Statistical Analysis Plan for Randomized Pragmatic Clinical Trial in a Community-Based Setting Comparing STIOLTO® RESPIMAT® vs. ICS-LABA plus LAMA in Patients with COPD

SAP No. 1237-0064

[redacted]

[redacted]

Fax: [redacted]

16. March 2021

Version 3.0

Signature Page for Statistical Analysis Plan
SAP No: 1237-0064
March 2021

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List of Abbreviations

Abbreviation or Special Term	Definition
AE	Adverse Event
[redacted]	[redacted]
AIRWISE	Assessment In a Real World setting of the effect of Inhaled Steroid-based triple therapy versus the combination of tiotropium and olodaterol on reducing COPD Exacerbations
CAT	COPD Assessment Test
CBC	Complete Blood Count
[redacted]	[redacted]
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
E&M	Evaluation and Management
EOS	End of Study
ER	Emergency Room
FDC	Fixed Dose Combination
GERD	Gastroesophageal Reflux Disease
GLM	General Linear Model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
[redacted]	[redacted]
[redacted]	[redacted]
HR	Hazard Ratio
ICD-10	International Classification of Diseases, Tenth Revision
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification

Abbreviation or Special Term	Definition
ICS	Inhaled Corticosteroid
IPV	Important Protocol Violations
IQR	Interquartile Range
ITT	Intent to Treat
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LOS	Length of Stay
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral Corticosteroid
OV	Office Visit
PDE4	Phosphodiesterase 4
PP	Per Protocol
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
RR	Risk Ratio
SABA	Short-Acting Beta Agonist
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SD	Standard Deviation
SM	Service Mark
SMQ	Standardized Medical Queries
SOC	System Organ Class
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TM	Trademark

1.0 INTRODUCTION

The background and rationale for this study can be found in the introduction to the study protocol (Section 1).

2.0 STUDY OBJECTIVES

The primary, secondary [redacted] Section 2, Study Objectives).

2.1 Changes in the Planned Analysis of the Study

Due to slower than expected enrollment despite mitigation efforts, a business decision was made to discontinue enrollment of new patients in the trial after the end of August 2019. Active patients will continue and any patient that is already randomized into the trial shall continue through the planned 12 months of the trial.

As a result of this early stopping and the limited sample size enrolled by the end of August 2019 (approximately 703 patients instead of the planned 3200 patients), the trial will be underpowered, therefore the null hypothesis of non-inferiority of Stiolto Respimat to Triple therapy as measured by time to first moderate or severe exacerbation will not be tested. No statistical inference will be done (i.e., no comparison with the NI margin, no calculation of p-value). Models, such as the Cox proportional hazards model and the negative binomial, will still be run on the ITT population to estimate the hazard ratio, rate ratio and confidence intervals.

Some changes were made to the thresholds for baseline blood eosinophil level, in sections 4.4.7, 4.4.8, 4.5.4.3 and 5.5.1, to reflect current GOLD recommendations.

[redacted]

[redacted]

After further review, due to the low number of patients and events, and the strong knowledge base Boehringer Ingelheim (BI) have for Stiolto, the safety team decided that the additional custom Boehringer Ingelheim searches which are standardized for relevant topics in COPD studies are optional. Therefore the following analyses will not be performed in Section 6.4.1: summary tables and listings to compare the incidence of AEs across treatment groups by medical concept (MedDRA Standardized Medical Queries (SMQ) or custom Boehringer Ingelheim searches which are standardized for relevant topics in COPD studies.

[redacted]

3.0 STUDY INVESTIGATIONAL PLAN

The details of the study design, AIRWISE: Assessment In a Real World setting of the effect of Inhaled Steroid-based triple therapy versus the combination of tiotropium and olodaterol on reducing chronic obstructive pulmonary disease (COPD) Exacerbations, are fully described in the study protocol (Section 4, Study Design).

3.1 Patient Randomization

Enrolled study patients will be randomized to either Stiolto Respimat or triple therapy in a 1:1 ratio. Development and validation of the randomization process is described in Appendix A.

3.2 Evaluation Schedule and Definitions

Consistent with the naturistic design, this study does not have a rigid visit schedule. It is anticipated that participating patients will undergo medical evaluation at regular intervals as part of standard clinical practice. However, the only required study visits are a baseline visit and a final end of study (EOS) visit at 12 months post enrollment.

3.2.1 Baseline

Baseline is defined as the first study visit date. After eligible patients interested in participating provide written informed consent, they will be randomized to either Stiolto Respimat or triple therapy. A blood sample will be drawn at the baseline visit for a complete blood count (CBC) including differential white cell count or historical CBC can be used if available. Additionally, participating patients will complete the COPD Assessment Test™ (CAT). The following data will be collected at baseline and recorded in the electronic Case Report Form (eCRF): eligibility criteria, demographics, selected pre-specified comorbid conditions, COPD history (diagnosis date, number of moderate and severe COPD exacerbations in the 12 months prior to study enrollment, pre-study COPD therapy, selected pre-specified COPD concomitant medications and reason for therapy escalation), blood eosinophil count, smoking status, CAT responses and study treatment.

3.2.2 On Study Visits

While there are no required on study visits, it is anticipated that patients who are being treated for COPD will undergo medical evaluation at regular intervals. On study data collection will occur as patients are followed according to their treating physician's routine clinical practice and judgment for the 12 month study period, including routine clinical visits, other patient contact (e.g., phone or e-mail), contact with another treating physician, or receipt of records. Data collected will include COPD exacerbations, selected pre-specified COPD concomitant medications, changes to study treatment, adverse events (AEs) leading to study treatment discontinuation, dose modification or trial withdrawal, and any serious adverse events (SAEs). Patients will be followed and data will be collected at each contact for the full 12 month study period regardless of study treatment changes or discontinuation during the study period.

3.2.3 EOS

The planned EOS visit will be 12 months after baseline. Data collection at EOS will include COPD exacerbations, selected pre-specified COPD concomitant medications, changes to study treatment, AEs leading to study treatment discontinuation, dose modification or trial withdrawal, and any SAEs. For the purposes of analysis, EOS visits up to 12 months (+30 days) post-Baseline will be included. EOS visits that occur after this window will be considered for inclusion in analysis on a case by case basis. However, only COPD exacerbations with an onset date up to and including 12 months post-Baseline will be included in analysis.

4.0 STATISTICAL METHODOLOGY

4.1 General Considerations

Statistical programming and analyses will be performed using SAS® version 9.4 or higher. Some analyses will utilize prospectively collected data from study sites. Other analyses will use administrative claims data from patients on [redacted] health plans (i.e., [redacted]

[redacted]) and targeted non-[redacted] plans. [redacted]

Patient characteristics, treatments and outcomes will be tabulated and summarized with descriptive statistics. The descriptive statistics will include means, medians, standard deviation (SD), minimum, maximum and interquartile range (IQR) (difference between the 25th and 75th percentiles) for continuous variables and counts and relative frequencies for categorical data. The descriptive statistics will be presented for the study population overall and by treatment arm.

Raw data (i.e., minimum and maximum values presented for range in continuous variables) will be reported out to the precision with which it was collected. Means will be reported to 1 decimal place more than the raw data. The standard deviation will be reported to 1 decimal place more than the mean. Percentages will be reported to 1 decimal place. Trailing zeros will be presented to maintain a consistent level of precision, e.g. 2.0 rather than 2.

4.2 Sample Size Determination

The sample size calculated for this study is 3200 patients with approximately 1600 patients in each treatment group. Sample size calculations are summarized in the study protocol (Section 6.3, Sample Size Determination). Due to early study termination, the actual sample size will be approximately 703 patients.

4.3 Missing Data

Except where otherwise noted, missing data will not be imputed and will be excluded from calculations.

4.4 Data Definitions and Calculations

4.4.1 Demographics

Age will be presented in years based on the patient's birth date and Baseline visit date. The age (years) will be categorized as follows:

- ≤55 years
- >55 to ≤65 years
- >65 to ≤75 years
- >75 to ≤85 years
- >85 years

4.4.2 Treatment Variables

COPD medication will be categorized as inhaled corticosteroid (ICS), long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), ICS-LABA, LAMA-LABA, ICS-LAMA-LABA, short-acting beta agonist (SABA), short-acting muscarinic antagonist (SAMA), SAMA/SABA, phosphodiesterase 4 (PDE4) inhibitors, methylxanthines, therapies, or other based on the COPD Medication Categorization List in Appendix B. This section will be updated

as necessary if new COPD therapies become available over the course of the study and are added to the eCRF.

Pre-Study Treatment

Pre-study treatment will be categorized into one of the qualifying maintenance therapies (LAMA monotherapy, LABA monotherapy, ICS/LABA fixed dose combination (FDC)) according to the COPD Medication Categorization List in Appendix B.

On-Study Treatment

Triple therapy is defined as any of the combination of ICS, LABA and LAMA drugs that a patient's physician chooses. Therefore, the following combination of COPD medications categories will count as triple therapy on study, differentiating between free combination and FDC:

- Triple Therapy Free Combinations
  - ICS + LABA + LAMA
  - ICS-LABA + LAMA
  - ICS + LAMA-LABA
- Triple Therapy FDC
  - LAMA-LABA-ICS

Patients may switch or discontinue study treatment over the 12 month observation period.

For the purpose of analysis, patients will be classified as Continued Original Randomized Treatment, Continued In-Class Randomized Treatment, or Off Randomized Treatment as described below. The categories are non-overlapping. Changes in targeted COPD concomitant medications do not apply to this classification.

- **Continued Original Randomized Treatment**: Patients taking the same COPD medication as originally initiated for randomized COPD study treatment.
  - Stiolto Respimat patients taking Stiolto Respimat.
  - Triple Therapy patients taking the same individual components of ICS plus LAMA plus LABA as initiated at Baseline.
- **Continued In-Class Randomized Treatment**: This definition only applies to Triple Therapy patients who made changes to the triple therapy components originally initiated for their randomized COPD study treatment (i.e., those not considered "Continued Original Randomized Treatment").
  - Triple Therapy patients taking any combination of ICS plus LABA plus LAMA that meets the study definition of triple therapy will be considered "Continued In-Class Randomized Treatment" if changed from original study medications.
- [redacted]

[redacted]

- **On Treatment**: Patient is categorized as Continued Original Randomized Treatment or Continued In-Class Randomized Treatment (the duration of time is from randomization until the patient is no longer in one of these two categories)
    - Patients who have a temporary treatment interruption of ≤ 28 days will still be considered On Treatment provided they resume treatment that meets the On Treatment definition within 28 days of when the treatment was first interrupted.
        - If the On Treatment study medication is resumed with a new start date ≤ 28 days of the stop date, it will be classified as a **temporary treatment interruption**.
        - If the On Treatment study medication is resumed with a new start of >28 days of the stop date, or if the On Treatment study medication is not resumed before EOS or last contact, it will be classified as a **treatment discontinuation**.
        - For Triple Therapy patients, a >28 day continuous window in which they are not receiving all 3 components of triple therapy will be considered treatment discontinuation. This could occur due to a >28 treatment interruption of a single component, or overlapping treatment interruptions of more than one component such that the patient does not receive triple therapy for a continuous window of >28 days.
- **Off Randomized Treatment**: Patient is categorized as Off Treatment (the duration of time is from when the patient is no longer On Treatment until EOS or last contact)

On Treatment will also be used for the safety analysis (Section 6.3).

<u>COPD Medication Class Categories</u>

The following targeted COPD concomitant medications will be defined for descriptive summary of COPD concomitant medication use by class at Baseline and EOS or last contact. Baseline COPD concomitant medications will be medications with "On-Study Concomitant" status designated in the eCRF and a start date on or prior to the patient's Baseline date. EOS COPD concomitant medications will be medications designated "On-Study Concomitant" in the eCRF with a status of "Ongoing" at EOS or the latest medication entry.

Targeted COPD Concomitant Medications at Baseline and EOS (Patients could contribute to multiple categories)

- SABA only
- SAMA only
- SAMA + SABA (free or FDC)
- PDE4 Inhibitors
- Methylxanthines
- Oxygen

- Not taking any targeted COPD concomitant medications

The following Study COPD medication class categories will also be defined for descriptive summary of Study COPD medication at EOS or last contact:

Study COPD Medications at EOS (Categories are non-overlapping)

- LAMA only
- LABA only
- LAMA + LABA
- ICS + LABA
- ICS + LAMA + LABA
- ICS-LAMA-LABA (FDC)
- Not taking any Study COPD Medications
- Discontinued all COPD Treatment: Patients not taking any COPD medication at EOS (no Study COPD medication use and no targeted COPD concomitant medication use).

Additionally, the following definitions described below will descriptively report changes in Study COPD medication at EOS or last contact.

- **Original Randomized Treatment**: Patients taking the same COPD medication at EOS as originally initiated for randomized COPD study treatment.
    - Stiolto Respimat patients taking Stiolto Respimat.
    - Triple Therapy patients taking the same individual components of ICS plus LAMA plus LABA as initiated at Baseline.
- **Step-Over In-Class Randomized Treatment**: This definition only applies to patients taking different treatment components at EOS as originally initiated for their randomized COPD study treatment (i.e., those not considered "Original Randomized Treatment").
    - Triple Therapy patients taking any combination of ICS plus LABA plus LAMA that meets the study definition of triple therapy at EOS will be considered "Step-Over In-Class Randomized Treatment" if changed from original study medications.
    - Stiolto Respimat patients taking a LAMA plus LABA regimen at EOS other than Stiolto Respimat.

4.4.3 CAT

4.4.3.1 Overview

The CAT will be administered at Baseline. It is a short (8-item), simple, patient-completed questionnaire that measures the impact of COPD on a patient's well-being and daily life.[1] Patients rate the following items on a 6-point (0-5) scale, where higher scores indicate worse

[1] Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34:648-654.

symptoms: Cough, Phlegm, Chest Tightness, Breathlessness, Activities at Home, Confidence Leaving Home, Sleep and Energy.

The CAT instrument is attached in Appendix C.

4.4.3.2 Scoring and Categorization

The CAT score will be calculated by summing responses from individual items, yielding scores ranging from 0-40, with higher scores indicating worse COPD-related health status. Total CAT scores will be descriptively summarized.

Total CAT scores will also be categorized as follows to enable Global Initiative for Chronic Obstructive Lung Disease (GOLD) A-D classification:

CAT < 10

CAT ≥ 10

For further descriptive summary, total CAT score will also be categorized as follows:

CAT < 10

CAT 10 to 20

CAT 21 to 30

CAT 31 to 40

4.4.3.3 Missing Data

The CAT score is calculated as the sum of the responses present. If more than two responses are missing, a score cannot be calculated; when one or two items are missing, their scores will be set to the average of the non-missing item scores.[1]

4.4.4 COPD and Exacerbation History

Years with COPD will be calculated using Baseline visit date and COPD diagnosis date.

COPD exacerbation history will be collected at Baseline as the number of moderate COPD exacerbations in the past year and the number of severe COPD exacerbations requiring hospitalization in the past year. To enable GOLD A-D classification, the number of prior moderate and severe COPD exacerbations in the past year will be categorized as follows:

- Moderate Exacerbations (did not lead to hospitalization): 0, 1, ≥ 2
- Severe Exacerbation (lead to hospitalization): 0, ≥ 1

Additionally, to enable classification of a high risk subgroup, the following exacerbation history category will be defined:

- ≥ 2 Moderate **or** Severe Exacerbations

4.4.5 GOLD A-D Classification

Patient's GOLD A-D classification will be defined at Baseline using CAT scores and exacerbation history as follows:

- GOLD A
  - CAT <10 AND
  - Moderate Exacerbation = 0 or 1 **AND** Severe Exacerbation = 0
- GOLD B
  - CAT ≥ 10 AND
  - Moderate Exacerbation = 0 or 1 **AND** Severe Exacerbation = 0
- GOLD C
  - CAT <10 AND
  - Moderate Exacerbation ≥ 2 **OR** Severe Exacerbation ≥ 1
- GOLD D
  - CAT ≥ 10 AND
  - Moderate Exacerbation ≥ 2 **OR** Severe Exacerbation ≥ 1

If a patient is missing either exacerbation history or CAT score is missing, then GOLD A-D will not be defined for that patient.

4.4.6 Baseline ICS Prior Use

Patients will be categorized by prior ICS use (yes/no) at Baseline. Baseline prior ICS use is defined as reporting any ICS use with a start date prior to baseline.

4.4.7 Blood Eosinophils

Baseline blood eosinophil level will be reported as an absolute count and also categorized as follows:

- <100 cells/uL
- 100 to <300 cells/uL
- 300 to <400 cells/uL
- ≥400 cells/uL

4.4.8 High Risk Classification

A subgroup of high risk patients with baseline blood eosinophil count ≥300 cells/uL and at least two moderate or severe exacerbations in the 12 months prior to baseline will be identified.

4.5 Analysis Assessments

4.5.1 Primary Endpoint Assessment

The primary endpoint is time to first moderate or severe COPD exacerbation over the 12 month study period. This endpoint is based on eCRF data as defined below.

An exacerbation must have at least two of the following symptoms reported on the eCRF as

occurring for ≥ 3 days:

- Cough
- Sputum production (volume)
- Change in sputum color
- Wheezing
- Shortness of breath
- Chest tightness

Additionally, the exacerbation must have required at least one of the following treatments as reported on the eCRF:

- Exacerbation treated with antibiotics
- Exacerbation treated with systemic steroids
- Hospitalization associated with exacerbation

COPD exacerbations will be classified based on treatment categories above as follows:

Moderate: Exacerbation treated with antibiotics and/or systemic steroids, but did not have hospitalization associated with it.

Severe: Hospitalization associated with exacerbation.

Time to first moderate or severe COPD exacerbation will be based on the patient's baseline visit and onset of exacerbation date up to and including the time of the planned EOS visit at 12 months. If there is a discrepancy between patient report and hospital records for onset of a severe exacerbation, hospital records will be used.

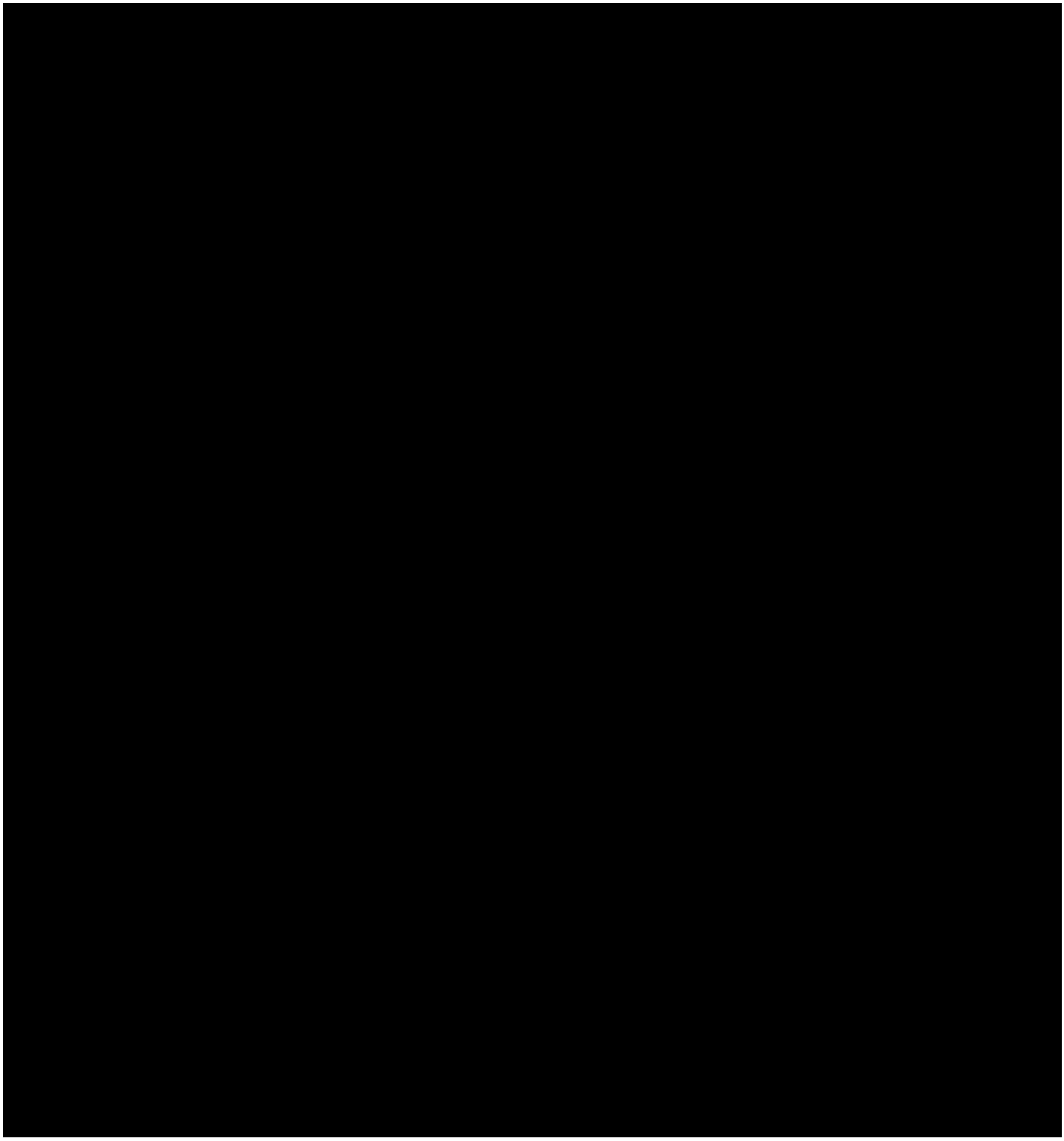
In the event of multiple COPD exacerbations, those occurring within 7 days duration of each other will be collapsed into one exacerbation event for analysis. If the start date of a subsequent exacerbation occurs within 7 days of the determined end date of a previous exacerbation, these two exacerbations will be collapsed into one event for analysis. In this case, the onset date will be the start date of the first event and the severity classification will be based on the treatment associated with the most severe exacerbation within the collapsed event.

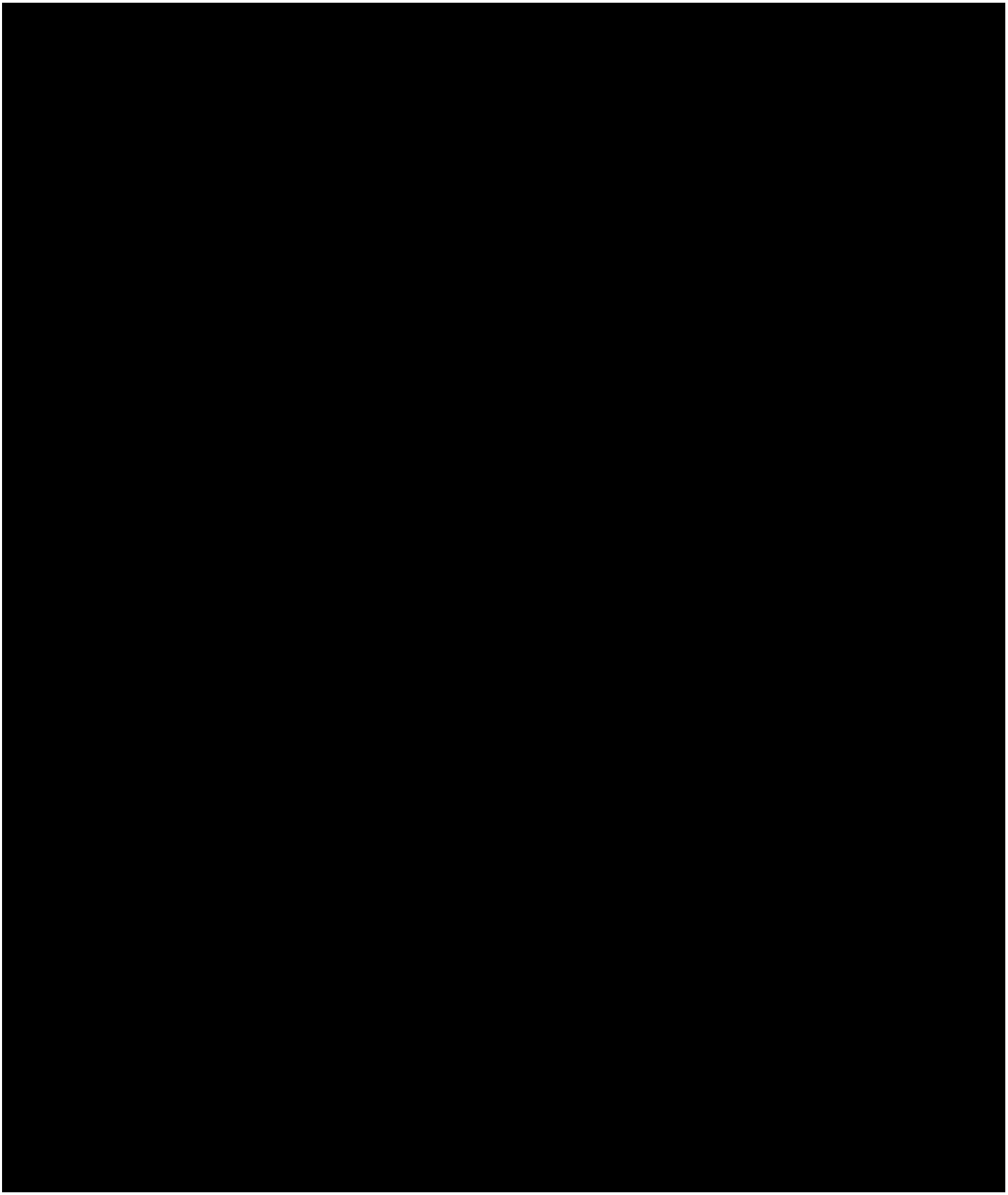
4.5.2 Secondary Endpoint Assessments

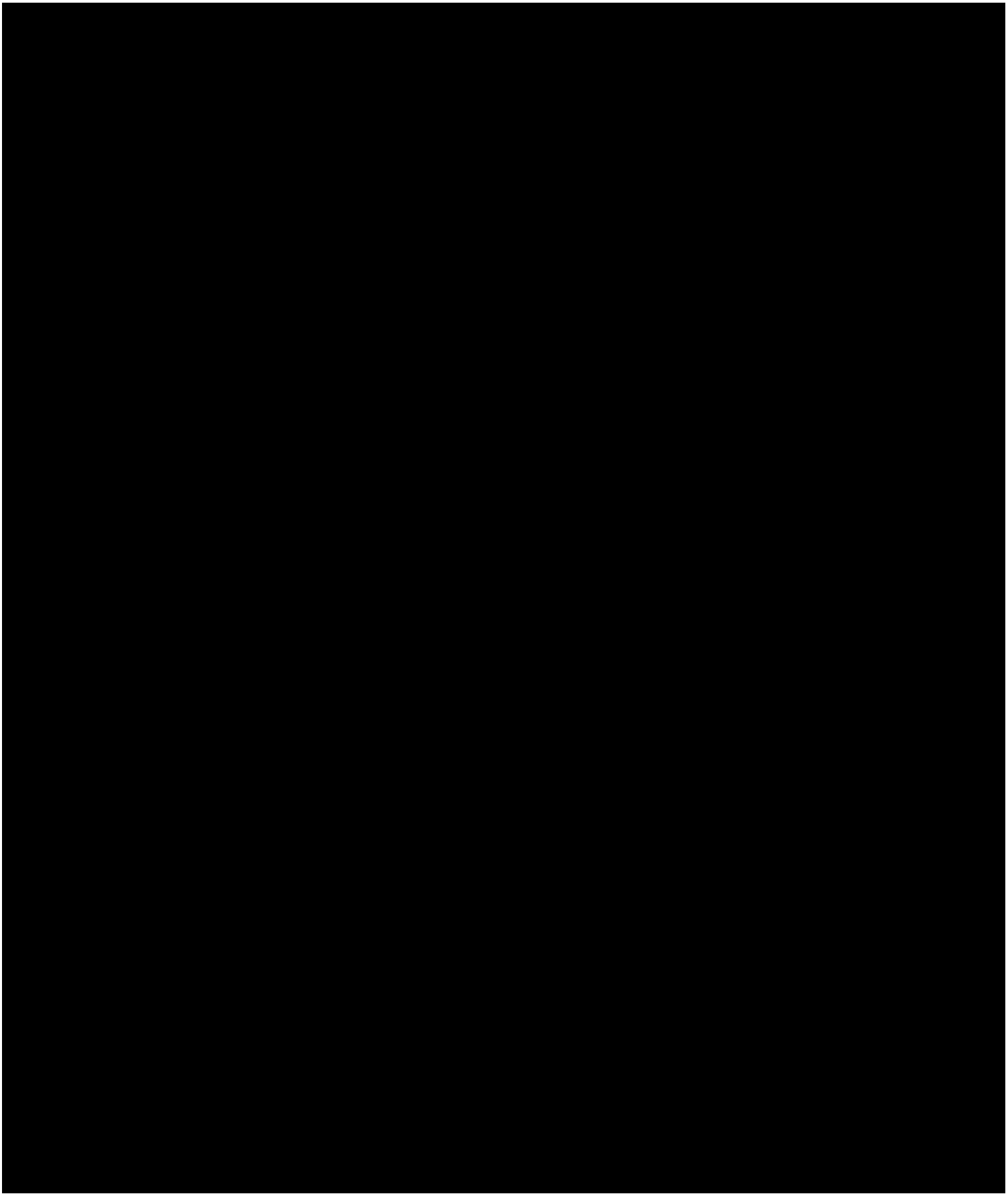
Secondary endpoints include:

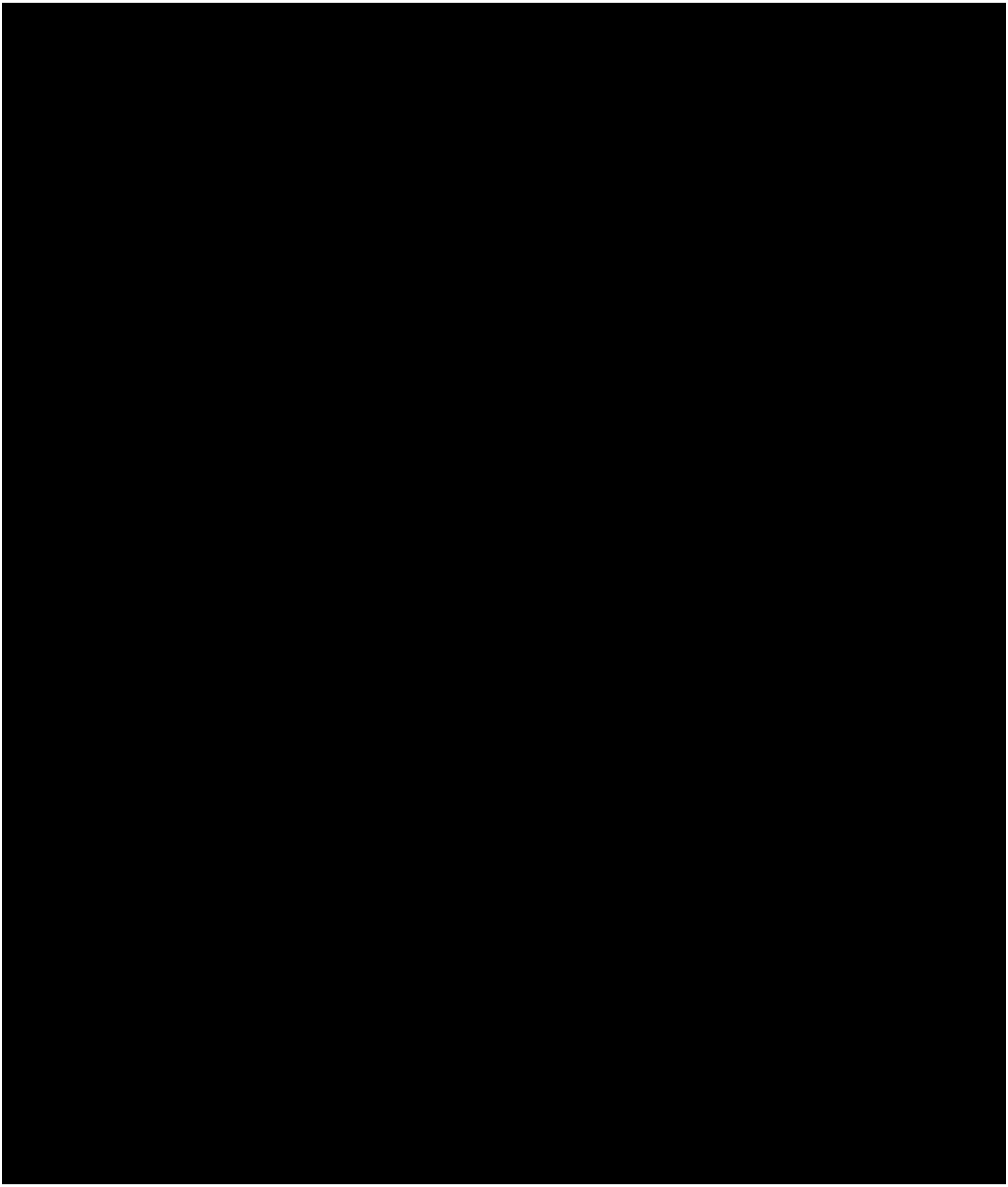
- Annual rate of moderate or severe COPD exacerbations over the 12 month observation period
- Time to first severe COPD exacerbation over the 12 month observation period
- Annual rate of severe COPD exacerbations over the 12 month observation period
- Proportion of patients with moderate or severe COPD exacerbations over the 12 month observation period

The secondary analyses for these secondary endpoints will use the COPD exacerbation defined as moderate or severe (as applicable) as collected in the eCRF and defined in section 4.5.1 above. All moderate and severe exacerbations with onset until time of planned EOS visit at 12 months will be included in these analyses.









[redacted]

5.0 STATISTICAL ANALYSES

The following populations are defined for analysis and reporting. Before the database lock, the team will review only table shells, not populated with actual data, to avoid bias.

5.1 Analysis Populations

5.1.1 Intent to Treat (ITT) Population

The ITT population includes all randomized patients allocated to their original randomized treatment group.

5.1.2 Per Protocol (PP) Population

No per-protocol set is defined and no analysis is planned. [redacted]

[redacted]

[redacted]

5.1.4 Safety Population

The Safety population includes all randomized patients who received a prescription of any study treatment (Stiolto Respimat or triple therapy).

5.2 Patient Disposition and Accountability

Patient disposition will be summarized for all enrolled patients. This will include the number and percentage of patients in the ITT [redacted] The number and percentage of patients who complete the full study observation period, defined as those who complete the end of study visit, will also be presented. Additionally, the primary reason for not completing the study observation period will be tabulated for patients who terminated participation in the study early.

5.3 Demographics and Baseline Clinical Characteristics

Demographic and baseline clinical characteristics will be summarized for the ITT population overall and by treatment group. Frequencies and percentages will be calculated for gender, race, ethnicity, smoking status, COPD exacerbation history categories, CAT categories, and GOLD A-D Classification, as defined in section 4.4. The number and percentage of patients with at least one of the pre-specified comorbid conditions will also be summarized along with the relative frequencies of type of comorbid condition (congested heart failure, hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease, type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), depression/anxiety, osteoporosis, gastroesophageal reflux disease (GERD)). Descriptive statistics will be calculated for continuous variables (age in years, years with COPD, baseline blood eosinophil count and baseline CAT score), as described in section 4.1.

5.4 Treatment Regimen

Pre-study COPD treatment regimen, prior Baseline ICS use, and reason for therapy escalation will be summarized for the ITT population overall and by treatment group. Frequencies and percentages will be calculated for COPD drug class as defined in section 4.4.2 above.

Use of targeted COPD concomitant medications will be summarized at baseline. Frequencies and percentages will be calculated for Targeted COPD Concomitant Medications by COPD drug class as defined in section 4.4.2 above. Additionally, use of free versus FDC of triple therapy at baseline will be summarized for Triple Therapy patients.

EOS COPD treatment regimen will be summarized for the ITT population by treatment group, including frequencies and percentages by COPD drug class for Study COPD Medications and Targeted COPD Concomitant Medications as defined in section 4.4.2 above. Frequencies and percentages will also be calculated for Original Randomized Treatment and Step-Over In-Class Randomized Treatment at EOS.

5.5 Effectiveness Analysis

5.5.1 Primary ITT Analysis

The primary effectiveness analysis will address the primary objective of this study: to compare the time to first moderate or severe COPD exacerbation between Stiolto Respimat and triple therapy. As the sample size is reduced (approximately 703 patients), the study is underpowered, so no test for non-inferiority of Stiolto Respimat compared to triple therapy will be performed. For the primary endpoint, COPD exacerbation defined as moderate or severe as collected in the eCRF will be used (section 4.5.1).

The primary analysis for the primary endpoint will be performed using the ITT population. Patients will be analyzed using the treatment arm to which they are randomized, even if they switched or discontinued study treatment. Patients will be censored at the time of last contact, death or day of planned EOS visit at 12 months (whichever occurs earlier), if they did not experience a moderate or severe COPD exacerbation before. This will be referred as ITT analysis.

For the primary endpoint, i.e. time to first moderate or severe COPD exacerbation, the Cox proportional hazards model with baseline ICS prior use as a covariate will be used to estimate the hazard ratio (HR) (Stiolto Respimat versus triple therapy),and the two-sided 95% Wald confidence interval (CI).

In addition, Kaplan-Meier curves will be presented with reported statistics including median survival time, as well as 95% CI for each group. If the median survival time is not reached, the first quartile will be reported instead.

[redacted]

5.5.3 Secondary Analyses

The secondary objectives of the study will be addressed through the secondary analyses detailed in the following sections. All secondary analyses will follow the ITT analysis as defined in Section 5.5.1 and will utilize the site-based exacerbation data from the eCRF.

5.5.3.1 Annual Rate of Moderate or Severe Exacerbations

This analysis will address the secondary objective to compare the annual rate of moderate or severe COPD exacerbations for patients on Stiolto Respimat with patients on triple therapy.

The annual rate of moderate or severe exacerbations analysis will utilize a negative binomial model with fixed effect of treatment (Stiolto Respimat versus triple therapy), logarithm of observational time as offset, and baseline prior ICS use as a covariate. Observational time is defined as a patient's date of planned EOS at 12 months or last contact or death date (whichever occurs earlier) – Baseline visit date + 1 day.[3] The rate ratio (Stiolto Respimat versus triple therapy) will be presented with 95% CI. Rates and 95% CI of each treatment group will also be presented.

5.5.3.2 Time to First Severe Exacerbation

This analysis will address the secondary objective to compare the time to first severe COPD exacerbation for patients on Stiolto Respimat with patients on triple therapy. For this analysis, only COPD exacerbation defined as severe as collected in the eCRF will be used.

As in the primary analysis described in section 5.5.1 above, this will be an ITT analysis. The Cox proportional hazards model with baseline ICS prior use as a covariate will be used to estimate the HR (Stiolto Respimat versus triple therapy), and the two-sided 95% Wald CI.

[redacted]

[3] Programming note: Observational time will be divided by 365.25 because this analysis is annual rate.

5.5.3.3 Annual Rate of Severe Exacerbations

This analysis will address the secondary objective to compare the annual rate of severe COPD exacerbations for patients on Stiolto Respimat with patients on triple therapy. This analysis will be conducted on the ITT population including all severe exacerbations during the study observation period even if a patient switches or discontinues their assigned randomized study treatment.

The annual rate of severe exacerbations analysis will utilize the same negative binomial model with fixed effect of treatment (Stiolto Respimat versus triple therapy), logarithm of observational time as offset, and baseline prior ICS use as a covariate. Observational time is defined as a patient's date of planned EOS at 12 months or last contact or death date (whichever occurs earlier) – Baseline visit date + 1 day.[3] The rate ratio (Stiolto Respimat versus triple therapy) will be presented with 95% CI. Rates and 95% CI of each treatment group will also be presented.

5.5.3.4 Proportion of Patients with Moderate or Severe Exacerbations

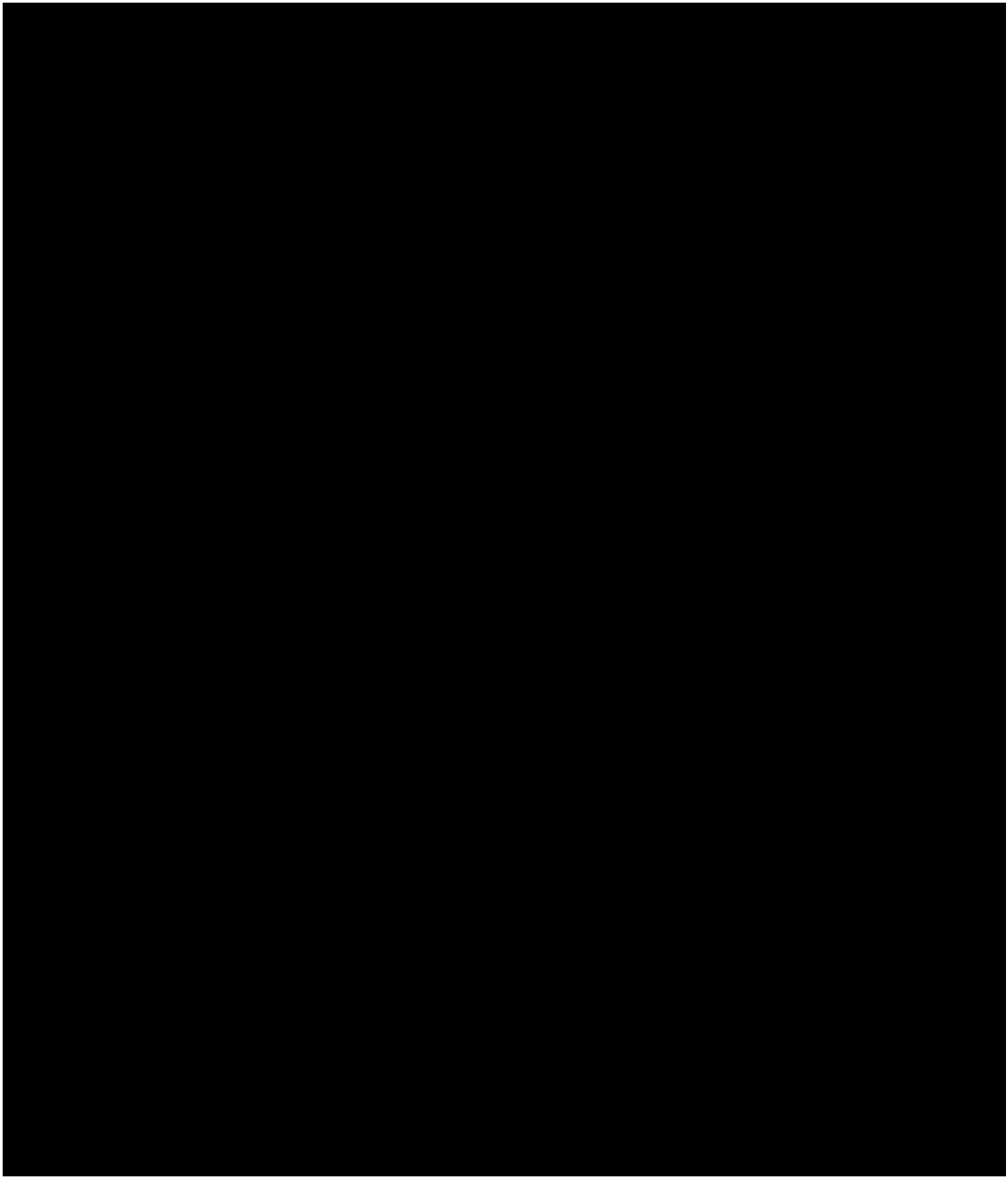
This analysis will address the secondary objective to compare the proportion of patients with at least one moderate or severe COPD exacerbation from Baseline to the day of planned EOS visit at 12 months for patients on Stiolto Respimat with patients on triple therapy. The proportion of patients with a moderate or severe COPD exacerbation during the study observation period will be descriptively summarized overall, by treatment group, and by baseline prior ICS use. A Cochran-Mantel-Haenszel (CMH) model with baseline ICS prior use as stratum will be used to estimate the Risk Ratio (RR) (Stiolto Respimat versus triple therapy) and Risk Difference (Stiolto Respimat – triple therapy) of moderate or severe COPD exacerbations along with 95% CI. Unadjusted proportions will also be presented.

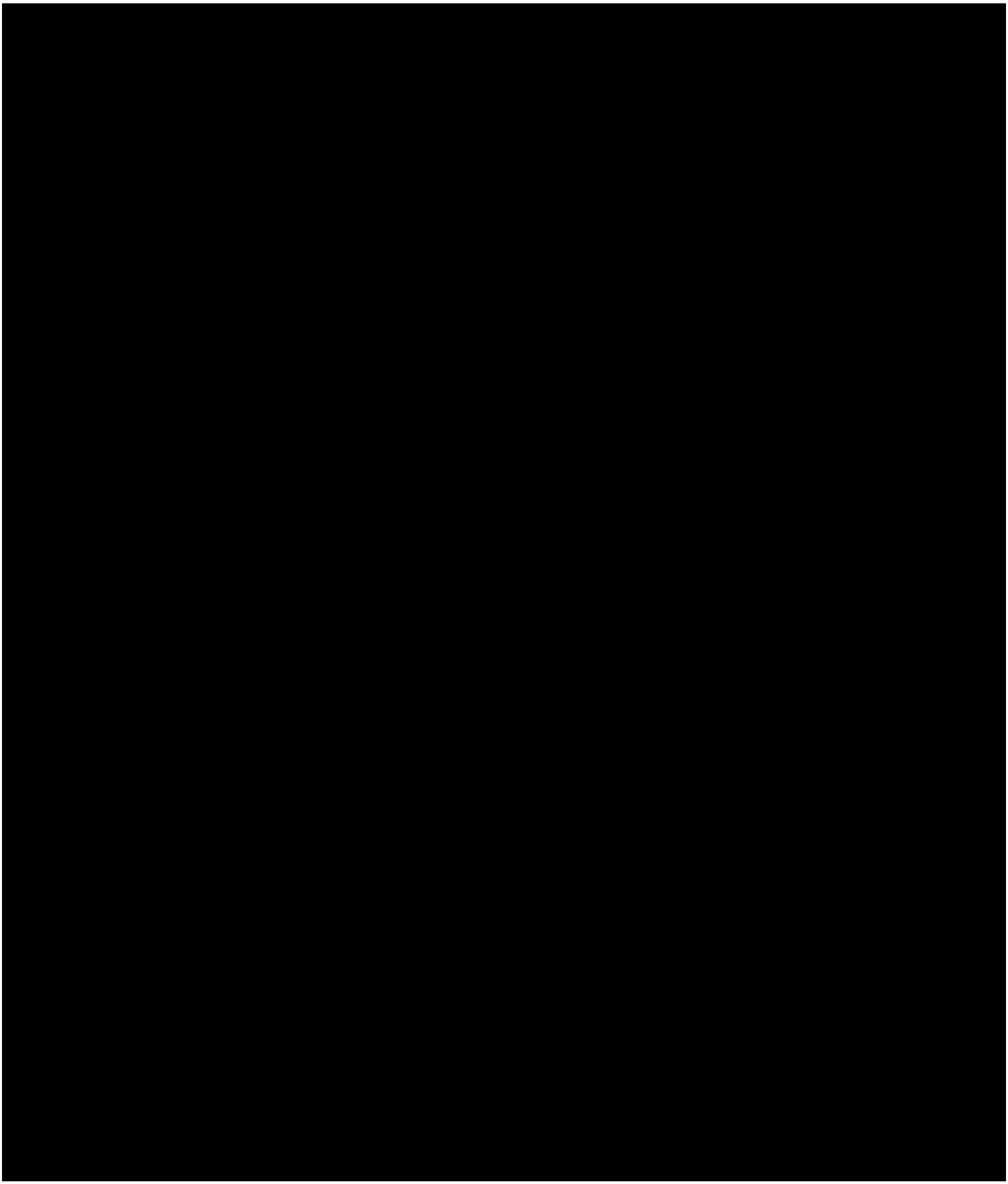
5.6 Patient Reported Outcome (PRO) Analysis

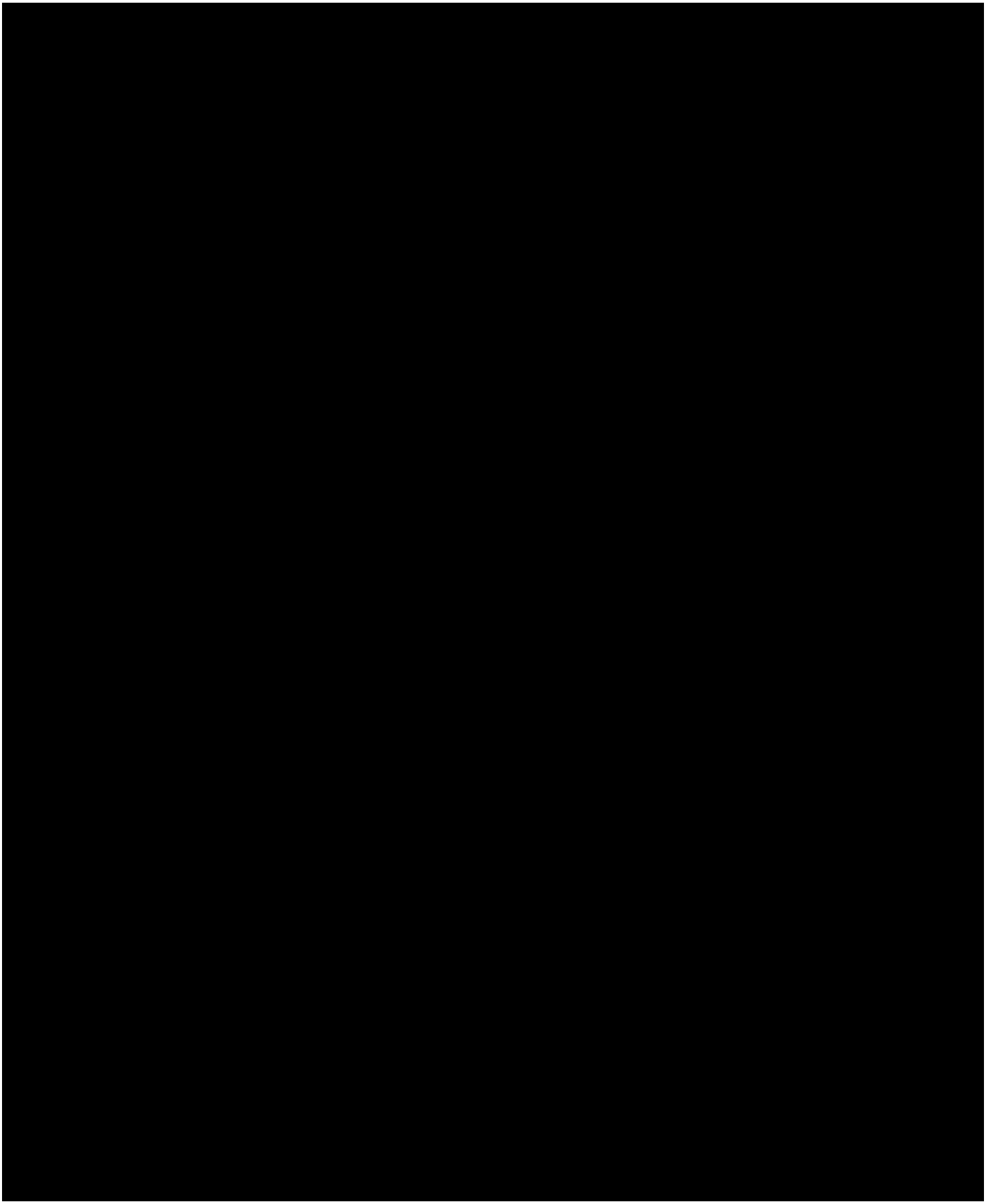
The impact of COPD on patients' health and quality of life will be assessed at baseline via the CAT. PRO analysis will be descriptive in nature and will not involve any statistical testing. Rather, summary statistics will be used to describe patient perceived health status impairment associated with COPD at baseline as described in section 4.4.3 above.

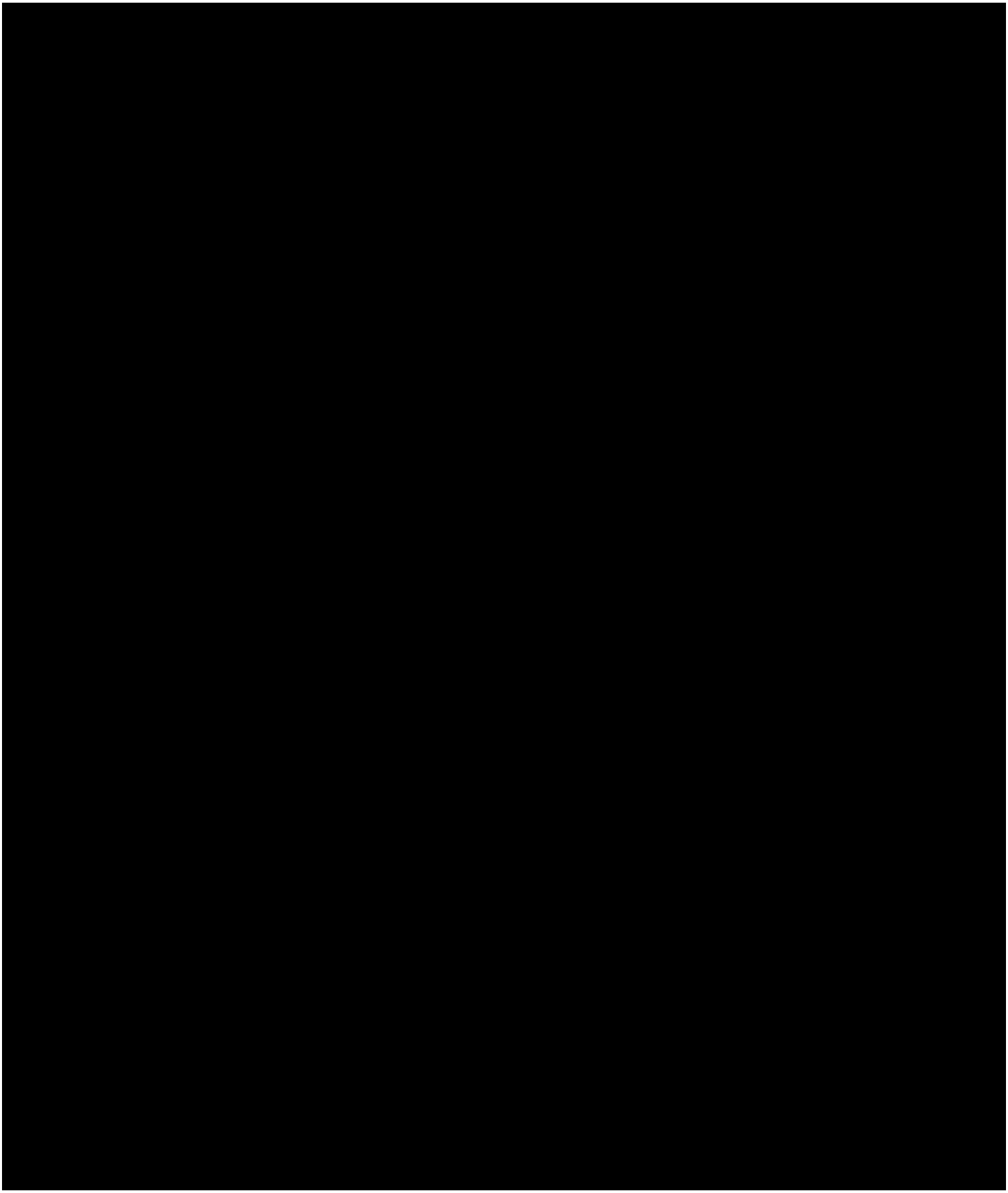
5.7 Concomitant Medications

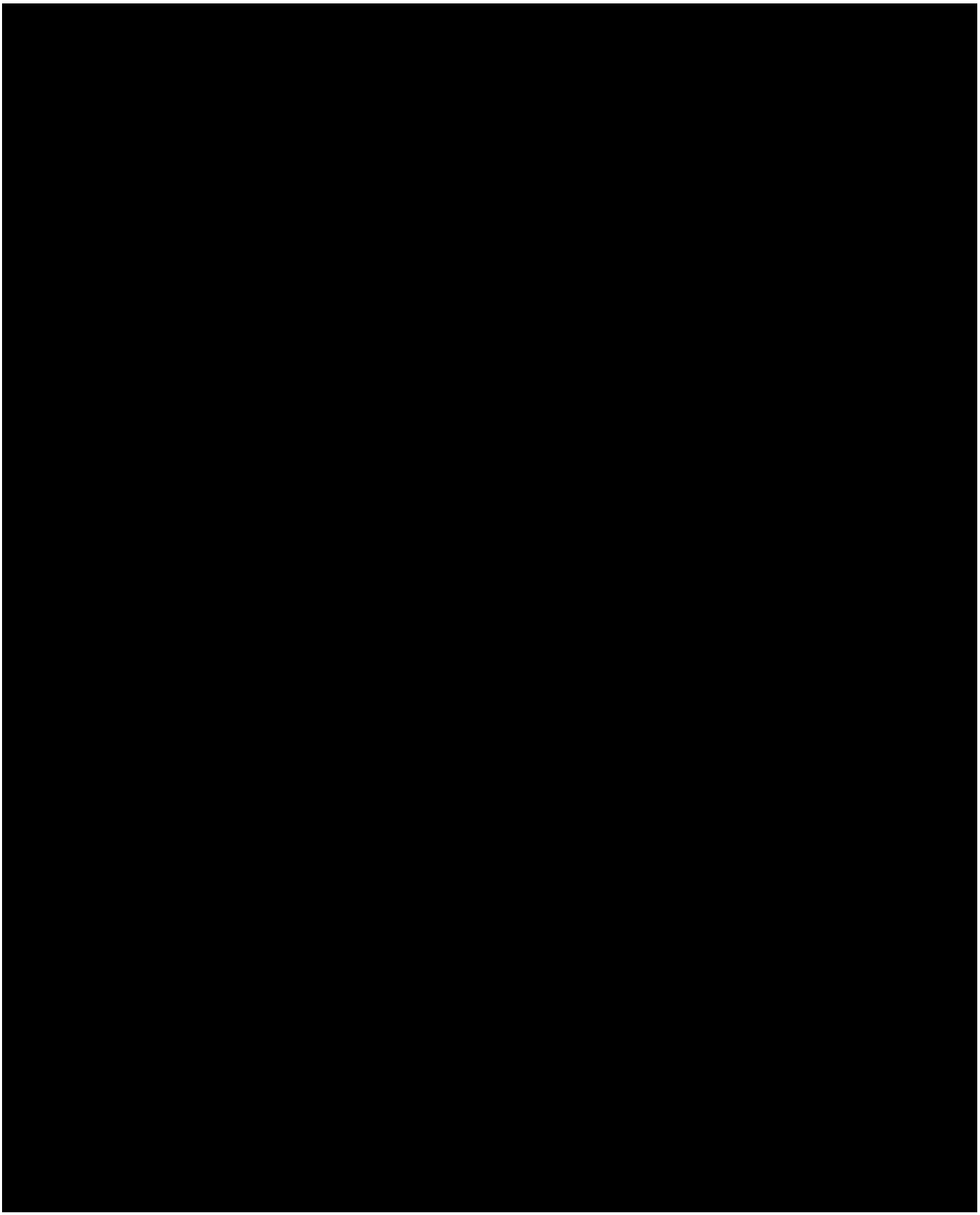
Pre-specified targeted COPD concomitant medications will be collected at Baseline as well as during on-study visits and EOS if applicable. The number and percentage patients taking on-study targeted COPD concomitant medications (designated "On-Study Concomitant" in the eCRF data) at any time during the 12 month observation period will be summarized by COPD Medication and Category (Appendix B) for the population overall and by treatment group.

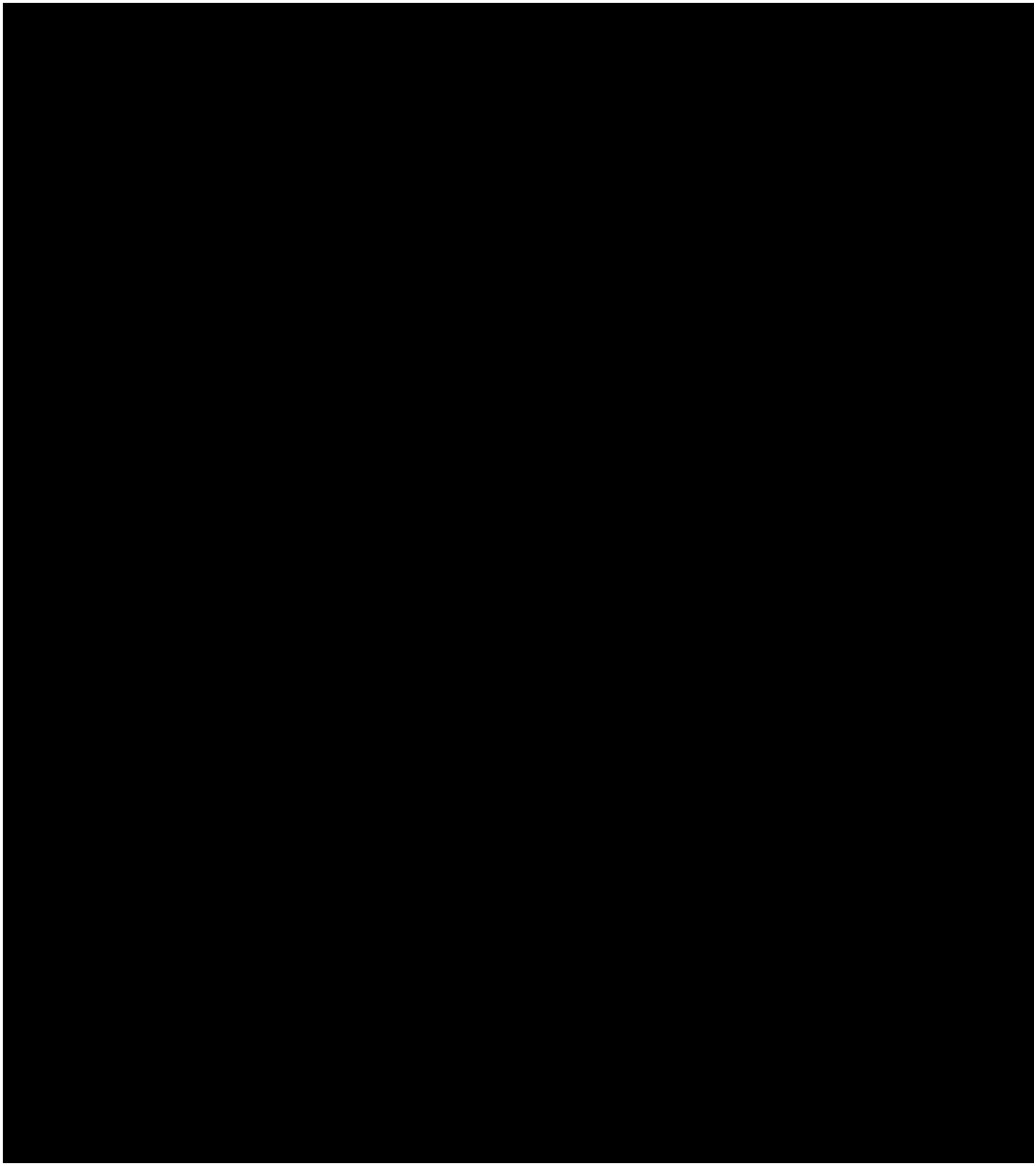


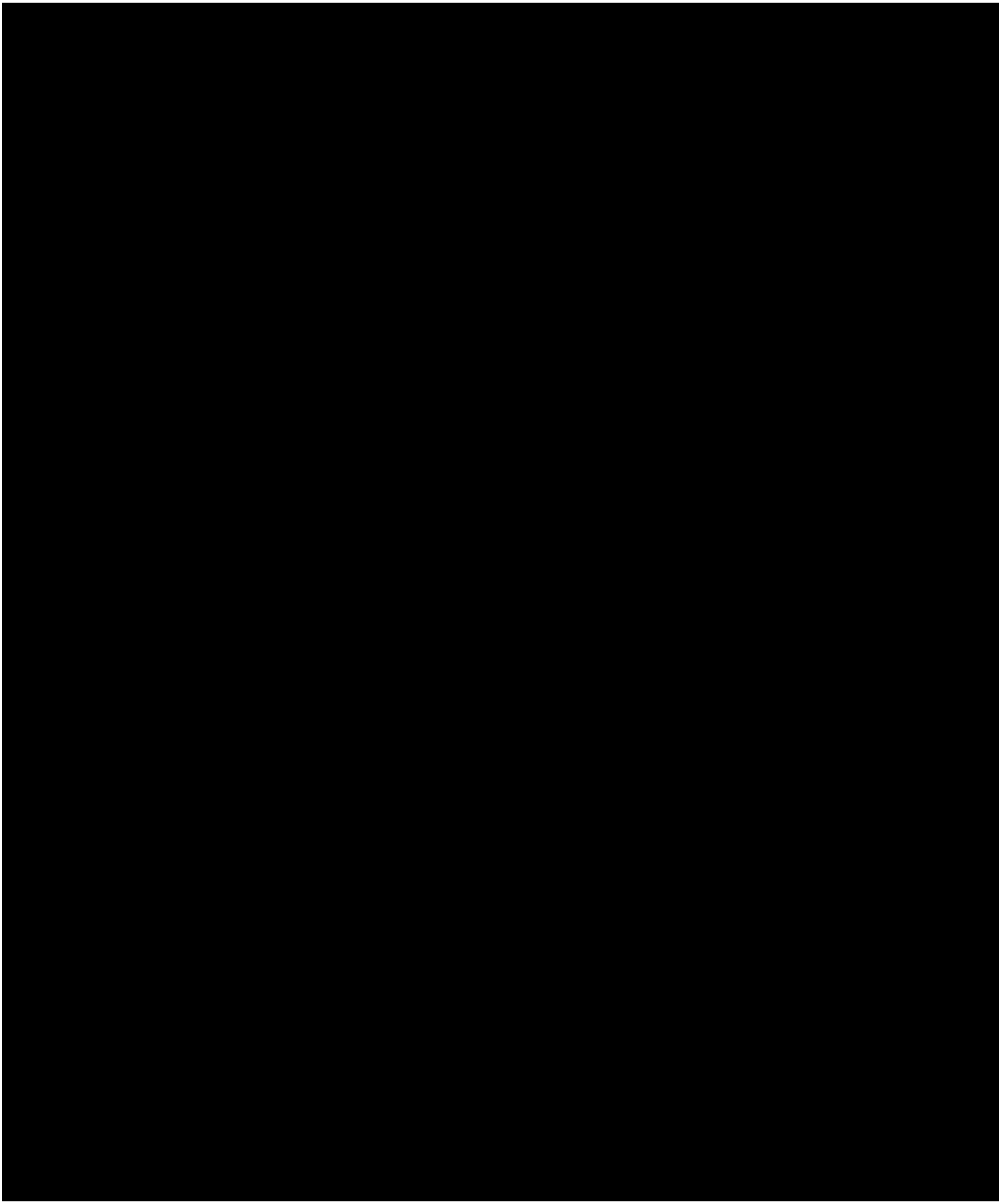


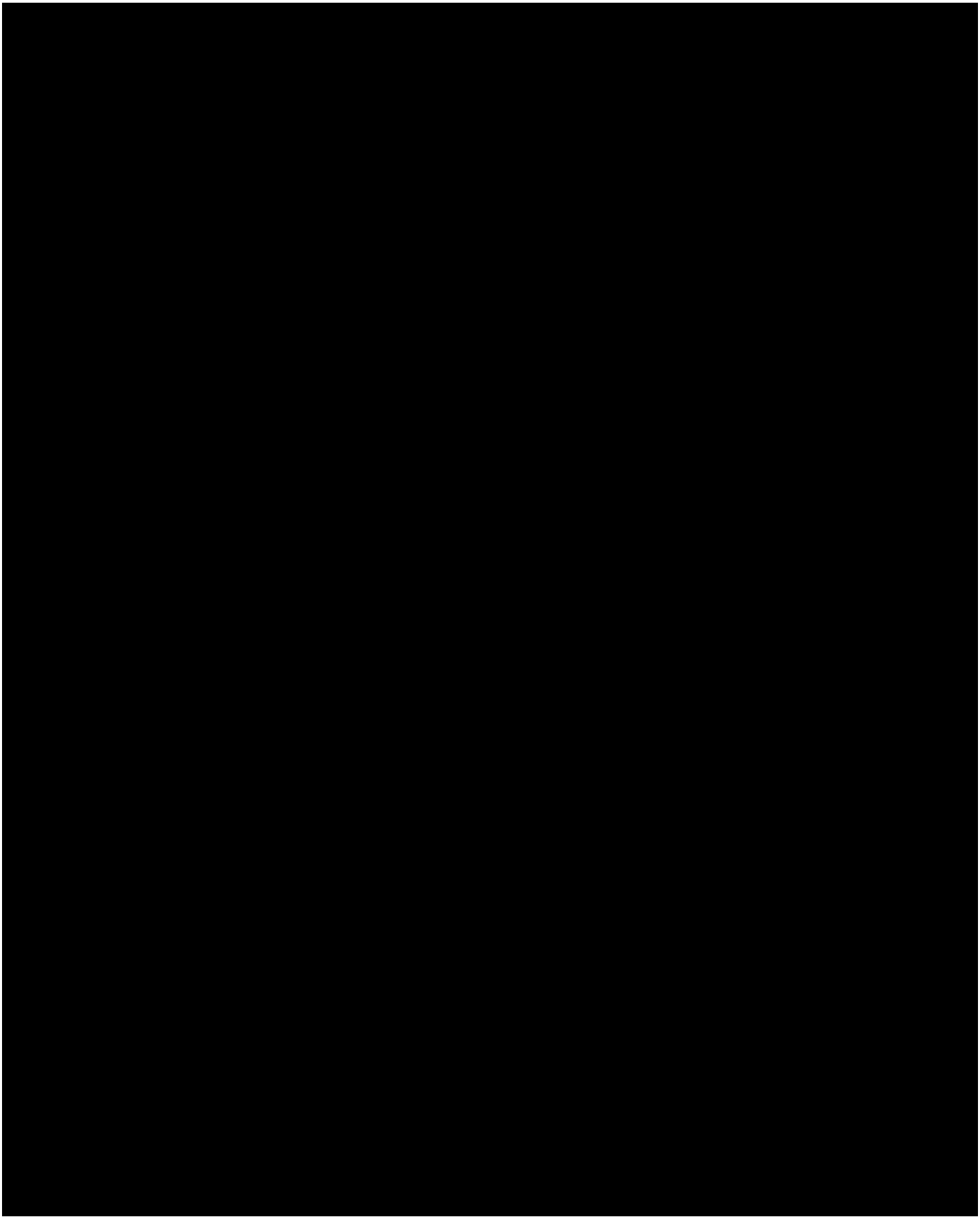












6.0 SAFETY

6.1 AEs

AEs collected during this study are defined in Section 7.1 of the Study Protocol.

6.2 SAEs

SAEs collected during this study are defined in Section 7.2 of the Study Protocol.

6.3 Reporting and Analysis Periods

AEs and SAEs will be reported from the time a patient signs consent until the EOS visit at 12 months or until the patient discontinues the trial. However, only "on treatment" AEs and SAEs will be included in analysis. "On treatment" medications for each treatment arm are defined in section 4.4.2. For the safety analysis time period, all AEs will be considered "on treatment" (see section 4.4.2) if the AE start date is within 21 days after the On Treatment study medication end date or until EOS, whichever comes first.

6.4 Analysis

All AE analyses will be reported on the safety population.

6.4.1 AE Analysis

AE analyses will be descriptive in nature. No hypothesis testing is planned prospectively. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

SAE data will be drawn from the Boehringer Ingelheim Safety Database, while other AEs collected as per protocol through the eCRF will be drawn from the study database. AE data for analysis will be merged from all sources for analysis.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary at the time of reporting. Summary tables and listings will be produced to compare the incidence of AEs across treatment groups, by Preferred Term (PT)/System Organ Class (SOC).

The frequency and percentage patients experiencing AEs and SAEs will be summarized by SOC and PT for the safety population overall and by treatment group as follows:

- All collected AEs, regardless of seriousness, relatedness, or collection context
- AEs leading to study treatment discontinuation, dose modification or trial withdrawal
- AEs leading to study treatment discontinuation (subset of the above table)
- AEs with a reasonable causal relationship to study treatment
- All SAEs
- Fatal AEs (subset of all SAEs)
- Listing of all SAEs

There will be no subgroup analyses for safety.

7.0 IMPORTANT PROTOCOL VIOLATIONS (IPVs)

IPVs will be reported in a listing. Potential IPVs include:

- Inclusion or Exclusion criteria not met.
- Informed Consent not documented prior to study randomization.
- Initial prescription provided for randomized study treatment was incorrect. (This does not include changes to study medication subsequent to initiation of study treatment.)

8.0 APPENDIX A: Randomization Development and Validation

At the time of this writing, the randomization process used by [redacted] has been tested, validated, and approved by the Boehringer Ingelheim Statistical team assigned to this project. To summarize, this project entailed an evaluation of the process[redacted] would use to generate a sample of 4000 patients using block randomization. That process included a random seed generation using the R package (R-project.org) of a number between one and one million. This seed was then used to first generate a sample of 40 patients for electronic data capture (EDC) validation and duplication by Boehringer Ingelheim. Following this initial validation and duplication by Boehringer Ingelheim, the same approved process was used to generate a sample of 4000 for duplication by Boehringer Ingelheim using a different random seed. At the time of this writing, both of these data sets have been validated.

For the final step, the actual randomization list was generated and passed to electronic data EDC while keeping all members of the statistical team from Boehringer Ingelheim blinded. Treatment and Control terms in the test data set were replaced with ‘Stiolto’ and ‘Triple Therapy’ and a

column was added to the randomization Excel sheet to sequentially list all patients by block from 1 to 4,000. At the time of this writing, all steps of this process have been accomplished.

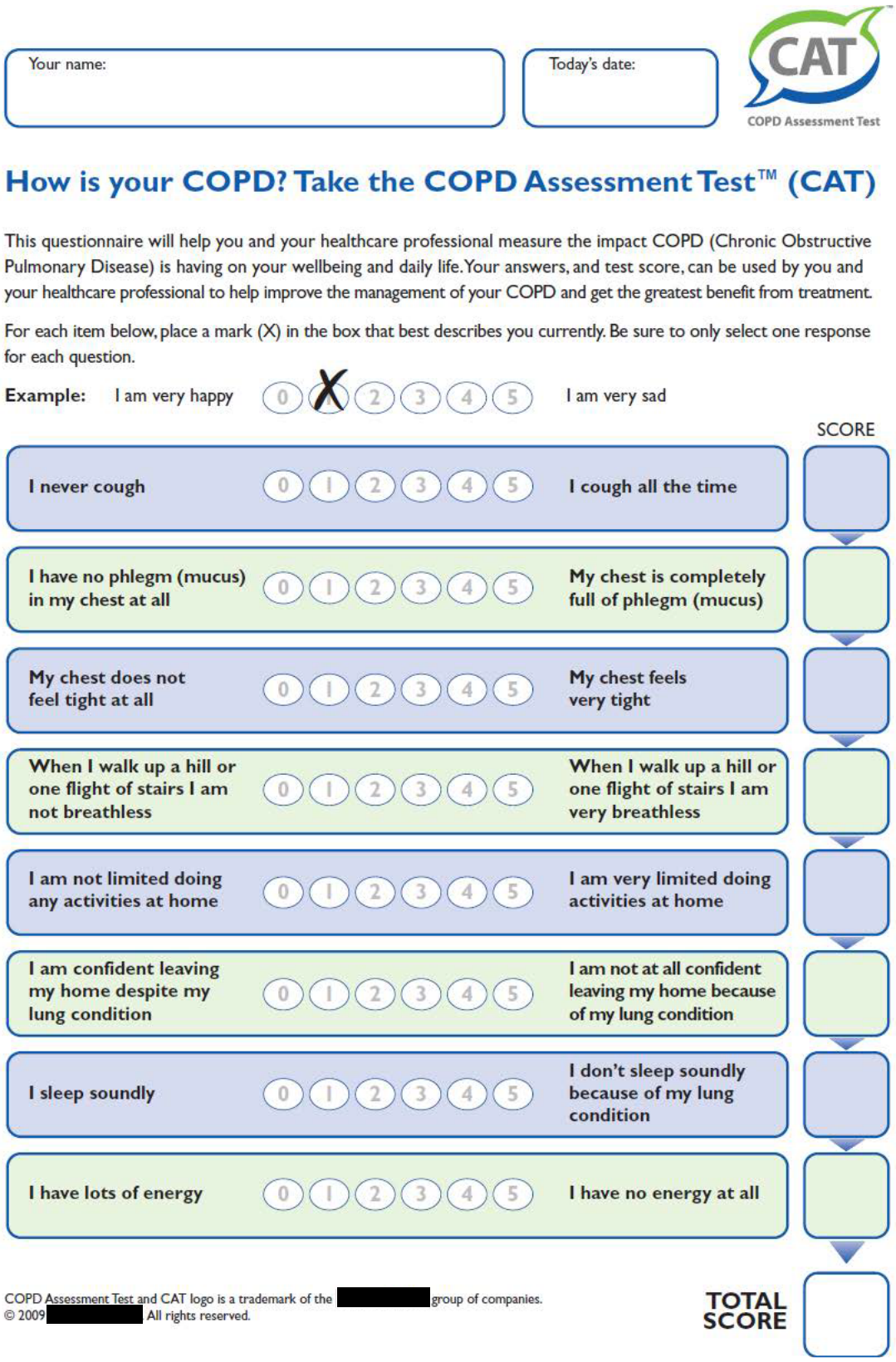
9.0 APPENDIX B: COPD Medication Categorization List

Category	COPD Medication
ICS	AEROBID
	AEROBID-M
	AEROSPAN
	ALVESCO
	ARNUITY ELLIPTA
	ASMANEX 14 METERED DOSES
	ASMANEX 60 METERED DOSES
	ASMANEX HFA
	ASMANEX TWISTHALER 120 ME
	ASMANEX TWISTHALER 14 MET
	ASMANEX TWISTHALER 30 MET
	ASMANEX TWISTHALER 60 MET
	ASMANEX TWISTHALER 7 METE
	BECLOVENT
	BECLOVENT ORAL/BECONASE
	BUDESONIDE
	FLOVENT
	FLOVENT DISKUS
	FLOVENT HFA
	FLOVENT ROTADISK
	FLUNISOLIDE
	FLUNISOLIDE ANHYDROUS
	PULMICORT
	PULMICORT FLEXHALER
	PULMICORT TURBUHALER
	QVAR
	VANCERIL
	VANCERIL DOUBLE STRENGTH
LABA	ARCAPTA NEOHALER
	BROVANA
	FORADIL AEROLIZER
	PERFOROMIST
	SEREVENT
	SEREVENT DISKUS
	STRIVERDI RESPIMAT
LAMA	INCRUSE ELLIPTA
	SEEBRI NEOHALER

	SPIRIVA HANDIHALER
	SPIRIVA RESPIMAT
	TUDORZA PRESSAIR
ICS-LABA	ADVAIR DISKUS
	ADVAIR HFA
	BREO ELLIPTA
	DULERA
	SYMBICORT
LAMA-LABA	ANORO ELLIPTA
	BEVESPI AEROSPHERE
	STIOLTO RESPIMAT
	UTIBRON NEOHALER
LAMA-LABA-ICS	TRELEGY
SAMA	ATROVENT
	IPRATROPIUM BROMIDE
SAMA/SABA	DUONEB
	IPRATROPIUM BROMIDE / ALBUTEROL SULFATE
	COMBIVENT RESPIMAT
	ALBUTEROL / IPRATROPIUM BROMIDE
SABA	ALBUTEROL
	ALBUTEROL INHALATION SOLUTION
	ACUNEB
	PROAIR
	PROVENTIL
	VENTOLIN
	XOPENEX
	LEVALBUTEROL
PDE4 Inhibitor	DALIRESP
	ROFLUMILAST
Methylxanthines	THEOPHYLLINE
	AMINOPHYLLINE
	ELIXOPHYLLIN
	QUIBRON T/SR
	T-PHYL
	THEO X
	THEO-24
	THEO-DUR
	THEOCHRON
	THEOLAIR SR
	UNI-DUR
	UNIPHYL

Therapies	OXYGEN
Other	OTHER

11.0 APPENDIX C: COPD Assessment Test™ (CAT)



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

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TOTAL SCORE