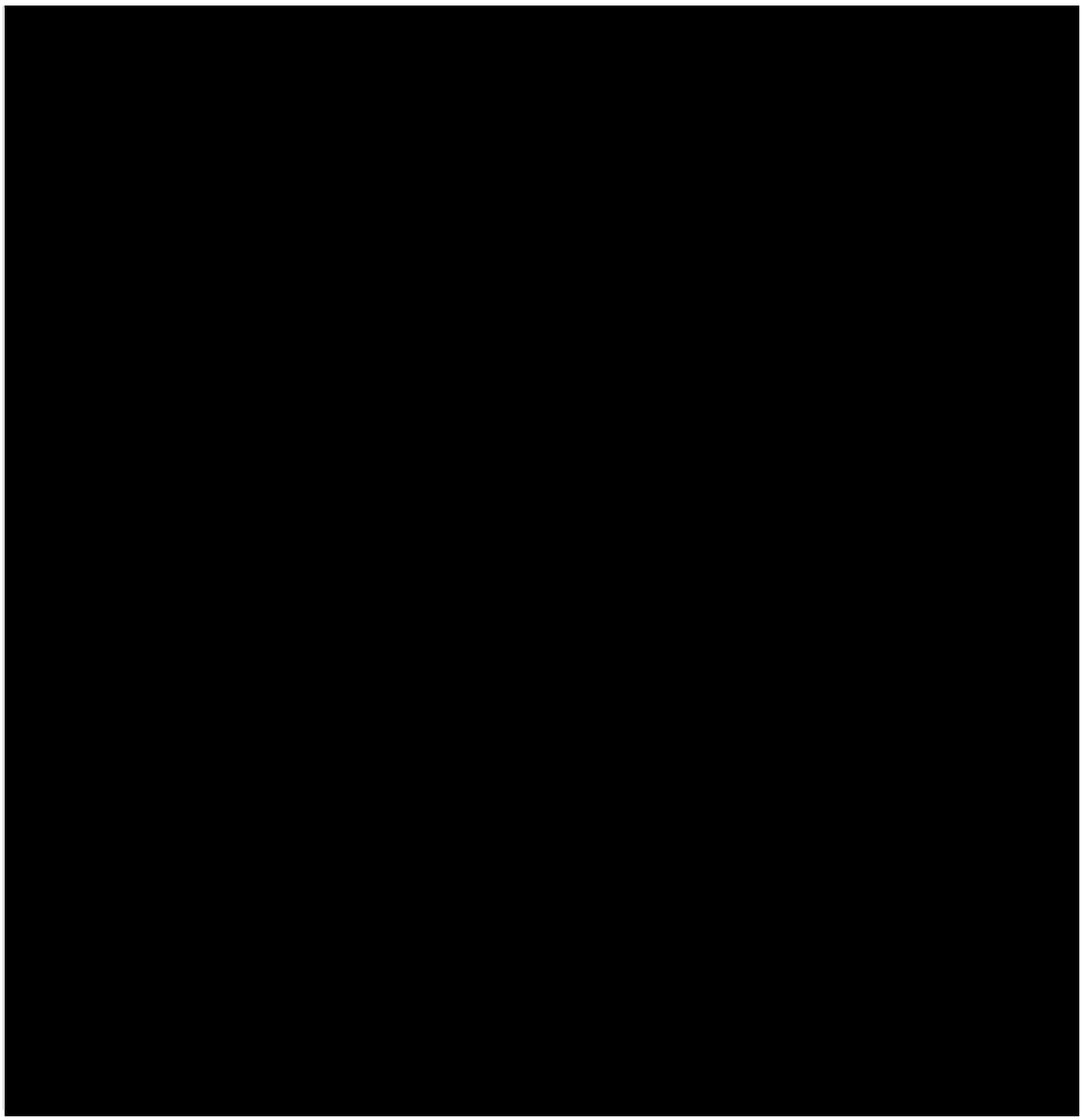
Appendix B Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT)

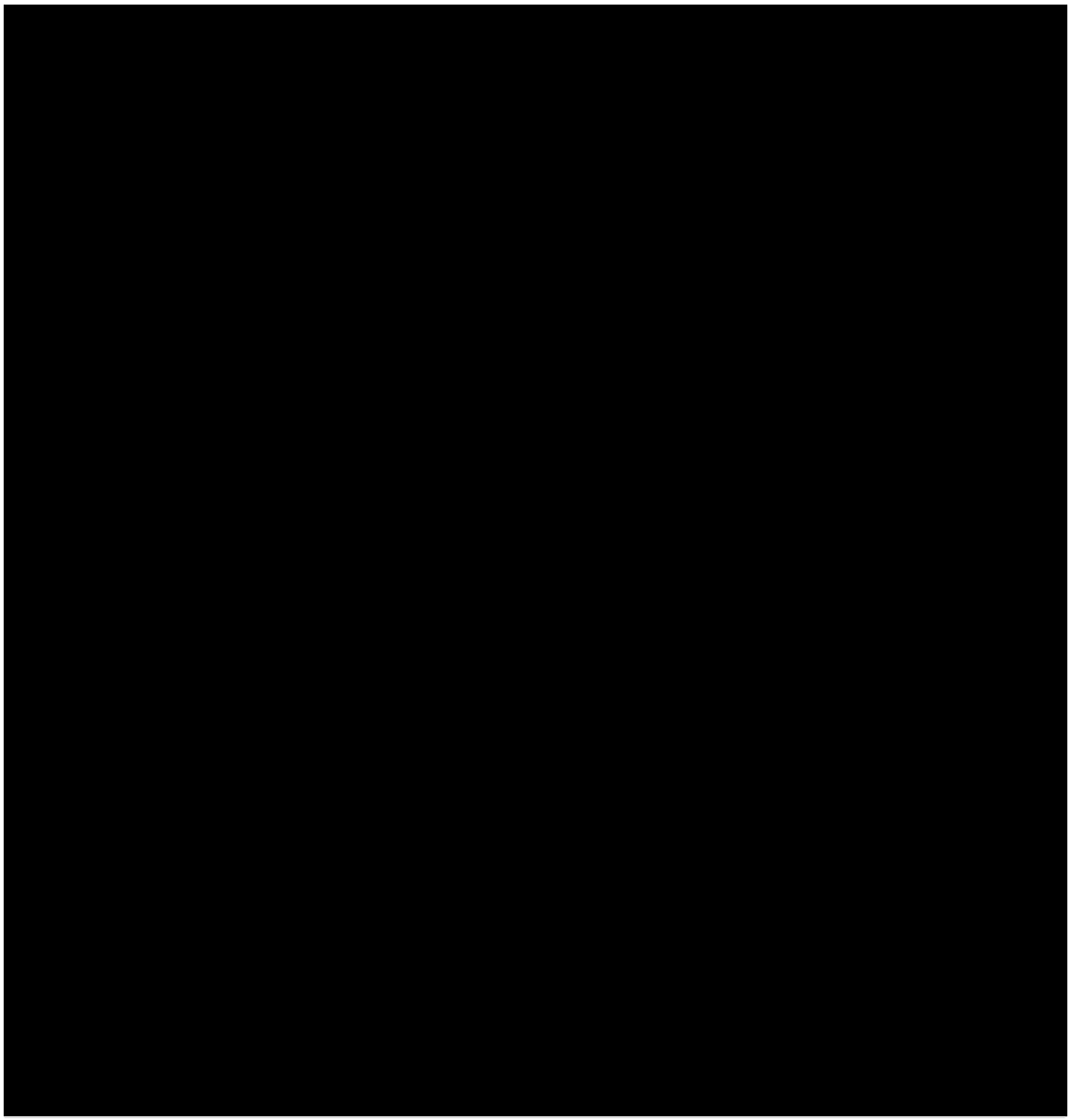


Appendix C COPD ASSESSMENT TEST (CAT)

Appendix A COPD Assessment Test

Appendix D EUROQOL QUESTIONANAIRE (EQ-5D-5L)

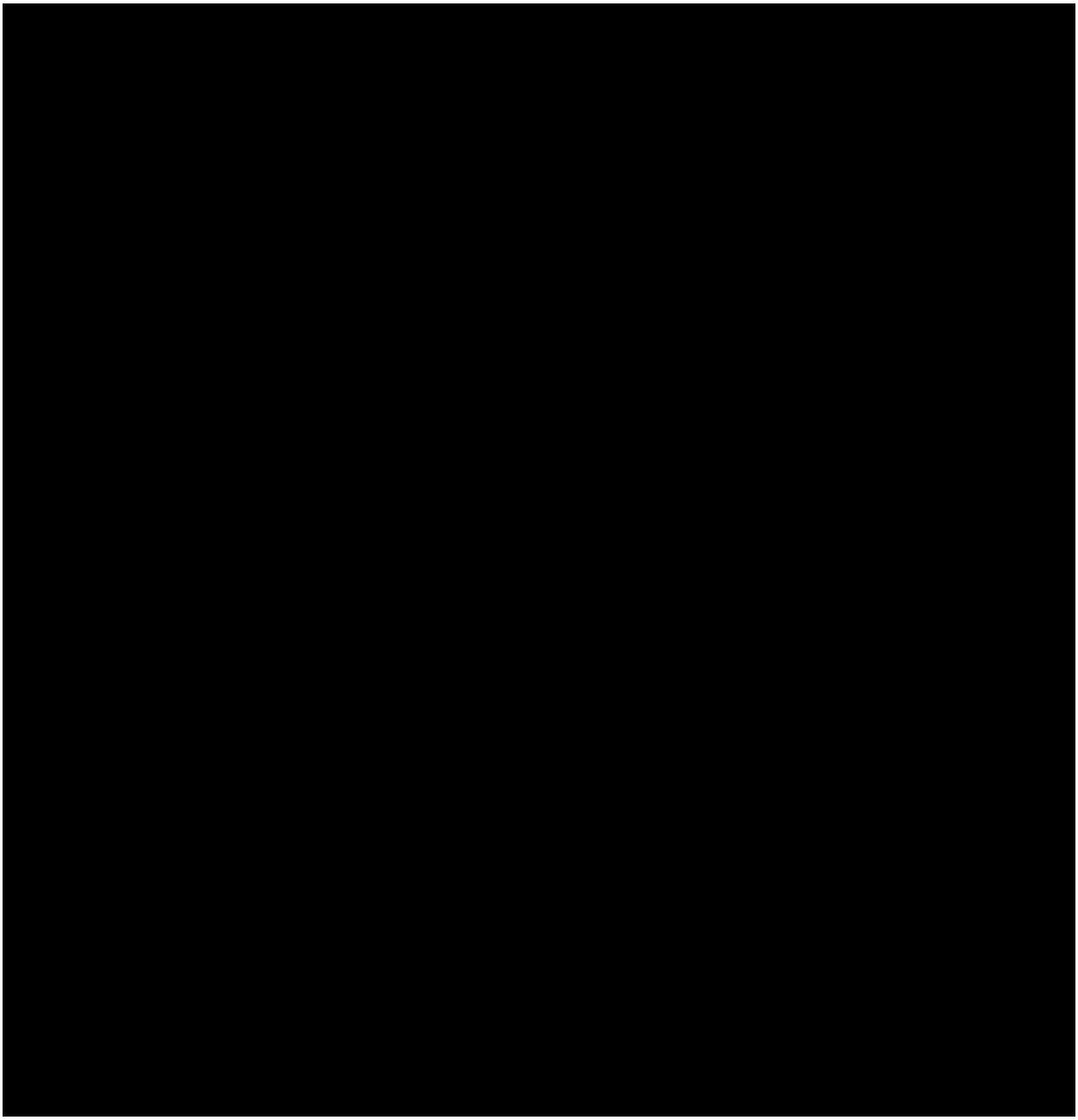


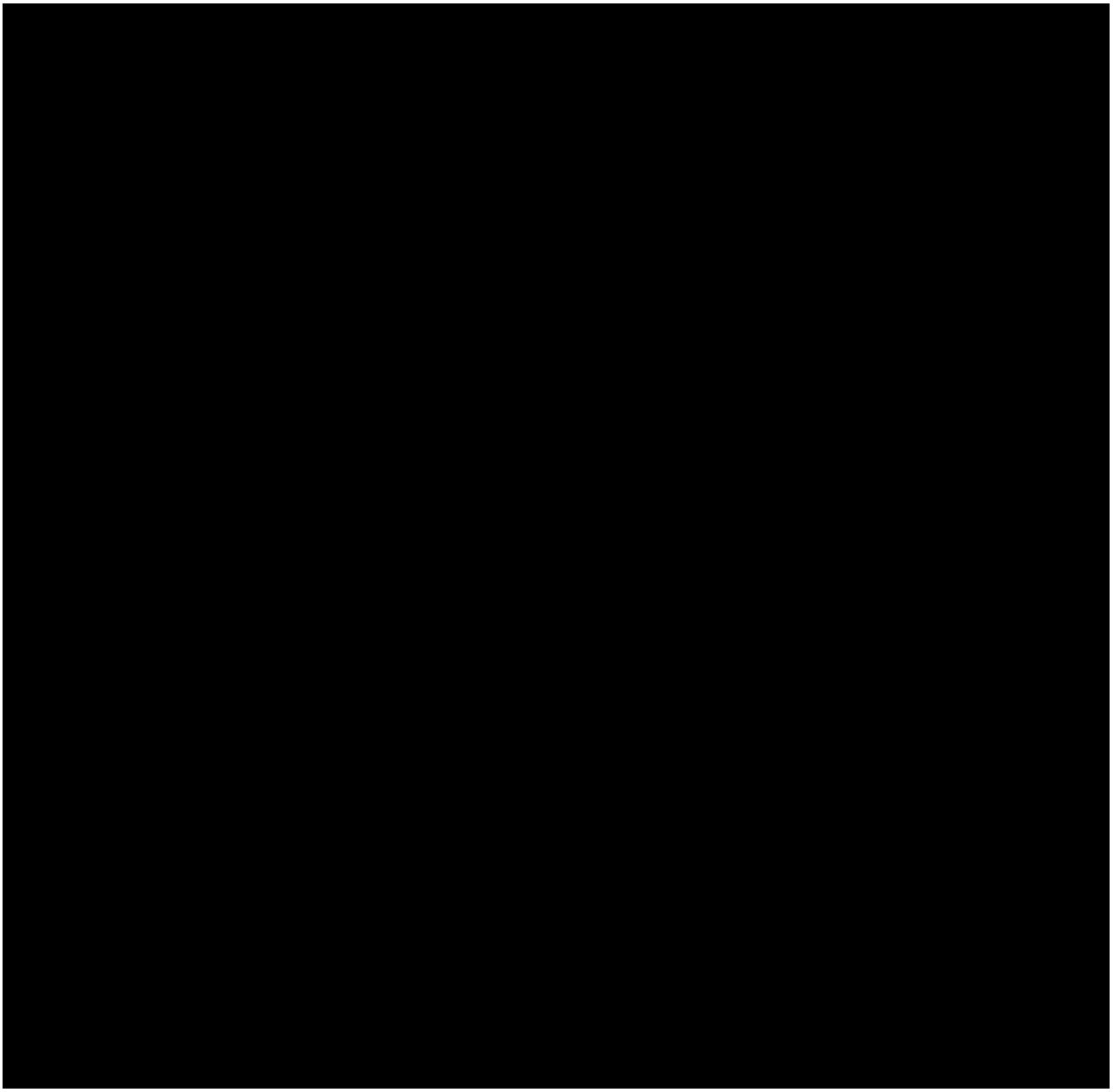


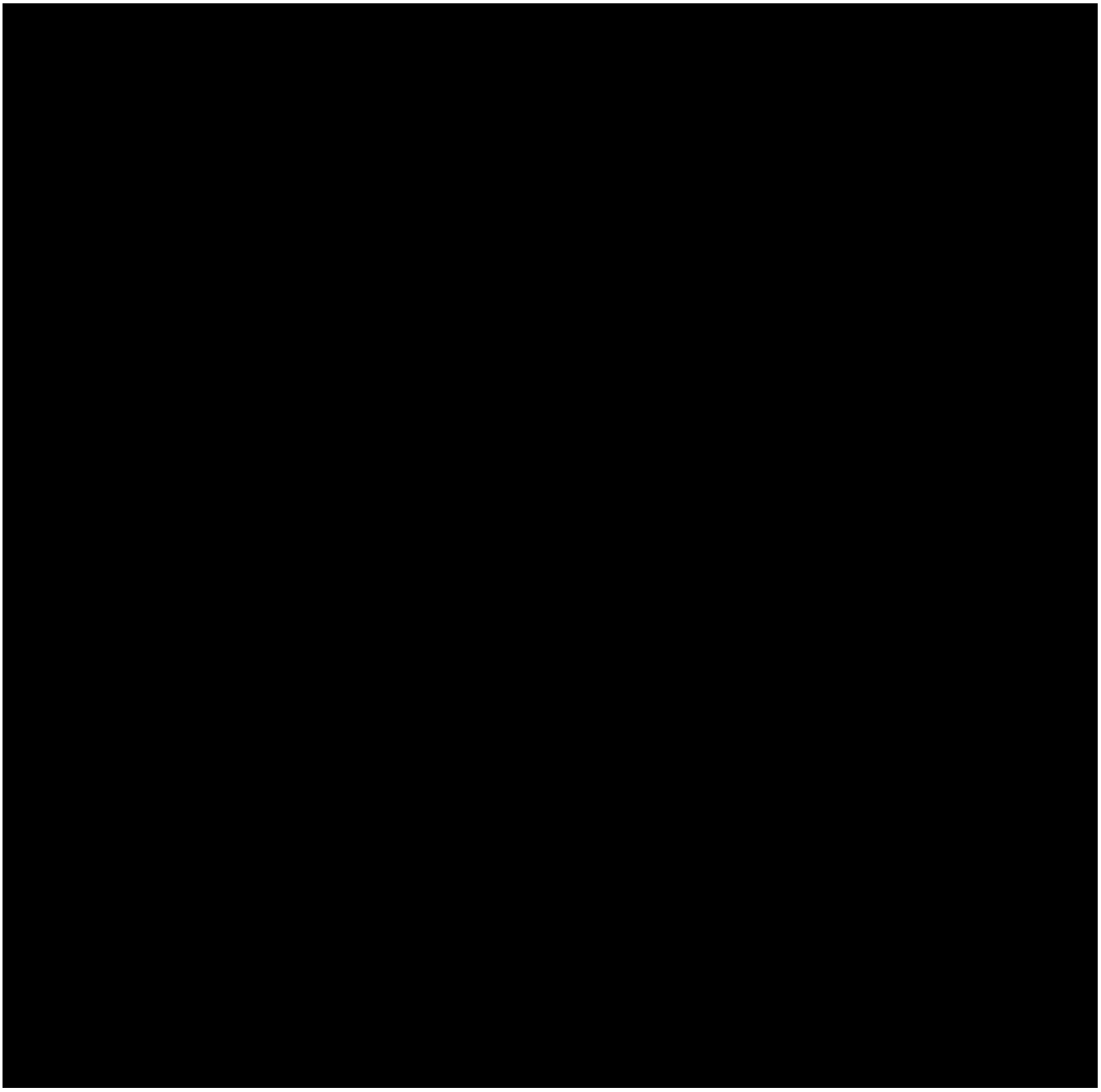
Appendix E ST GEORGE'S RESPIRATORY QUESTIONANAIRE (SGRQ)

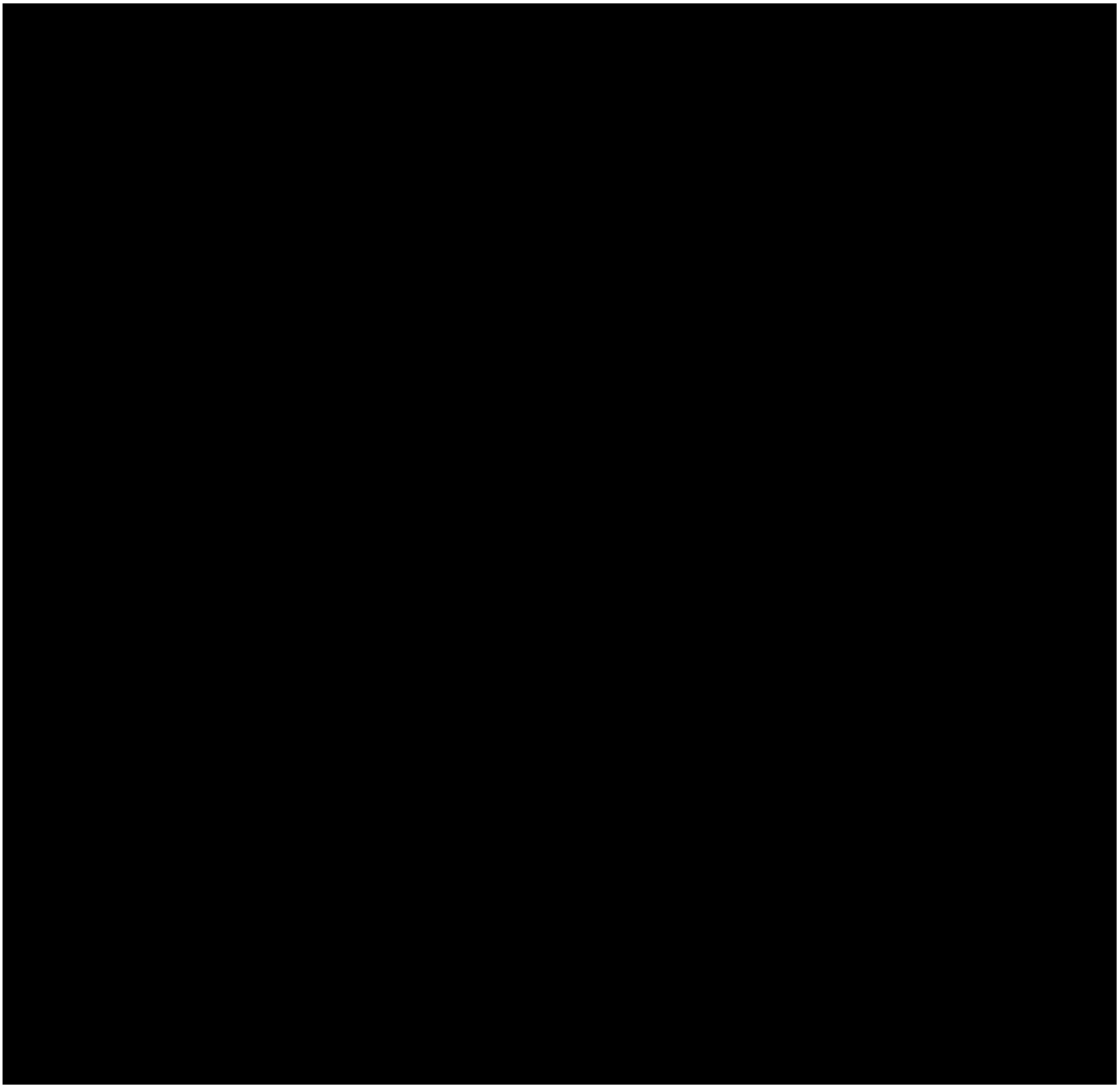
[redacted]

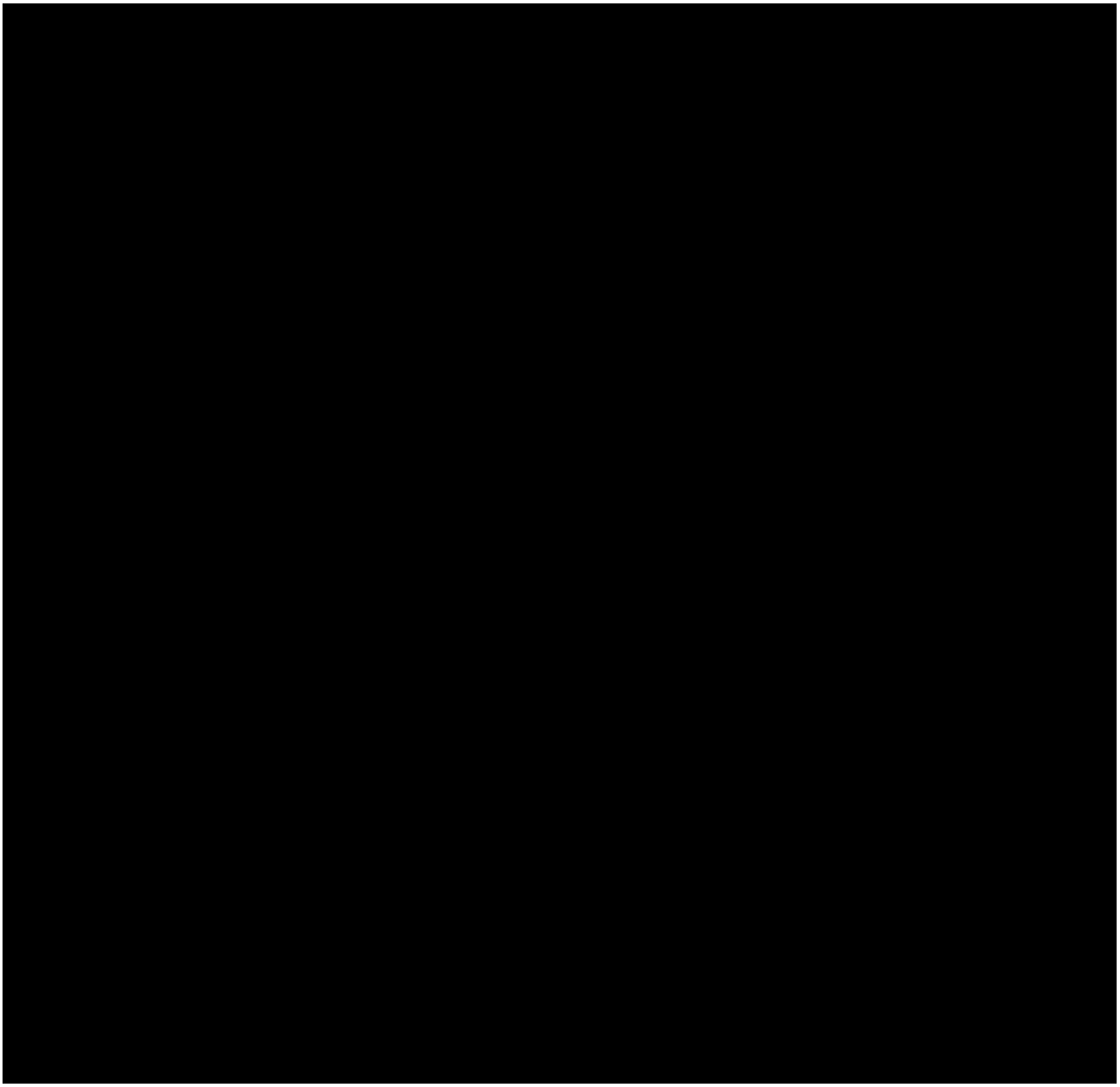
[redacted]



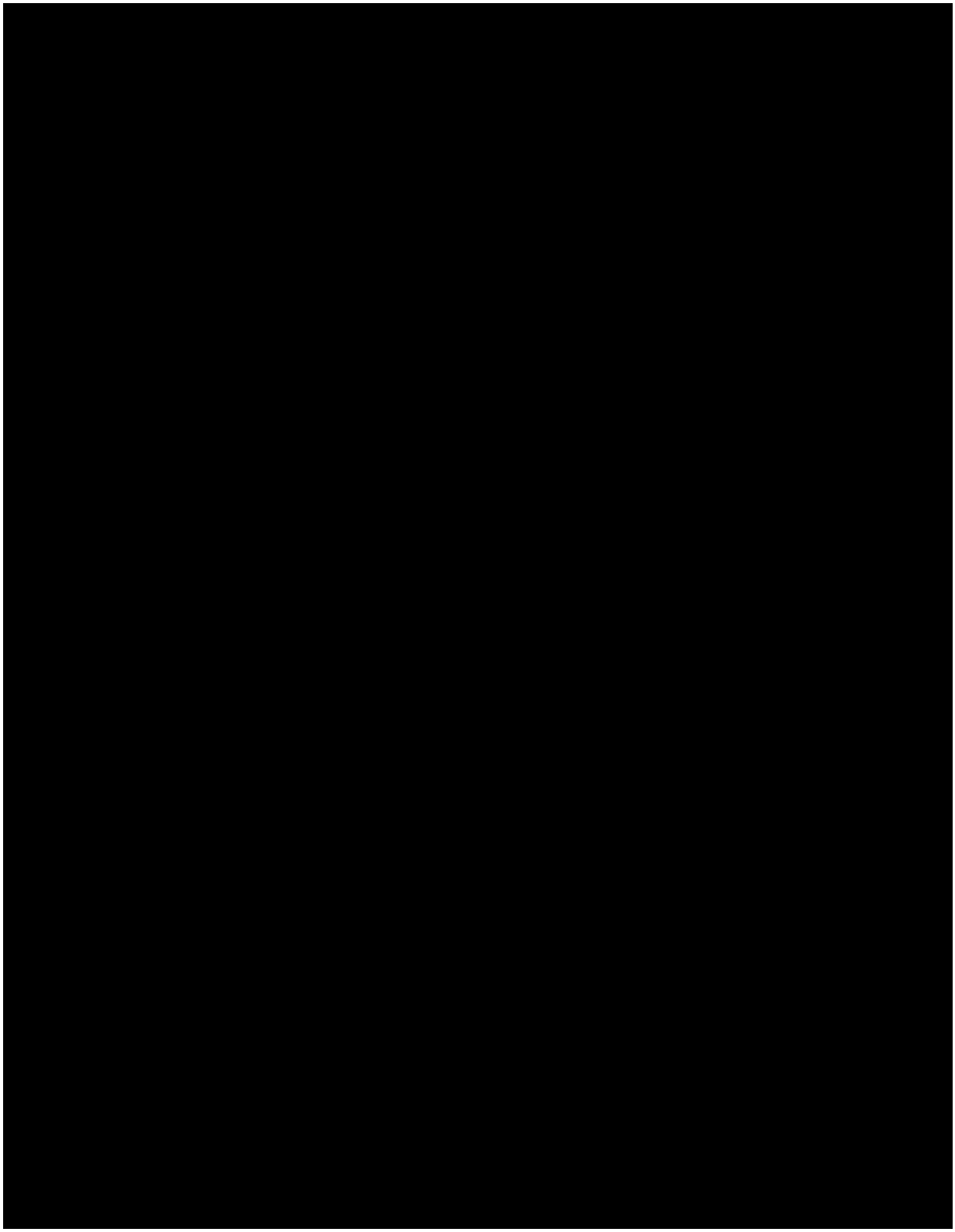


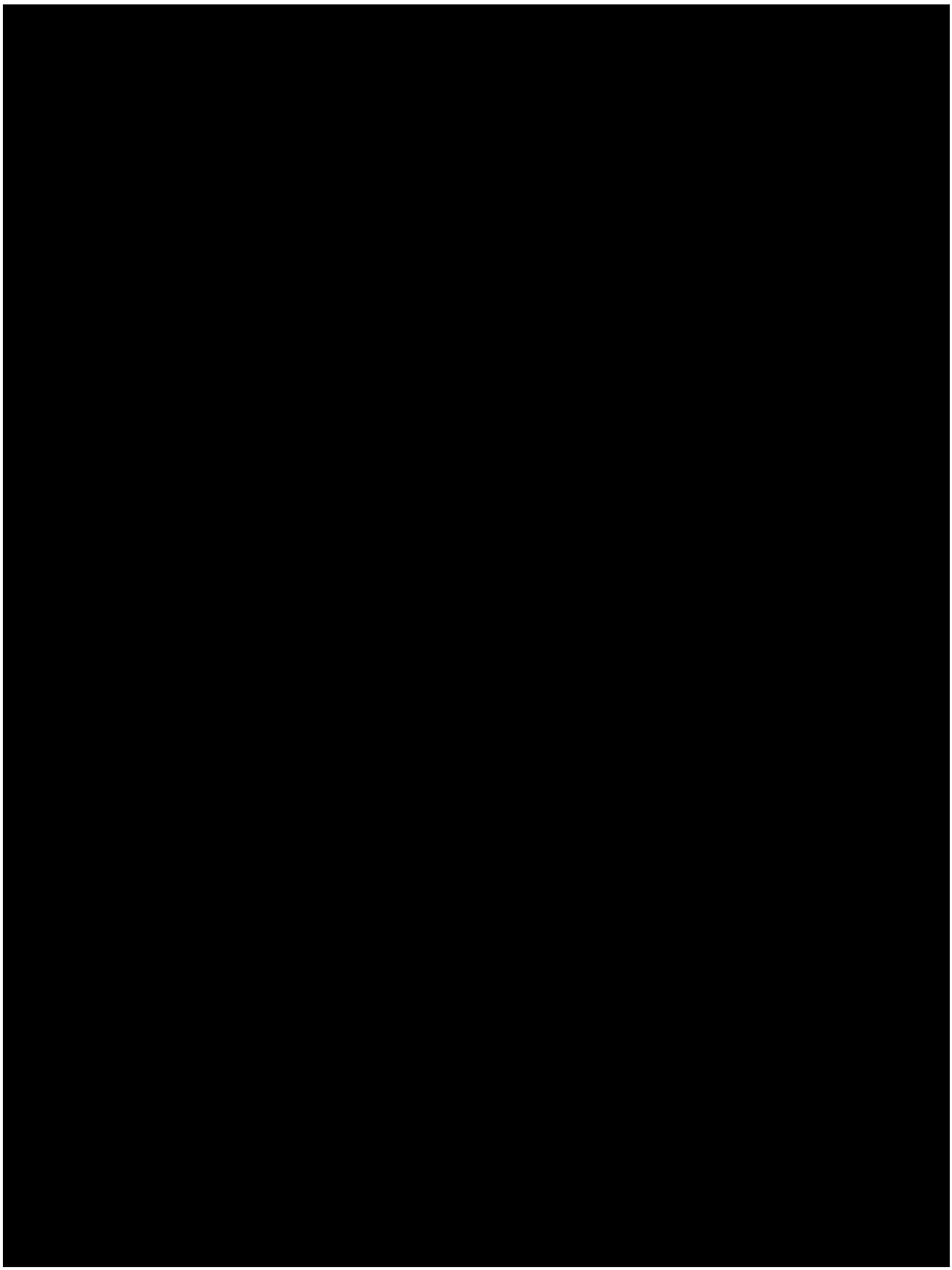


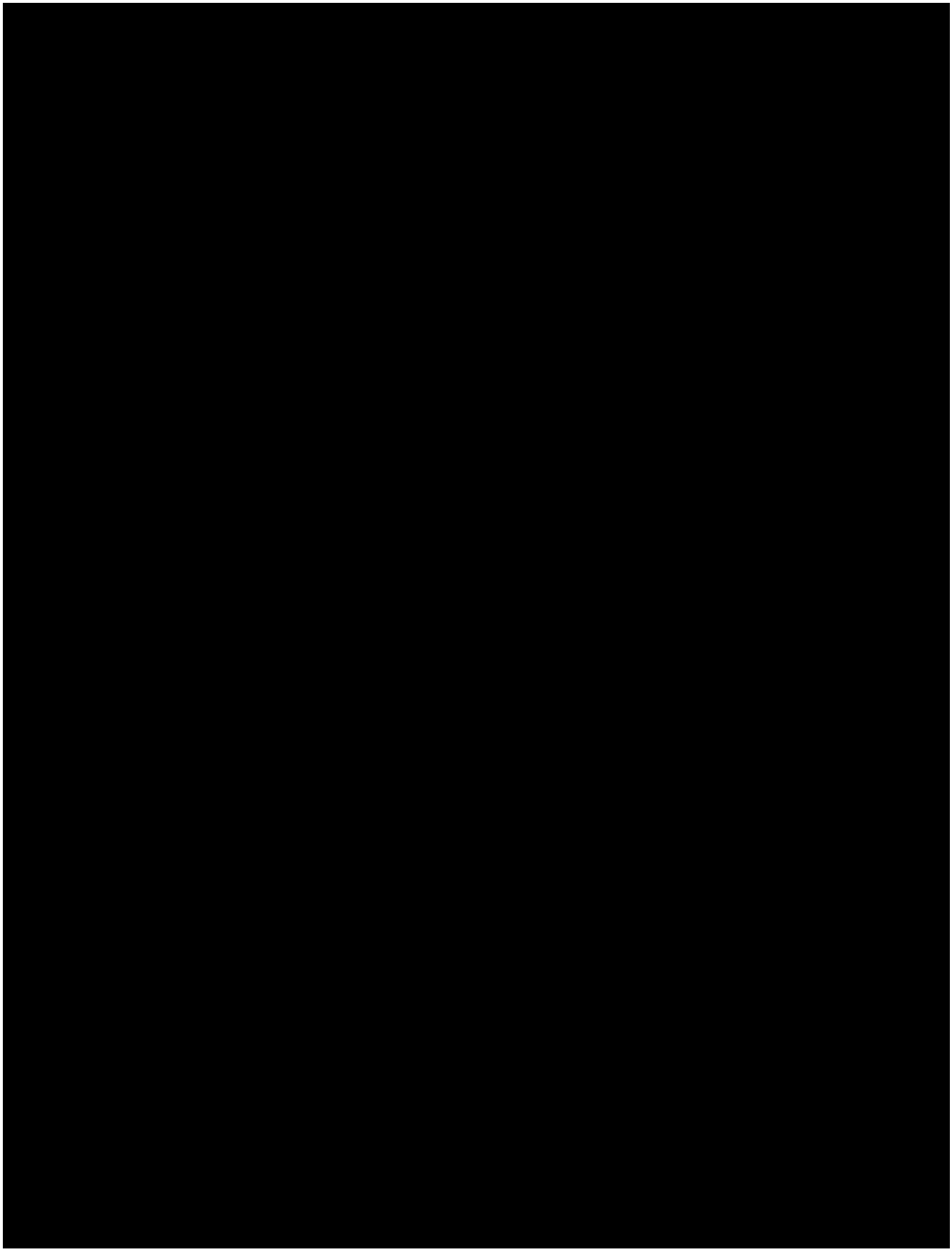


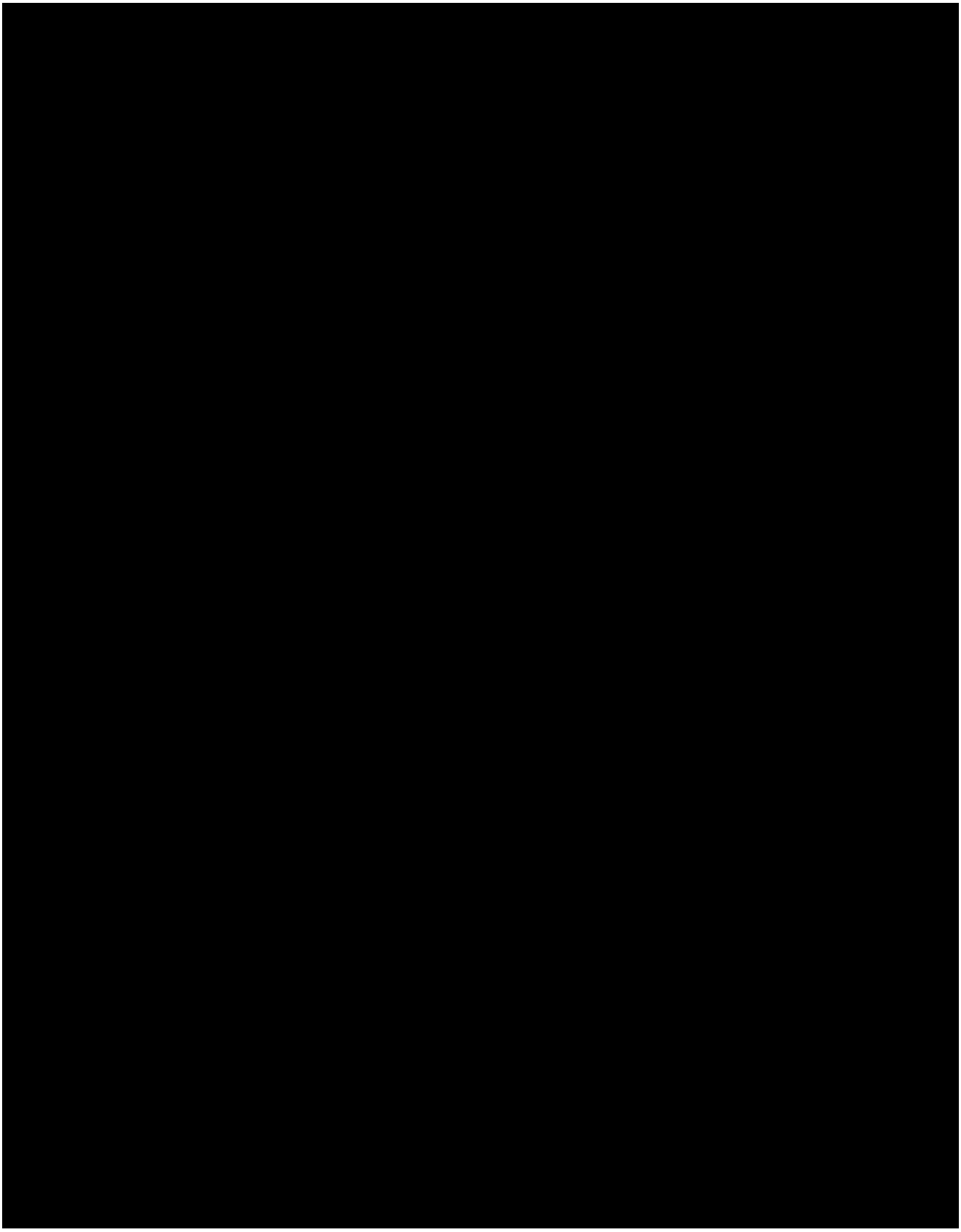


Appendix F SGRQ Scoring Algorithm









Appendix G List of opportunistic infections

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis – only systemic or extensive mucosal or cutaneous candidiasis.
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (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.

Appendix H Definition of anaphylaxis

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

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

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.

Appendix I Low, medium and high dose of inhaled corticosteroids

Source: Adapted from Global Initiative for Asthma (GINA) 2017 guidelines

Appendix J Handling of missing data

Rate of AECOPD

The covariates in the model may change in different cases. The following code is for explanatory purposes only and that actual covariates included are as described in the main text of the SAP.

1. The following SAS code extracts samples from the posterior distribution of model parameters (including the dispersion parameter) using a Bayesian negative binomial log-link model with an offset variable which is equal to the log of the observed exposure time for each patient. Before doing so, we will need to digitalize all the variables in the model using

```
data ck1;set ck;
   txval=tx;
   st1val=0;
   if STRATUM1='LESS THAN 250 PER CUBIC MILLIMETRE' then st1val=1;
   reg1val=0;
   reg2val=0;
   if reg=1 then reg1val=1;
   if reg=2 then reg2val=1;
   mtx=txval;
   mst1=st1val;
   mreg1=reg1val;
   mreg2=reg2val;
   mx=xval;
run;
```

   Note that 'xval' denote the other covariates that have been digitalized in the dataset and 'mx' denote is a copy of the covariates (we need this for technical reason). Then we can use the following Bayesian negative binomial model

```
proc genmod data=ck1;
     ods select PostSummaries PostIntervals;
     model aseq =mtx mst1 mreg1 mreg2 mx/ dist=negbin link=log
offset=logdur;
     bayes seed=17 nmc=10000 nbi=5000 coeffprior=normal outpost=ckout;
run;
```

2. For each draw (after thinning) the expected number of events is calculated for the period before and after withdrawal for each subject. This depends upon the length of time before and after withdrawal. Denote these as y1_hat and y2_hat. The design matrices for an individual patient are modified to assign the withdrawing patient to the desired treatment arm for the observed or unobserved period. This depends on the missing data imputation methods. If it is the pattern mixture model, patients will be imputed according to the group they were randomized to. For control-based model, both placebo and treatment patients will be imputed using the estimated coefficients pertaining to the placebo group. Then according to the derivation for the conditional distribution Y2|Y1, we can sample using the following statement: rand('NEGATIVEBINOMIAL',(invK_hat+y1_hat)/(invK_hat

+y1_hat + y2_hat), invK_hat + y1) where invK_hat is the inverse of the sampled dispersion parameter, and y1 is the actual count before withdrawal. The entire number of exacerbations (observed and unobserved) is then: y1 + rand('NEGATIVEBINOMIAL',(invK_hat+y1_hat)/(invK_hat +y1_hat + y2_hat), invK_hat + y1). The sample code is provided below.

```
%let rn=40;
proc surveyselect data=ckout seed=23  method=srs n=&rn out=cksamples; run;
data cksamples2(keep=Intercept mtx mst1 mreg1 mreg2 mx Dispersion _imputation_);set cksamples;by iteration;
_imputation_+1;
run;

data ckrep(drop=mtx mst1 mreg1 mreg2 mx);
set ck1;
 do _imputation_=1 to &rn;
 output;
 end;
run;
proc sort data=ckrep;by _imputation_;run;
proc sort data=cksamples2;by _imputation_;run;
data ckrep2;merge ckrep(in=a) cksamples2(in=b);by _imputation_;if a=1 and b=1;run;

data ckrepimp(drop=td lin rate1 rate2 k ratep kp p ad);set ckrep2;
if ext=0 then do;
td=plandur-aval;
lin=Intercept+mtx*txval+mst1*st1val+mreg1*reg1val+mreg2*reg2val+mx*xval;
rate1=exp(lin);
rate2=rate1;
if (Dispersion<=0.00000001) then k=100000000;
else k=1/Dispersion;
ratep=rate2*(1+k*ASEQ)/(1+k*rate1*aval);
kp=k/(1+k*ASEQ);
```

```
p=1/(1+kp*ratep*td);
ad=RAND('NEGBINOMIAL',p,1/kp);
aseqplus=aseq+ad;
end;
else aseqplus=aseq;
ad=aseqplus-aseq;
run;
```

3. These imputed numbers are then analysed in a new series of further GENMOD runs (one for each draw), using the model for the primary analysis. However an offset will now be the log of planned treatment period. Derived parameters from the model such as least squares means for treatment and their differences. The sample SAS code is

```
proc genmod data=ckrepimp;
   by  _imputation_;
   model aseqplus =txval st1val reg1val reg2val/ dist=negbin link=log
offset=logplanneddur;
   ods output ParameterEstimates=Pest;
run;
```

4. Then we combine across imputation data sets using Rubin's formula using the MIANALYZE procedure. These and their confidence interval limits are then exponentiated to derive relative rates. Of note, the rule will be applied on the log risks and log risk ratio.

```
proc sort data=pest out=pest2;by Parameter _imputation_;run;
proc mianalyze data=pest2;
  by Parameter;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=pout;
run;



/* estimated RR and corresponding 95% CI */
    data pouttx;
      set pout;
      if Parameter="txval";
      rr = exp(estimate);
```

rrL = exp(lclmean);

rrU = exp(uclmean);

run;

5. For control-based PMM-MI, we will replace the following command in Step 2 under "**data** ckrepimp"

   lin=Intercept+mtx*txval+mst1*st1val+mreg1*reg1val+mreg2*reg2val+mx*xval;

   by

   lin=Intercept+0*txval+mst1*st1val+mreg1*reg1val+mreg2*reg2val+mx*xval;

   This way, we will use the control rate to impute the missing data.

6. For tipping-point analysis, we will replace the following command in Step 2 under "**data** ckrepimp"

   lin=Intercept+mtx*txval+mst1*st1val+mreg1*reg1val+mreg2*reg2val+mx*xval;

   by

   lin=Intercept+(mtx+delta)*txval+mst1*st1val+mreg1*reg1val+mreg2*reg2val+mx*xval;

   where "delta" is a sequence of positive numbers representing the diminishing treatment effect for patients in the treatment group needing imputation. A table of p-values for the treatment effect in the analysis model with the imputed data and the "delta" value will be provided.

Change from baseline in FEV1

Pattern mixture model by multiple imputation

1. Partially impute data using Markov Chain Monte Carlo (MCMC) method to obtain 40 datasets with monotone missing pattern:

```
proc mi data=&DSTIN seed=&seed nimpute=40 out=monotone;
  mcmc impute=monotone;
  var base &chg_all;
run;
```

   where `&chg_all` includes change from baseline in FEV1 at all visits.

2. For each of the imputed dataset with monotone missing pattern, the remaining missing data will be imputed by a regression model

```
proc mi data=monotone seed=&seed nimpute=1 out=data_imp;
  by _imputation_;
  class trt01pn sex eosbgp1n cntygr1 endtrs1;
  var sex hgtbl eosbgp1n cntygr1 trt01pn endtrs1 base
      &chg_all;
  monotone reg;
run;
```

3. Analyze the 40 imputed datasets by the ANCOVA model described in Section 2.4.4.2:

```
proc mixed data=data_imp method=reml;
by _imputation_;
class usubjid trt01pn sex cntygr1 eosbgp1n avisitn;
model chg12 = trt01pn sex hgtbl cntygr1 eosbgp1n avisitn
        trt01pn*avisitn base base*avisitn /ddfm=kr residual;
repeated avisitn / subject=usubjid type=un;
  lsmestimate trt01pn*avisitn 'Tx wks 16-24 avg minus pbo wks 16-24 avg' 0 0
1 1 1 0 0 -1 -1 -1/ divisor=3;
  lsmeans trt01pn*avisitn / pdiff cl e;
  ods output LSMeans=LSMeans_imp Diffs=Diffs_imp
LSMEstimates=LSMEstimates_imp;
     run;
```

4. Apply Rubin's rule to combine analysis results:

```
proc sort data= LSMEstimates_imp;
  by trt01pn _imputation_;
run;

proc mianalyze data= LSMEstimates_imp;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=LSMEstimates_Res;
run;
```

Pattern mixture model by control-based multiple imputation

This approach is similar to the standard method described above, except for Step 2. After obtaining datasets with monotone missing patterns in Step 1, the following steps will be repeated to sequentially impute missing data at each time point:

1) For time point *t*, separate the imputed datasets into two parts: `imp_&t`, containing all placebo patients and those from the active treatment groups that have missing change from baseline in FEV1 at time *t*; and `rest_&t`, containing the rest of the patients from the active treatment groups.

2) Impute missing values at *t* based on the model estimated from placebo group patients:

```
proc mi data=imp_&t seed=&seed.&t nimpute=1
out=imputed_&t;
```

```
  by _imputation_;
  class sex eosbgp1n cntygr1 endtrs1;
  var sex hgtbl eosbgp1n cntygr1 endtrs1 base
      &chg_prior chg_&t;
  monotone reg (chg_&t);
run;
```

where `chg_&t` is change from baseline in FEV1 at `t` and `&chg_prior` includes change from baseline in FEV1 at all visits prior to *t*. No prior value will be included when imputing the first post-randomization time point.

3) Combine the imputed data `imputed_&t` with `rest_&t`.

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