Trial Statistical Analysis Plan

c08870355-04

BI Study No.:	352.2069
Title:	Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over three years [FOOTPRINTS®]. Including Protocol Amendment 1, 2, 3, 4, 5 [c02362157-07]
Investigational Product(s):	Not applicable
Responsible study statistician(s):	[redacted] Phone +[redacted] Fax +[redacted]
Date of statistical analysis plan:	01 APR 2022 SIGNED
Version:	Version 4.0 Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
A1AT	Alpha-1 Antitrypsin
A1ATD	Alpha-1 Antitrypsin Deficiency
AE	Adverse Event
ALD	Adjusted Lung Density
ALQ	Above Limit of Quatification
ANCOVA	Analysis of Covariance
[redacted]	[redacted]
ANOVA	Analyis of Variance
AUC	Area Under the Curve
BI	Boehringer Ingelheim
BLQ	Below Limit of Quantification
BM	Biomarker
BMI	Body Mass Index
BSA	Body Surface Area
BODE	Body-Mass Index, Airflow Obstruction, Dyspnoea, and Exercise Capacity
[redacted]	[redacted]
CAT	COPD Assessment Test Questionnaire
[redacted]	[redacted]
CfB	Change from Baseline
CI	Confidence Interval
[redacted]	[redacted]
COPD	Chronic Obstructive Pulmonary Disease
[redacted]	[redacted]
CT	Computed Tomography
CSAP	Cumulative Statistical Analysis Plan
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DBLM	Database Lock Meeting
DBP	Diastolic Blood Pressure
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDV	End Diastolic Volume
EF	Ejection Fraction
[redacted]	[redacted]
EMA	European Medicines Agency
EoT	End of Text
ERS	European Respiratory Society
ERV	Expiratory Reserve Volume

Term	Definition / description
[redacted]	[redacted]
FEV1	Forced Expiratory Volume in 1 second
FEF	Forced Expiratory Flow
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Haemoglobin
[redacted]	[redacted]
HU	Hounsfield unit
HV	Healthy Volunteers
IC	Inspiratory Capacity
ICH	International Conference on Harmonisation
IDEA	International Document Management and Electronic Archiving System
[redacted]	[redacted]
IPD	Important Protocol Deviation
IVC	Inspiratory Vital Capacity
[redacted]	[redacted]
LOG	Logarithm
LV	Left Ventricle
MedDRA	Medical Dictionary for Regulatory Activities
MESI	Medical Event of Special Interest
MMPs	Matrixmetalloproteinases
mMRC	Modified British Medical Research Council Questionnaire
MMRM	Mixed Model Repeated Measures
MQRM	Medical Quality Review Meeting
MRI	Magnet Resonance Imaging
[redacted]	[redacted]
NE	Not Evaluated
OBS	Observed Subjects Set
OC	Observed Cases
[redacted]	[redacted]
pCfB	Percent Change from Baseline
PD15	Percentile Density at 15%
[redacted]	[redacted]
PFT	Pulmonary Function Test
[redacted]	[redacted]
PPSBM	Per-Protocol Set (Biomarker Subjects)
PR	Pulse Rate
[redacted]	[redacted]
PT	Preferred Term

Term	Definition / description
PTT	Pulmonary Transit Time
Q1	Lower Quartile
Q3	Upper Quartile
QC	Quality Check
rCFB	Relative Change from Baseline
REML	Restricted Maximum Likelihood
RPM	Report Planning Meeting
RNA	Ribonucleic Acid
ROC	Receiver Operating Characteristic
RV	Residual Volume
RV	Right Ventricle
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SCR	Screened Subjects Set
SD	Standard Deviation
SDL	Subject Data Listing
SG	Subject-Group
SGRQ	St George's Respiratory Questionnaire
SOC	System Organ Class
[redacted]	[redacted]
SpO_2	Oxygen saturation
SV	Systolic Volume
TLC	Total Lung Capacity
TLVpred	Predicted Total Lung Volume
TMF	Trial Master File
TMM	Trimmed Mean of M-values
TSAP	Trial Statistical Analysis Plan
VA	Alveolar Volume
[redacted]	[redacted]
WHO-DD	World Health Organization-Drug Dictionary
6 MWT	6 Minute Walk Test

3. INTRODUCTION

As per ICH E9 [1], the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Study Protocol (CSP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CSP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CSP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

[redacted]

As stated in the CSP, an interim analysis was conducted after data from the 52-week (1st interim) and 104-week (2nd interim) assessment were available for at least 70% of subjects entered in the study. [redacted]

Statistical analyses that were performed at the 1st interim analysis are described in TSAP Version 2.0. In TSAP Version 3.0 additional analyses performed at the 2nd interim analysis are described. TSAP Version 4.0 describes the analyses performed at the end of the study.

SAS® Version 9.4, or a later version, and R software (4.0.2 or later version) will be used for analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

4.1 ADDITIONS/NEW ANALYSES

Descriptive statistics will be computed for each subject group (ex-smoking controls, COPD GOLD 1, COPD GOLD 2, COPD GOLD 3, and COPD with A1AT deficiency (A1ATD)) as well as for COPD GOLD 1, 2, and 3 combined.

4.2 CHANGES

There were no changes to the planned analyses as compared to what was described in the CSP. However, the structure of the planned analyses in the TSAP is not consistent to Section 7 of the CSP. This change was necessary to allow for a better understanding of order and importance of the conducted analyses.

4.3 CLARIFICATIONS

This TSAP provides clarification on main outcomes listed in CSP Section 5.1.1. A more precise definition is provided in Section 5.1.

The terms “assessment(s)”, “endpoint(s)” and “outcome(s)” as well as the term “subject(s)” and “patient(s)” will be used interchangeably within this document.

The description ‘ex-smoking controls’ will be used in analysis outputs instead of ‘Healthy subjects’ to characterise better this type of population.

5. ENDPOINT(S)

Whenever applicable, the following variables are defined for all continuous assessments. Change from baseline always refers to the absolute changes, unless otherwise specified.

- Observed values at baseline and at each post-baseline visit
- Change from baseline (CfB) at each post-baseline visit, defined as

  CfB_k = post-baseline value at visit k – baseline value
- Relative change from baseline (rCfB) at each post-baseline visit, defined as

  $rCfB_k$ = (post-baseline value at visit k – baseline value) / (baseline value) x100

Unless otherwise specified, these variables are summarized and analysed.

5.1 PRIMARY ENDPOINT(S)

The main outcome measures of the study are described in CSP Section 5.1.1. To clarify the CSP wording, the main outcomes are also listed here:

- Absolute change from baseline in lung density based on PD15 adjusted for lung volume (ALD) [g/L/year] (up to week 156) (for definition of ALD see Section 9.2)
- Annual rate of lung function decline based on FEV1 [mL/year] (up to week 156)
- Number of exacerbations during study (up to week 156)
- Duration of exacerbations during study [days] (up to week 156)
- Occurrence of an at least moderate exacerbation during study (up to week 156)
- Occurrence of a severe exacerbation during study (up to week 156)

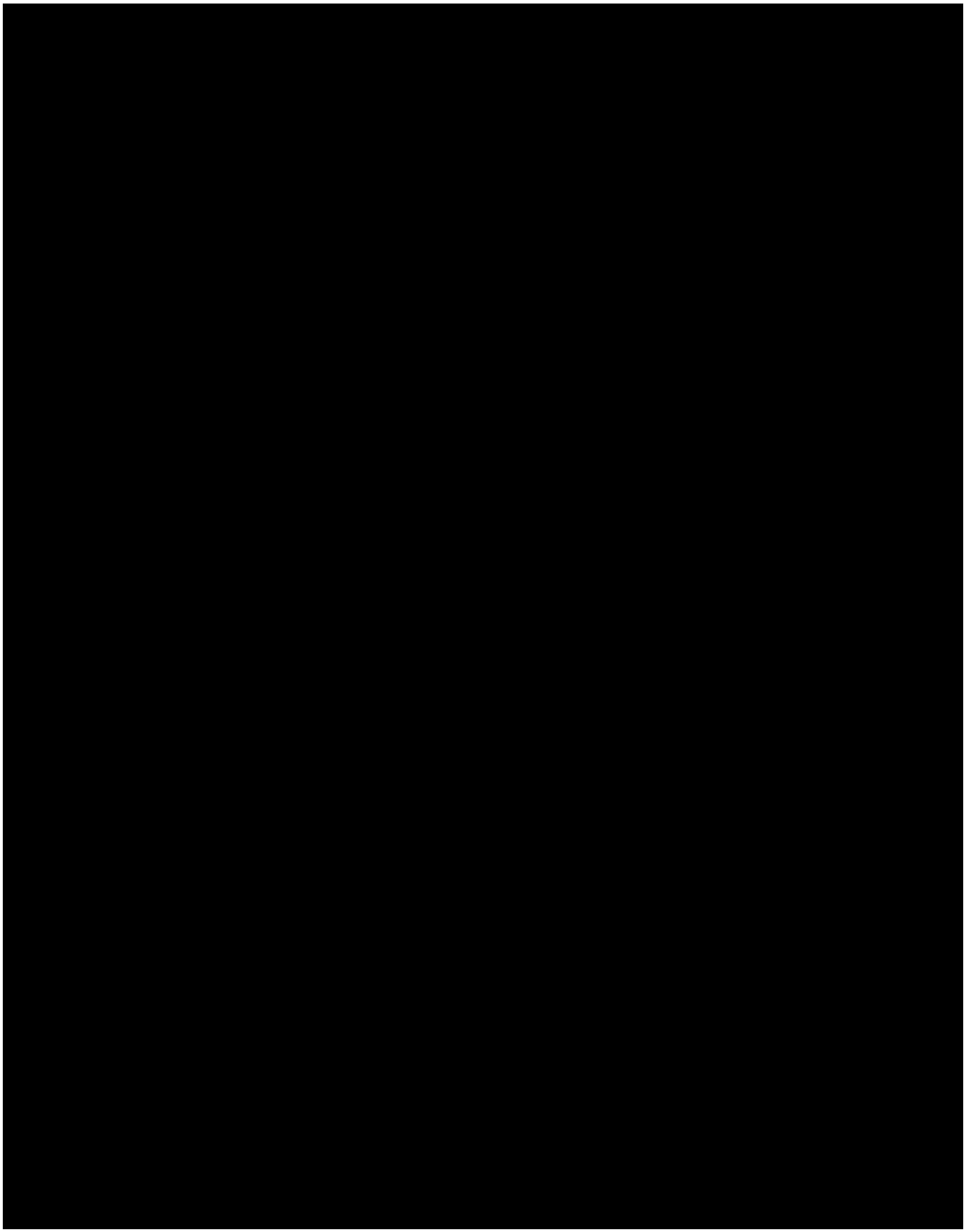
5.2 SECONDARY ENDPOINT(S)

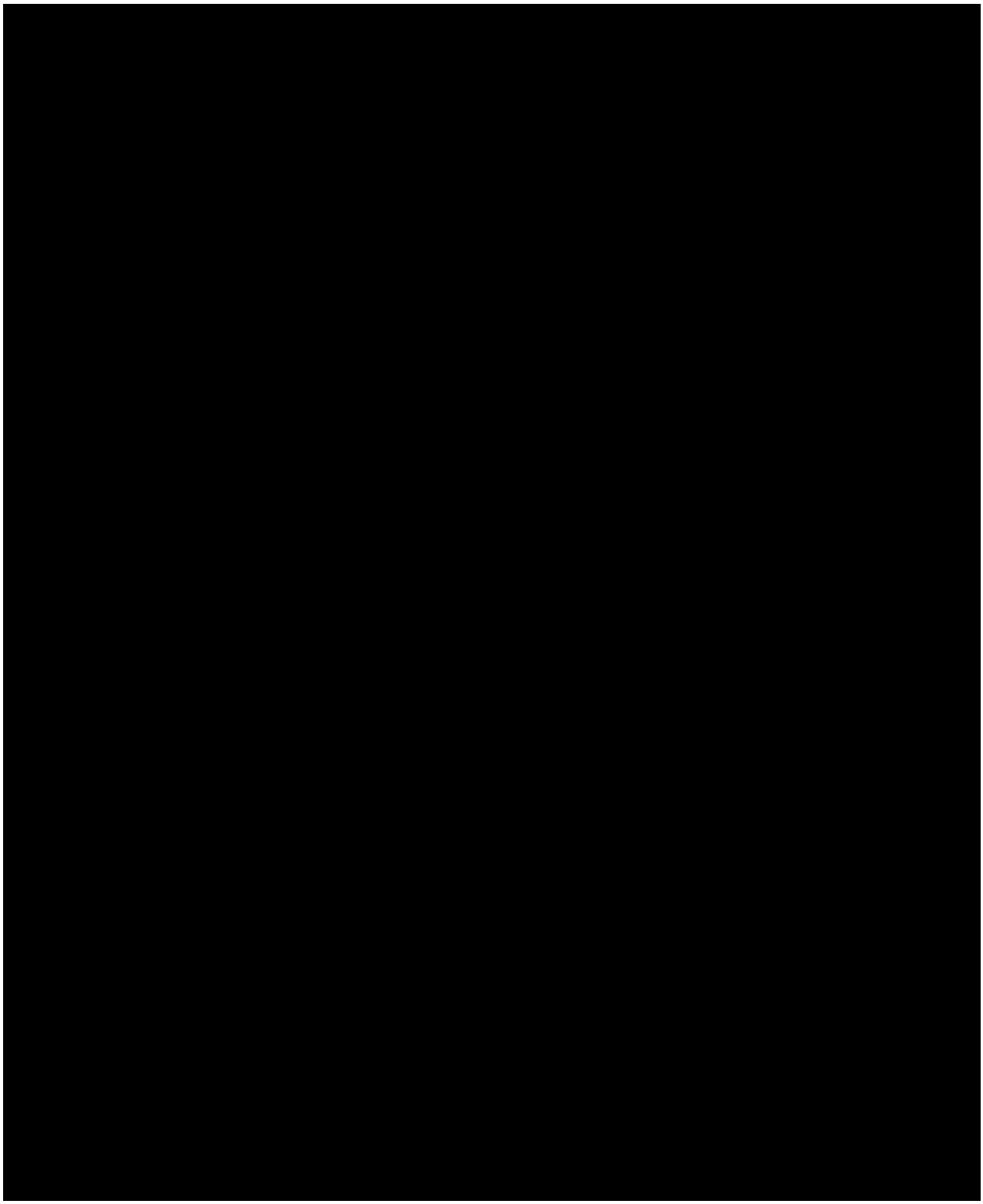
5.2.1 Key secondary endpoint(s)

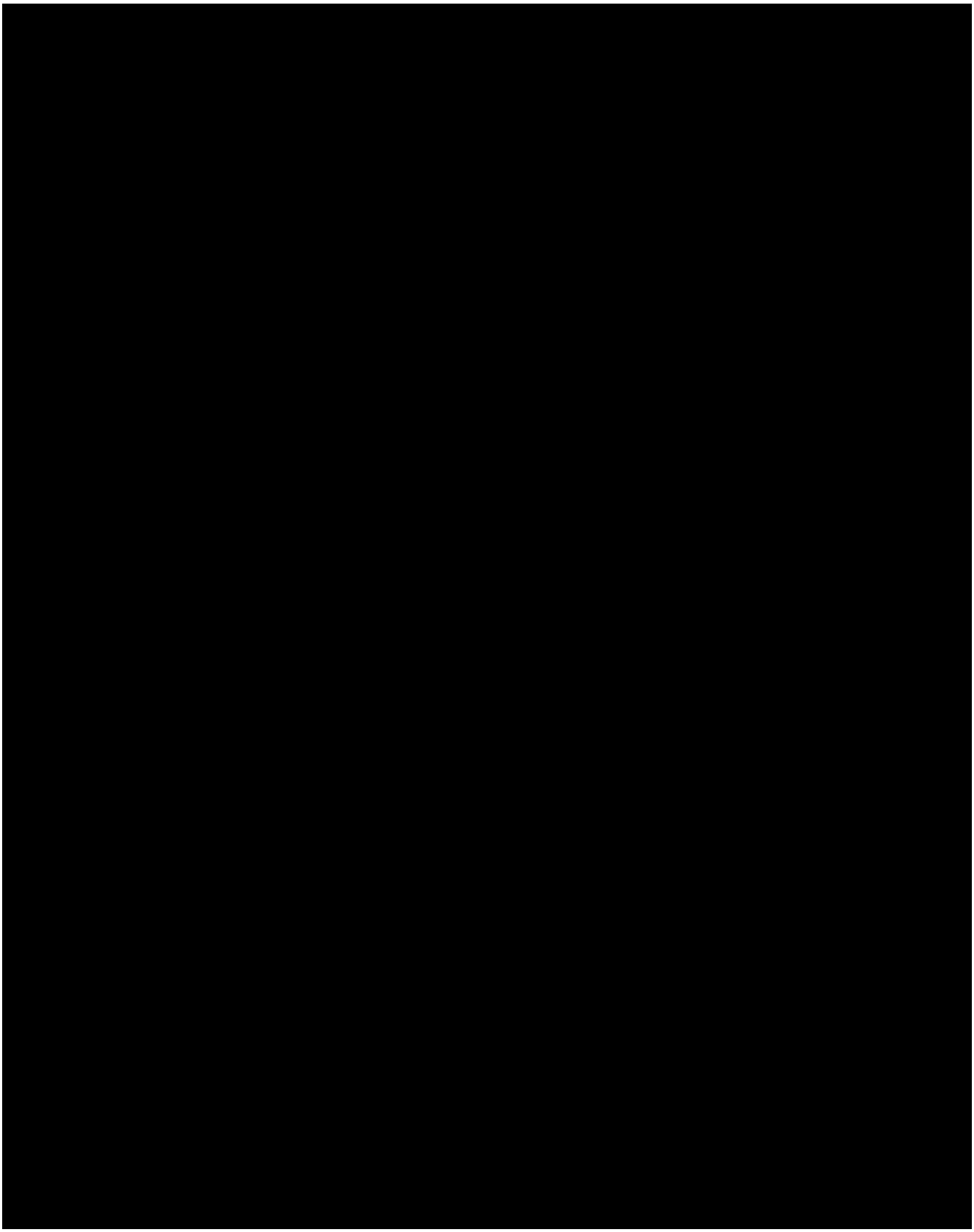
Not applicable.

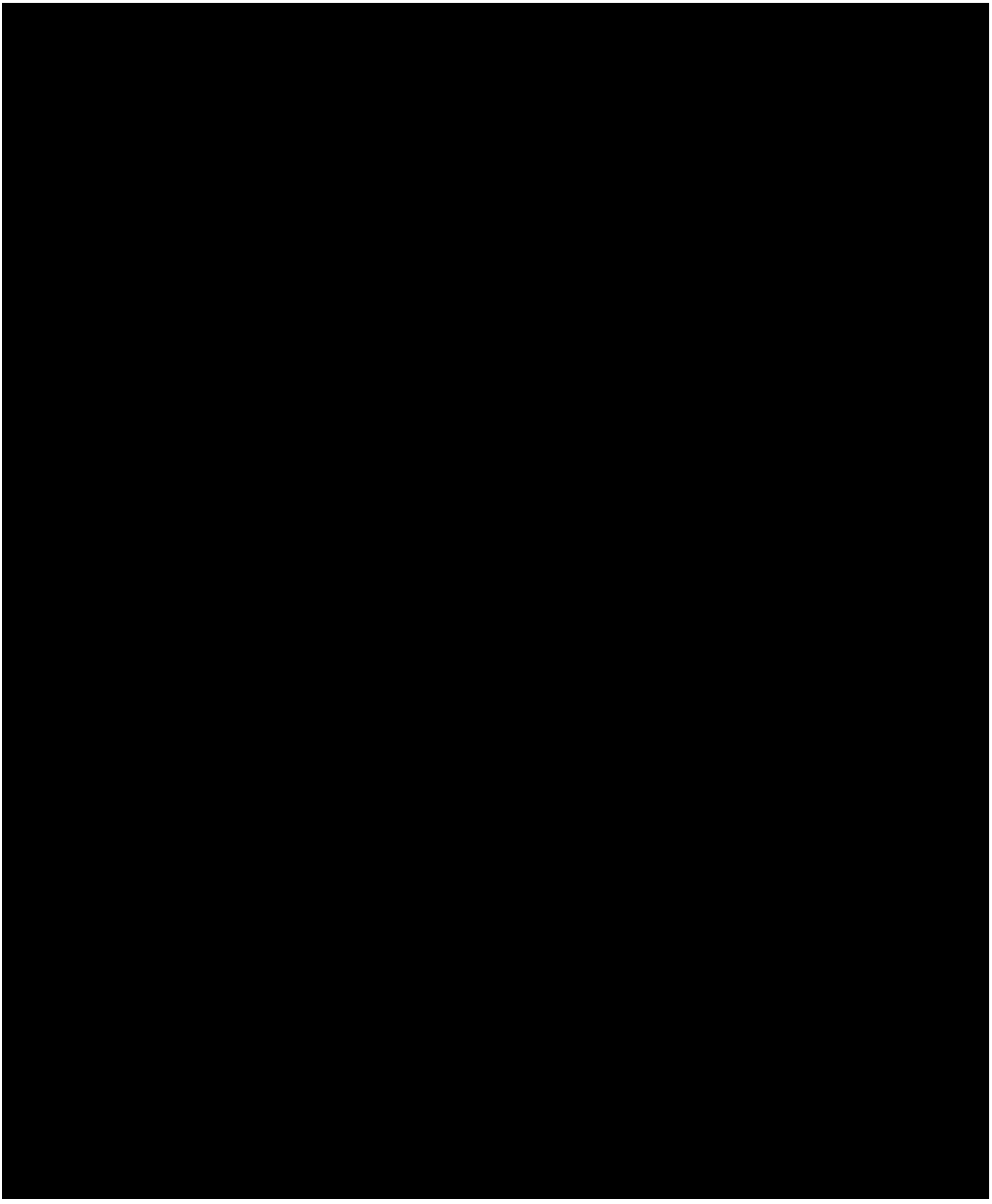
5.2.2 (Other) Secondary endpoint(s)

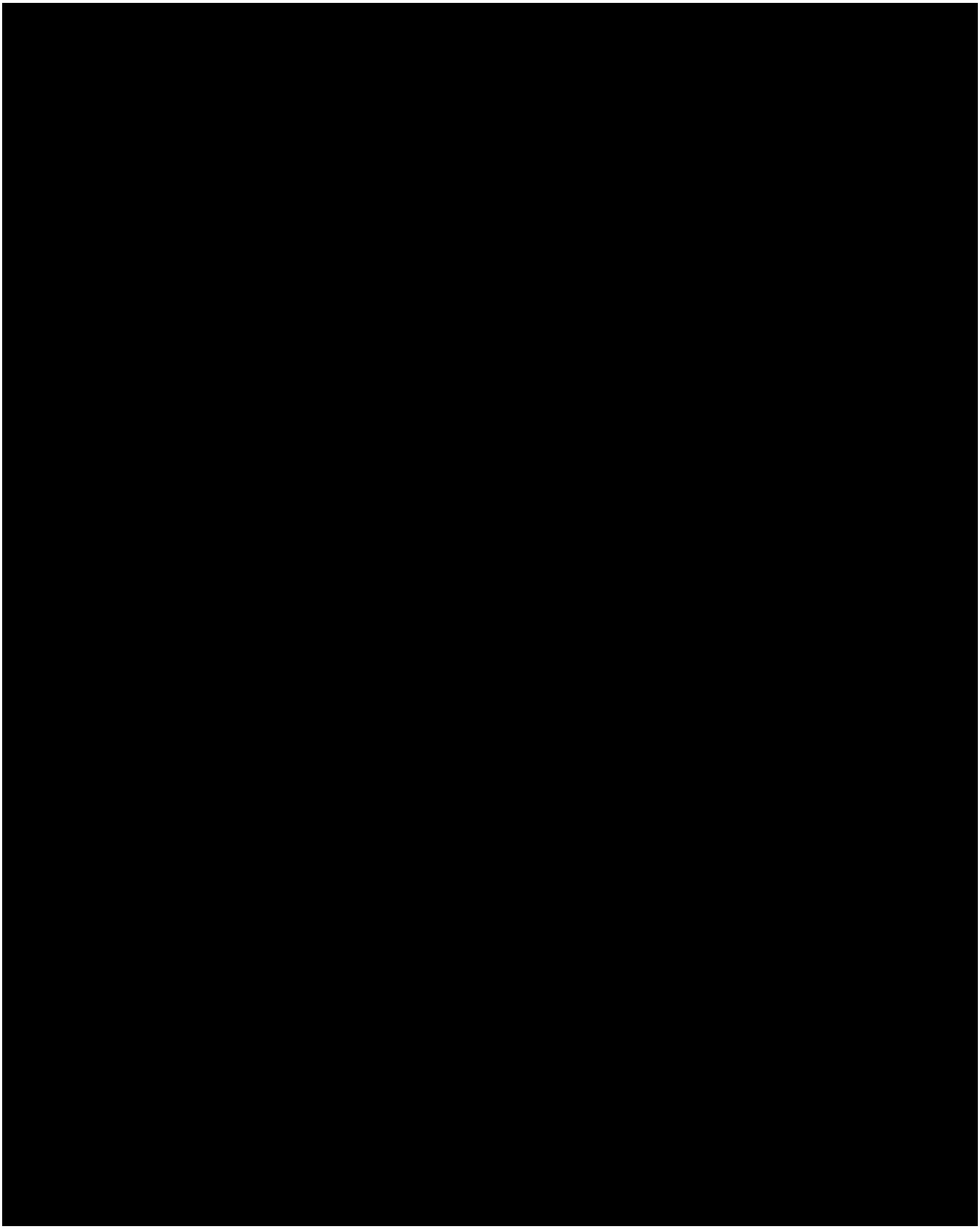
Not applicable.

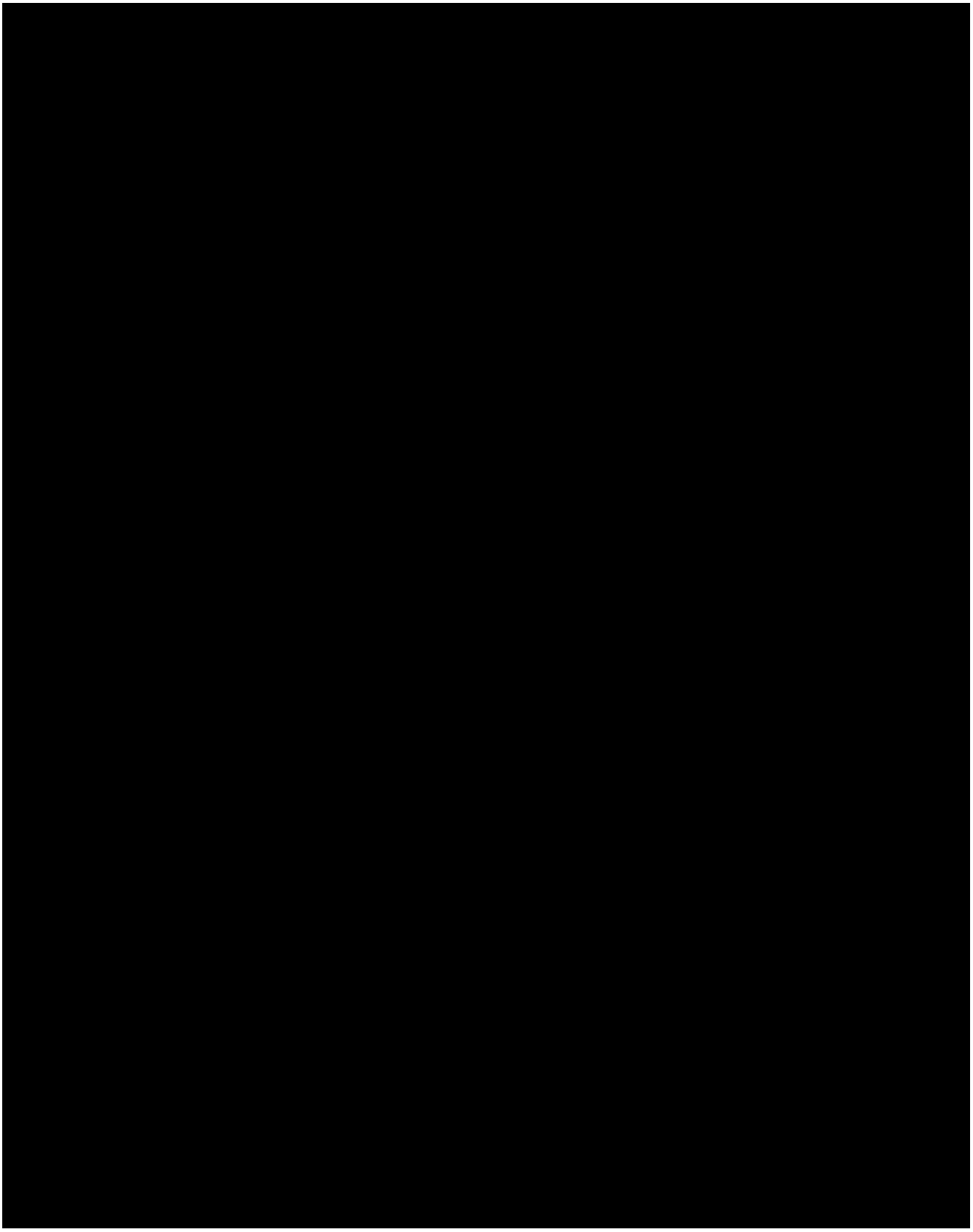


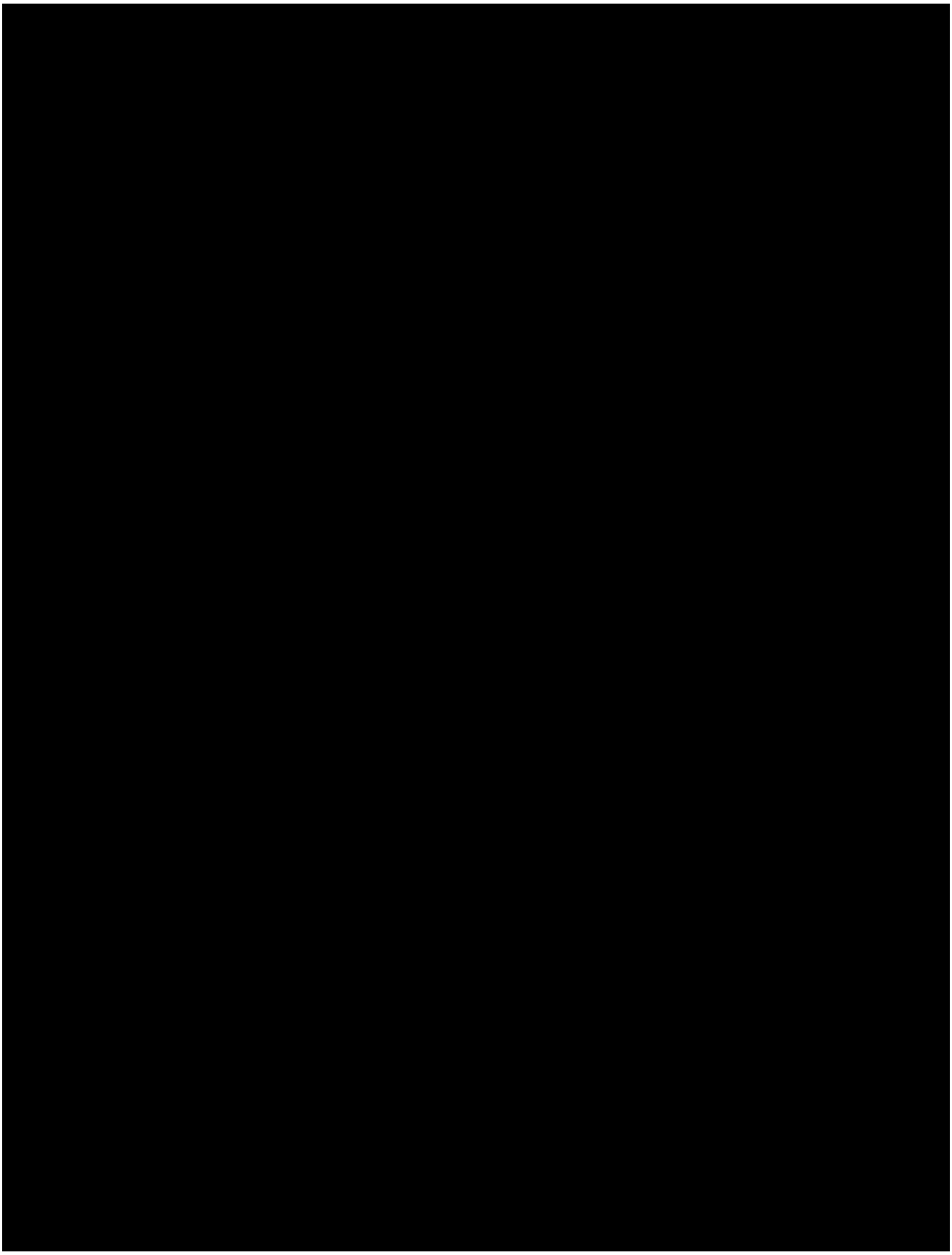


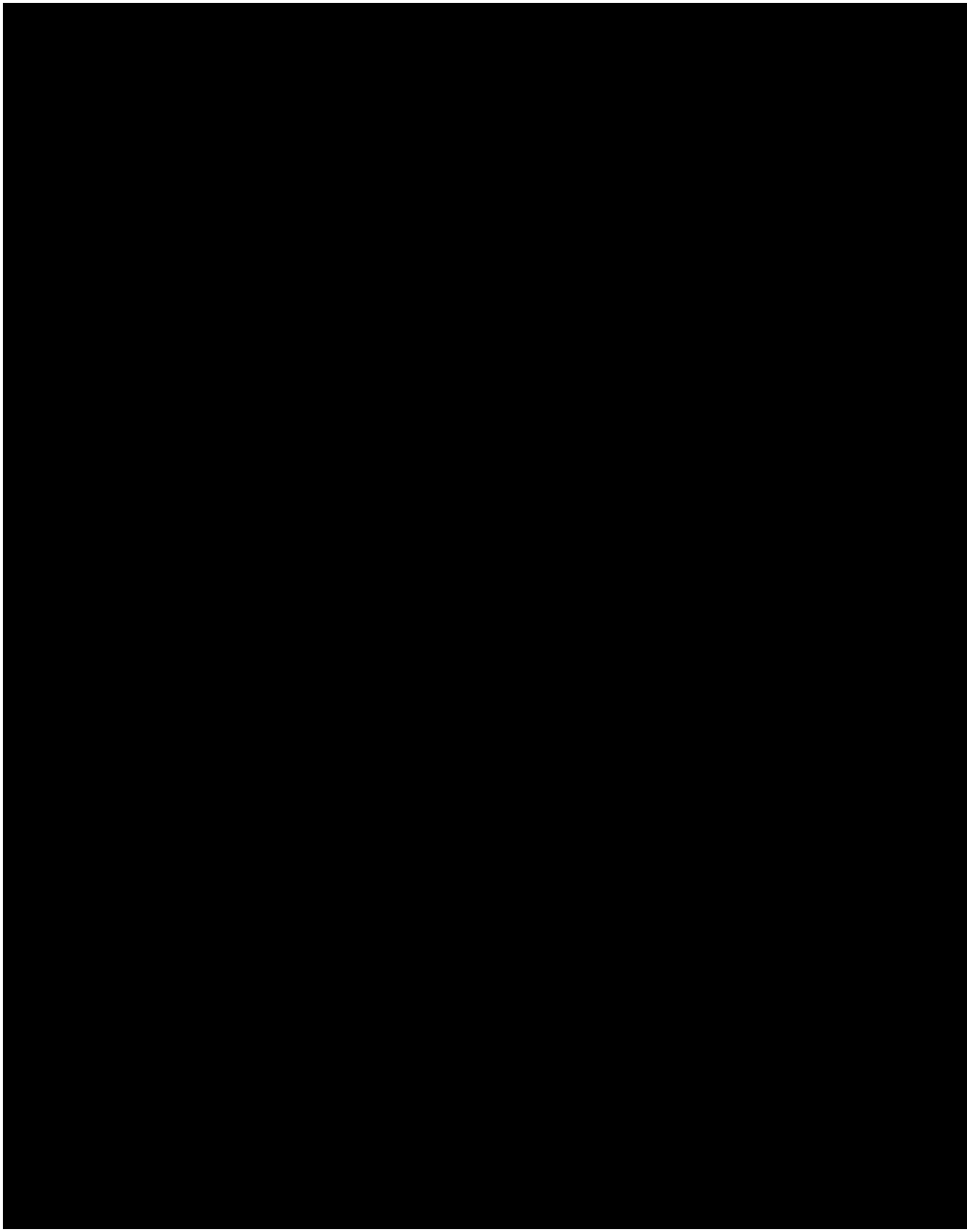


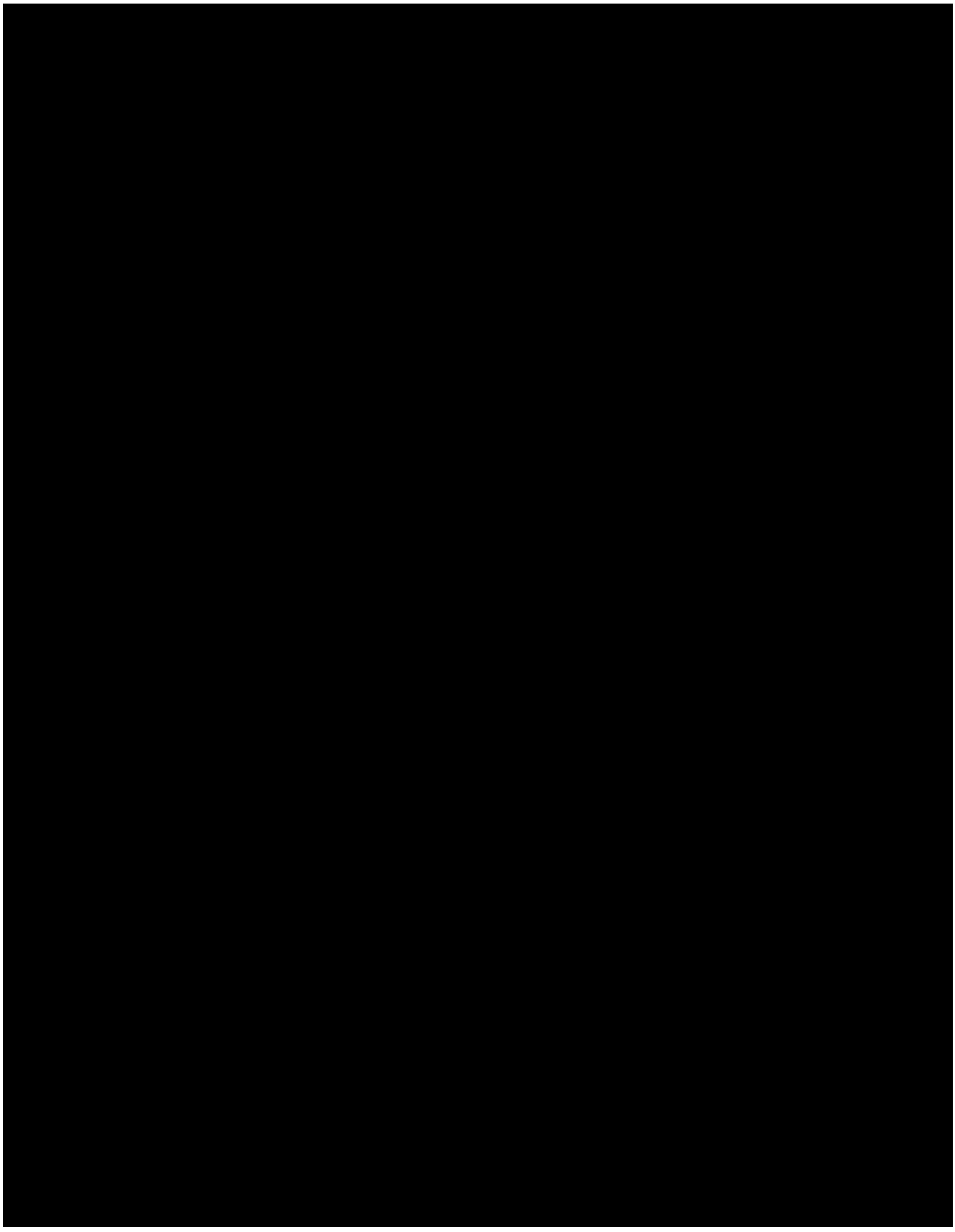


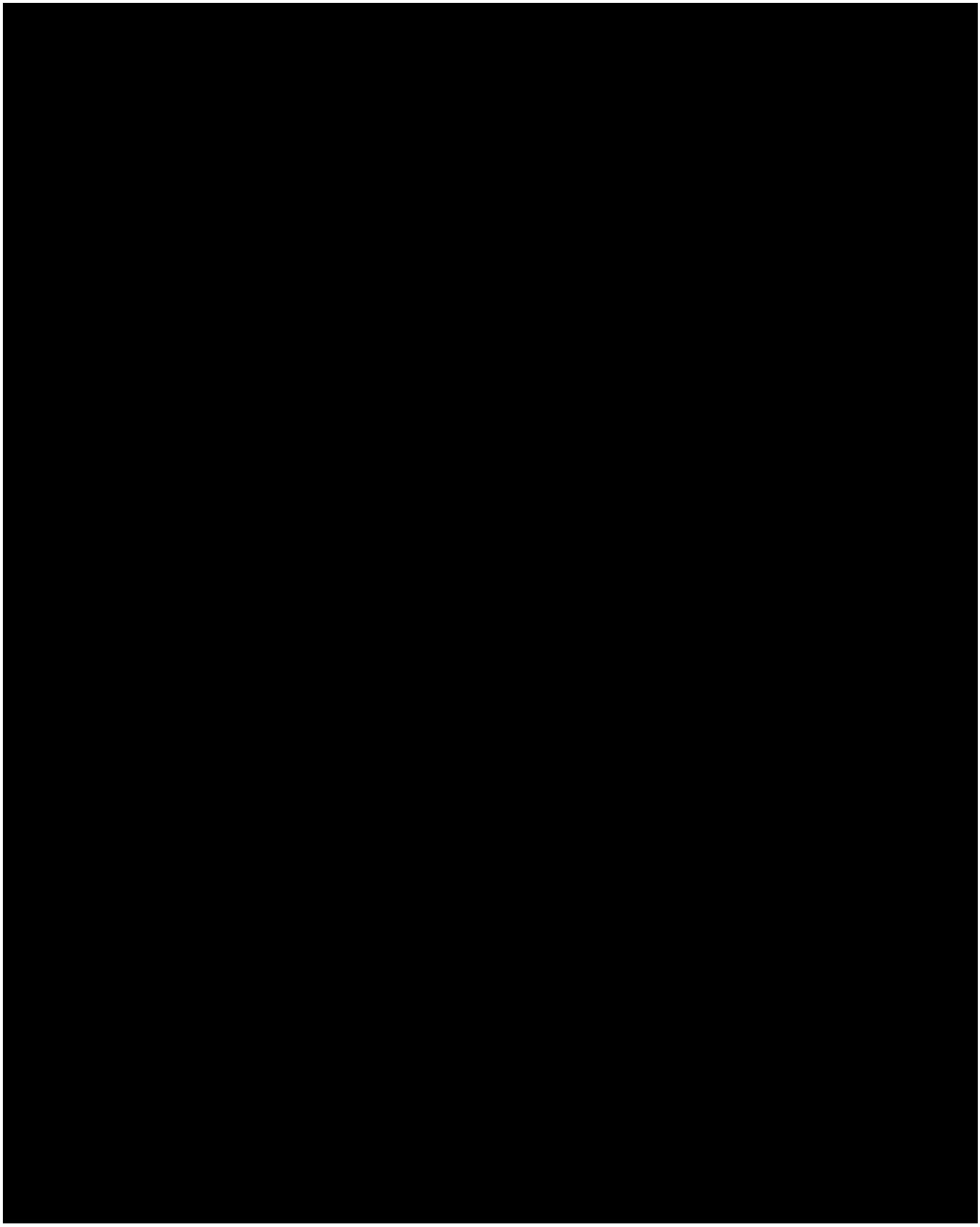


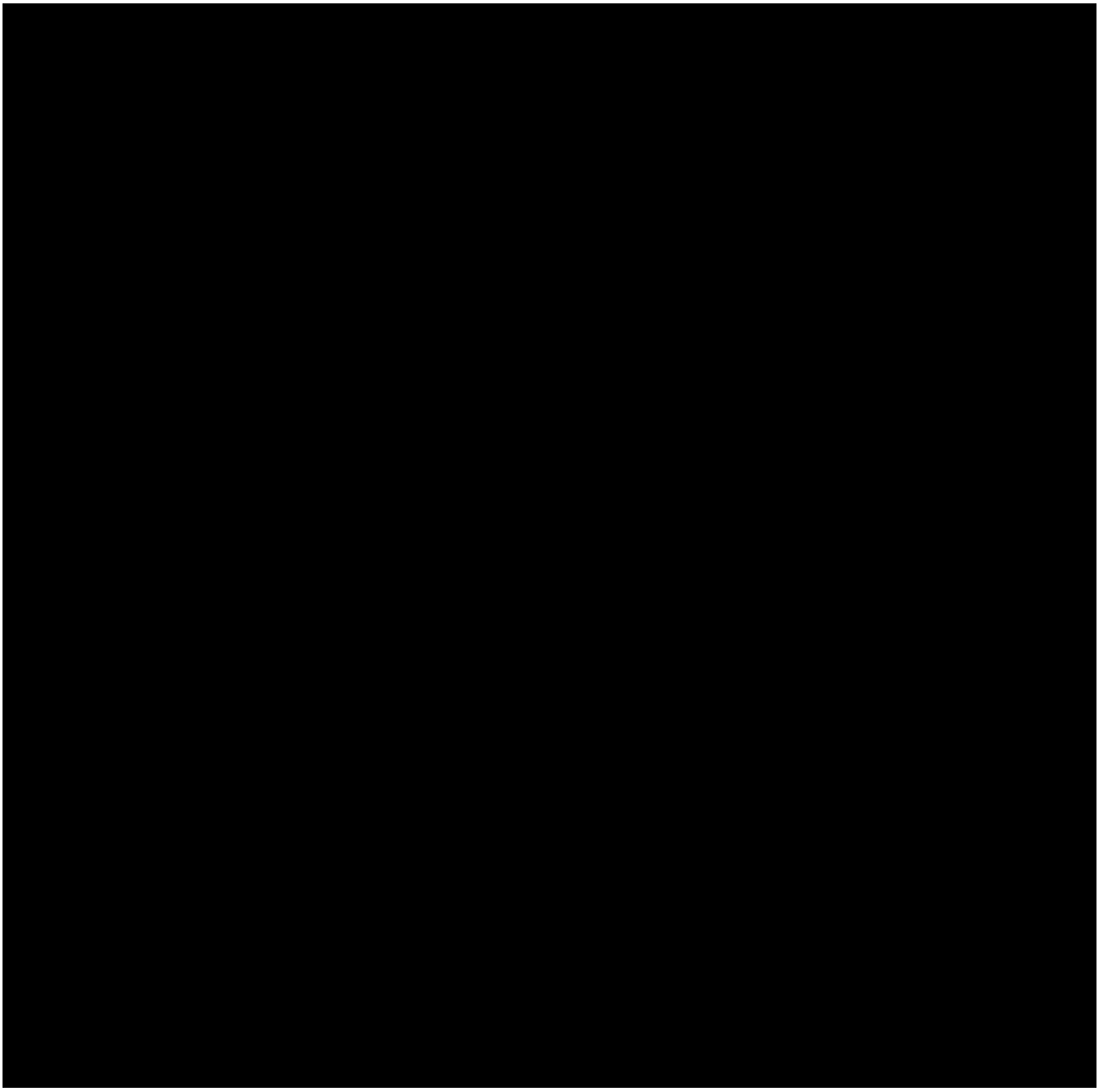












6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

No treatment or investigational drug is administered to the subjects. All analyses will be presented based on the diagnosis group entered in the eCRF (ex-smoking controls, COPD GOLD 1, COPD GOLD 2, COPD GOLD 3, and COPD with A1AT deficiency (A1ATD)) as well as for COPD GOLD 1, 2, and 3 combined, unless otherwise specified. A reclassification of subjects into the above mentioned diagnosis groups will be done based on spirometry data at baseline to investigate the extend of misclassified subjects (see Section 9.6).

[redacted]

6.2 IMPORTANT PROTOCOL DEVIATIONS

A subject's deviation from the CSP is considered "important" if it can be expected that the deviation had a distorting influence on the biomarker or clinical assessments, or could affect the subject's safety/rights.
Subjects with potentially important protocol deviations (iPDs) in the study will be documented in the iPD log file [c26595312]. The following list of potentially iPDs in Table 6.2:1 will be used; note that this is a working list and may not be finalised until the final Report Planning Meeting (RPM) or database lock meeting (DBLM). Potentially important protocol deviations will be handled according to BI standards [4]. During the study conduct, protocol deviations should be monitored and guidance for improving / teaching the respective sites should be discussed during the study Medical Quality Review Meetings (MQRMs).
iPDs flagged with an * in the following table, were also programmed from the database.

Table 6.2: 1 Important protocol deviations

Category / Code			PD Decode /Description	Comment/ Example	Excluded from subject set
A			Entrance Criteria Not Met		
	A1		Inclusion criteria not met		
		A1.01	Subjects who are smokers or ex-smokers without a smoking history of ≥ 20 pack years for at least 9 months	Ex-smoking control: IN3 COPD: IN7	PPSBM To be decided on a case by case basis for the number of pack years
*		A1.02	Subject is aged <40 or >70	Ex-smoking control: IN4 COPD: IN3	None
*		A1.03	Subjects have a BMI of <18 or > 35 kg/m^2	Ex-smoking control: IN5 COPD: IN4 COPD and A1AT: IN7	None
		A1.04	Subjects without post-bronchodilator FEV1 ≥ 80% of predicted normal and without a post-bronchodilator FEV1/FVC ≥ lower limit of normal	Ex-smoking control: IN6	PPSBM
		A1.05	Subjects without a mean D_{LCO} of ≥ 70% of predicted normal at Visit 1	Ex-smoking control: IN7	PPSBM
		A1.06	Subjects without a diagnosis of COPD as defined in CSP	COPD: IN5 [Manual check. Final decision at the DBLM based on genotype data.]	PPSBM
		A1.07	Subjects without COPD status of mild, moderate, or severe as defined in CSP	COPD: IN6 COPD and A1AT: IN5 [Manual check. Final decision at the DBLM based on genotype data.]	PPSBM
		A1.08	Subjects who are smokers or ex-smokers without a smoking history of ≥ 10 pack years	COPD and A1AT: IN4	PPSBM To be decided on a case by case basis for the number of pack years
		A1.09	Subjects not on stable therapy for at least 4 weeks prior to Visit 1	Ex-smoking control: IN9 COPD: IN9 COPD and A1AT: IN9	PPSBM

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code			PD Decode /Description	Comment/ Example	Excluded from subject set
		A1.10	Subjects without documented A1AT deficiency of ZZ genotype	COPD and A1AT: IN2 [Manual check. Final decision at the DBLM based on genotype data.]	PPSBM
*		A1.11	Subject is aged <30 or >70	COPD and A1AT: IN6	None
		A1.12	Subjects have a BMI of <18 or >30 kg/m^2	Ex-smoking control: IN5 COPD: IN4 Applies to MRI subset only.	None
		A1.13	Subject not able to perform all study related procedures	Ex-smoking control: IN8 COPD: IN8 COPD and A1AT: IN8	None
		A1.14	Males and females must be healthy at the discretion of the investigator	Ex-smoking control: IN2	None
	A2		Exclusion criteria violated		
		A2.01	Previous participation in this study or another trial within 6 weeks	Ex-smoking control: EX1 COPD: EX12 COPD and A1AT: EX15 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.02	Respiratory tract infection in 4 weeks prior to Visit 1 or during screening period	Ex-smoking control: EX2 COPD: EX2 COPD and A1AT: EX2 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.03. 01	Significant pulmonary disease or other medical conditions	Ex-smoking control: EX3 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.03. 02	Significant pulmonary disease other than COPD or other medical conditions	COPD: EX1 COPD and A1AT: EX1 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.04	Documented history of asthma	Ex-smoking control: EX4 COPD: EX4 COPD and A1AT: EX3	None

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code			PD Decode /Description	Comment/ Example	Excluded from subject set
		A2.05	Planned surgery during study	Ex-smoking control: EX5 COPD: EX9 COPD and A1AT: EX12 [Manual check. Final decision at the DBLM based on medical judgement.]	None
		A2.06	Blood withdrawal of more than 100mL within past 6 weeks prior to visit 1 and between Visit 1 and 2.	Ex-smoking control: EX6 COPD: EX10 COPD and A1AT: EX13	None
		A2.07	Significant alcohol or drug abuse within past 2 years prior to Visit 1	Ex-smoking control: EX7 COPD: EX13 COPD and A1AT: EX16	None
		A2.08	Women who are pregnant, nursing or who plan to become pregnant while in the study	Ex-smoking control: EX8 COPD: EX18 COPD and A1AT: EX19	None
		A2.09	MRI inclusion criteria not met (see CSP for details)	Ex-smoking control: EX10 COPD: EX20 Applies to MRI subset only.	None
		A2.10	A malignancy for which the subject has undergone resection, radiation, or chemotherapy within past 5 years	COPD: EX3 COPD and A1AT: EX7	None To be decided on a case by case basis.
		A2.11	Hospitalisation for respiratory failure during the year prior to Visit 1	COPD: EX5 COPD and A1AT: EX8 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.12	History of cystic fibrosis	COPD: EX6 COPD and A1AT: EX9 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.13	Clinical diagnosis of bronchiectasis requiring specific treatment	COPD: EX7 COPD and A1AT: EX10 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code			PD Decode /Description	Comment/ Example	Excluded from subject set
		A2.14	A clinically relevant abnormal baseline hematology, blood chemistry	COPD: EX8 COPD and A1AT: EX11 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.15	Known active tuberculosis	COPD: EX11 COPD and A1AT: EX14 [Manual check. Final decision at the DBLM based on medical judgement. This decision will overwrite the programmed result.]	PPSBM
		A2.16	Inability to comply with restrictions regarding medication, diet, and lifestyle	COPD: EX14 COPD and A1AT: EX17 [Manual check. Final decision at the DBLM based on medical judgement.]	None
		A2.17	Newly added anti-inflammatory treatment within 4 weeks prior to Visit 1.	COPD: EX15 COPD and A1AT: EX5 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.18	Subjects with change in therapy within 4 weeks prior to Visit 1	COPD: EX16 COPD and A1AT: EX18 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.19	Subjects on treatment with PDE-4 inhibitors (e.g. Roflumilast) and maintenance treatment with Methylxanthines (e.g. Theophylline).	COPD: EX17 COPD and A1AT: EX6 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.20	Current and planned A1AT augmentation therapy.	COPD and A1AT: EX4 [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		A2.21	Subjects who are heterozygous or homozygous for the A1AT Z or S allele	Ex-smoking control: EX11 COPD: EX21	PPSBM
		A2.22	Subjects presenting with an immunocompromising condition	Ex-smoking control: EX12 COPD: EX22 COPD and A1AT: EX21	PPSBM

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code			PD Decode /Description	Comment/ Example	Excluded from subject set
B			Informed Consent		
	B1		Informed consent not given	Date of informed consent missing.	All
	B2		Informed consent given too late	Date of informed consent obtained not prior to any study related procedure (including re-consenting).[Manual check. Final decision at the DBLM based on medical judgement.]	None
D			Concomitant Medication		
	D2		Restricted medication use		
		D2.01	Restricted medication use prior to Visit 1	Medication/therapy dose not stable at least 4 weeks before Visit 1. Washout period of 3 months or 6 half-lives (whichever is greater) prior to Visit 1 not met. See CSP table 4.2.2: 1 for full list of medications. [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		D2.02	Restricted medication use between Visits 1 and 2	Use of exacerbation medication without extension of screening period. See CSP table 4.2.2: 1 for full list of medications. [Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
		D2.03	Restricted medication use during the observational period	Use of Biologic antagonists or other investigational drugs during the observational period [Manual check. Final decision at the DBLM based on medical judgement.]	None
		D2.04	Restricted medication use prior to PFT testing	Increase in dose or addition of oral steroids within 14 days before PFT testing. Administration of theophyllines within 14 days before PFT testing. Administration of antibiotics within 14 days before PFT testing. [Manual check. Final decision at the DBLM based on medical judgement.]	None

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code			PD Decode /Description	Comment/ Example	Excluded from subject set
F			Incorrect timing		
*	F1		For the screening visit: Visit within 4 weeks of COPD exacerbation	[Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
G			Study Specific protocol deviations		
	G1		Change in smoking status	I.e. if a subject begins smoking during the study.	None
Z			Other		
	Z1		Other PD affecting outcome of interest and possibly safety	[Manual check. Final decision at the DBLM based on medical judgement.]	PPSBM
	Z2		Other PD affecting safety only	[Manual check. Final decision at the DBLM based on medical judgement.]	None
	Z3		Serious GCP non-compliance	[Manual check. Final decision at the DBLM based on medical judgement.]	None
Q			Non important covid related PDs		
	Q1		Missed examination	[Manual check. Final decision at the DBLM based on medical judgement.]	None
	Q2		Missed visit	[Manual check. Final decision at the DBLM based on medical judgement.]	None

6.3 SUBJECT SETS ANALYSED

The following subject sets are planned to be investigated:

Table 6.3: 1 Definition of populations

Analysis Population	Definition
Screened subjects set (SCR)	All subjects enrolled in the study, following the receipt of informed consent.
Observed subjects set (OBS)	All subjects, from the SCR, who are eligible to enter the observation period.
Per-protocol set (biomarker subjects) (PPSBM)	All subjects, from the OBS, who have no IPDs affecting the clinical or biomarker assessments.
MRI set	All subjects, from the PPSBM, with MRI performed at baseline

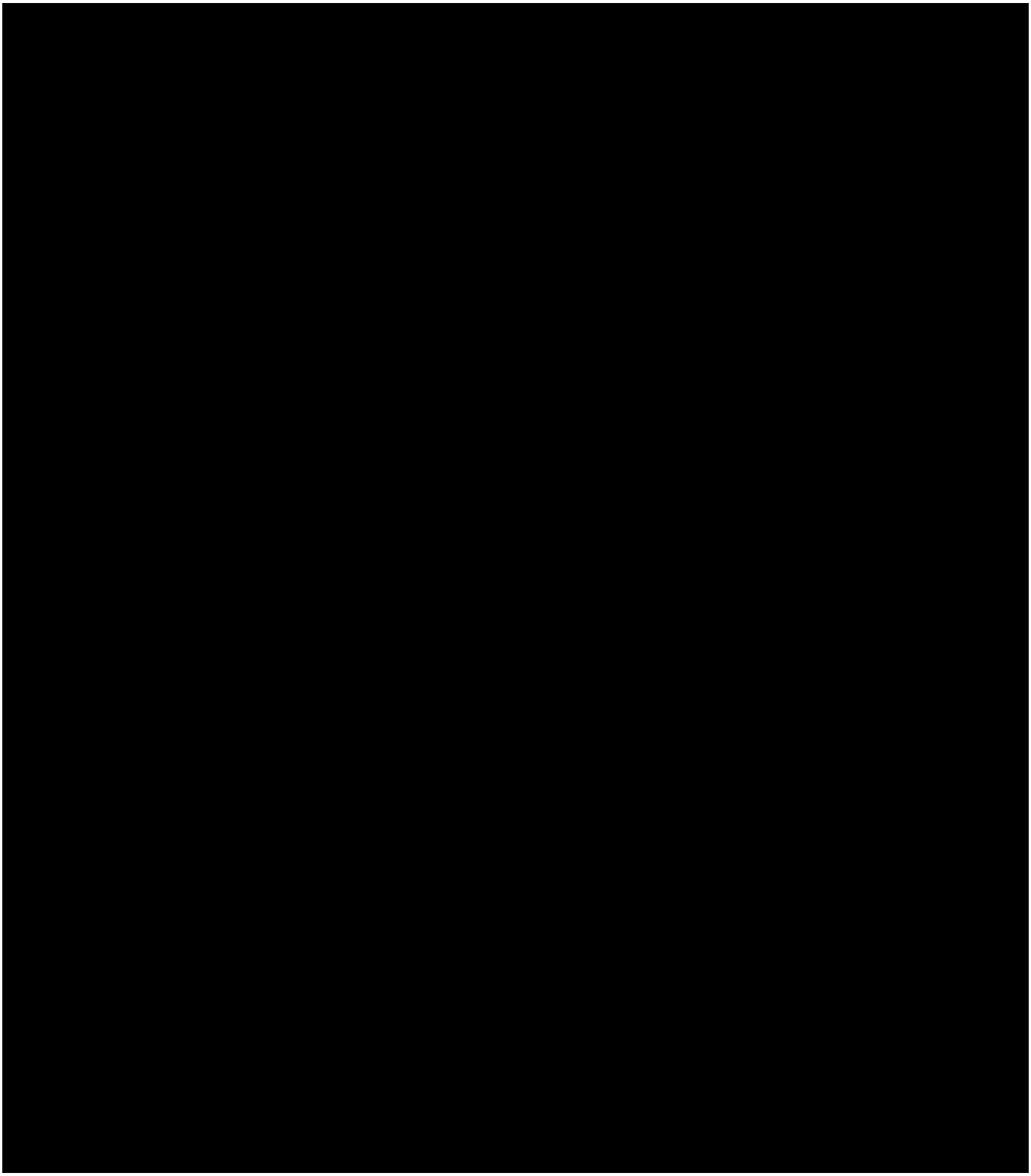
Table 6.3:2 shows which analysis set is used for each class of assessment:

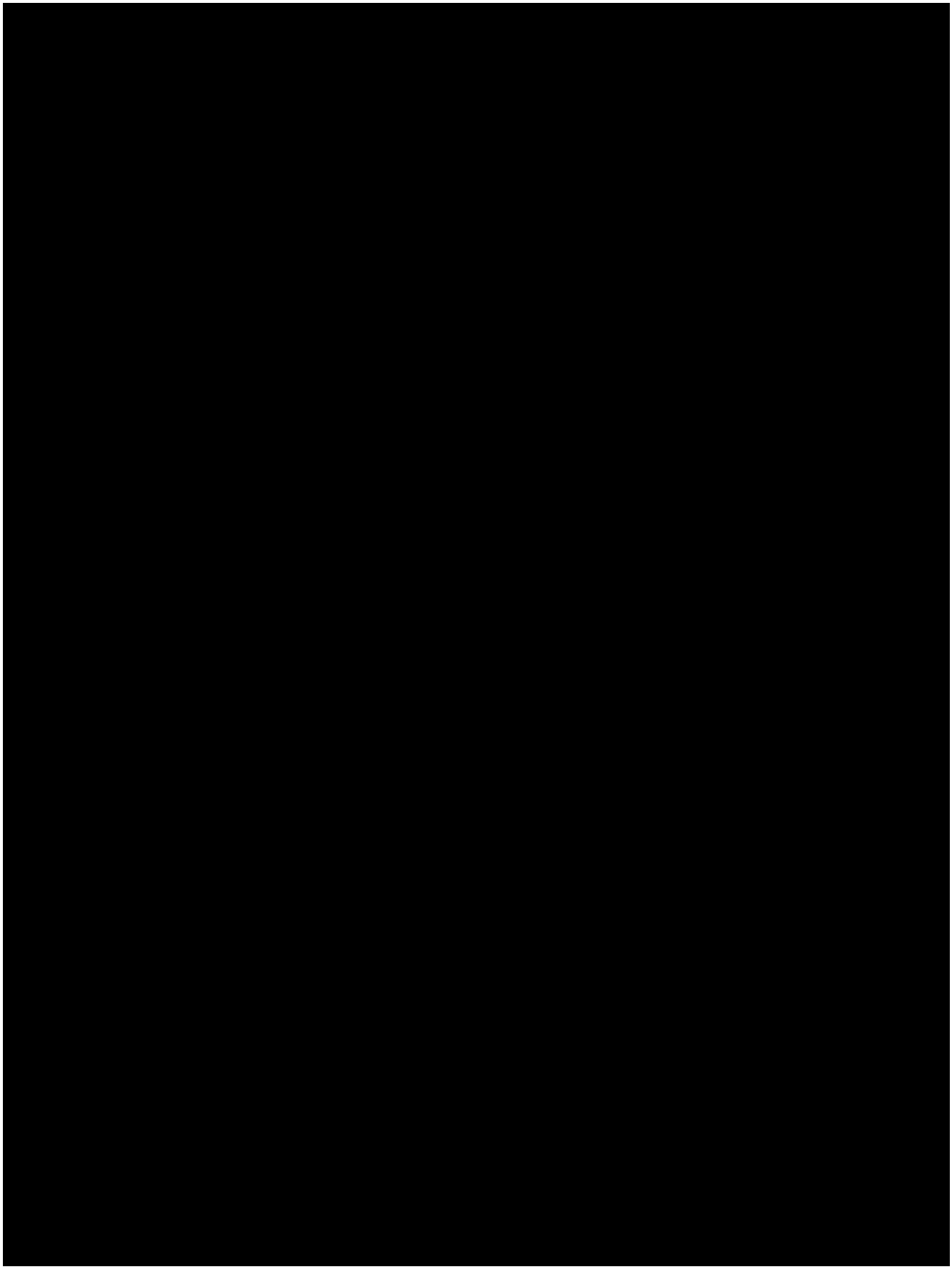
Table 6.3: 2 Subject sets for planned analyses

Planned analysis	Subject set
Disposition	Screened subjects set
Demographic data	Observed subjects set Per-protocol set (biomarker subjects)
Clinical and biomarker assessments	Per-protocol set (biomarker subjects)
Safety analyses	Observed subjects set

All analyses will be performed on observed cases (OC). Note that the number of subjects with available data for an assessment may differ. For details, see Section 6.6 “Handling of missing data”.

[redacted]





6.5 POOLING OF CENTRES

No pooling of centres will be performed.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Every effort should be made to collect complete data for each time point at each test day.

6.6.1 Observed case (OC) analysis

Observed case analysis implies the analysis of data exactly as observed, without the use of any imputation techniques.

6.6.2 Missing or partial dates

For incomplete date information, e.g. date stopping smoking or exacerbation dates, the midpoint of the possible interval will be used. If only the year is present, the day and month

will be imputed as 01 July; if year and month are present, the day will be imputed as 15. If the year is missing, the date will be considered missing.

For partial start and stop dates for background medication, concomitant therapies, and additional treatments, the following derivations will be used to impute the missing dates where deemed necessary:

- If the day of the end date is missing, then the end date is set to last day of the month.
- If the day and month of the end date are missing, then the end date is set to 31st December of the year.
- If the day of the start date is missing, then start date is set to first day of the month.
- If the day and month of the start date are missing, then the start date is set to 1st January of the year.

All other cases need to be assessed by the study team on an individual basis, using the above points as guidance.

6.6.3 Spirometry and Body plethysmography

No imputation method will be implemented for missing data.

In case of use of restricted medication during the observational period (biologic antagonists or other investigational drugs), all respective data (see Section 5.3.1.1 and Section 5.3.1.2) collected from the first use of these medications onwards will be excluded from all analyses. Regarding concomitant medication and the restrictions stated in CSP Section 4.2.2.1, only respective data during the 15 day window will be excluded from analysis. These exclusions are documented in the conmed log file [c28419093].

If an exacerbation (or MESIs like pneumonia, pulmonary fibrosis, asthma-chronic pulmonary disease overlap syndrome) occurred or is not resolved 15 days prior to a visit with PFT testing, respective data from this visit will be excluded from the analysis. If a MESI is considered relevant to impact data from all follow up visits, all collected data from the MESI onset date onwards will be excluded from the analysis. These exclusions are documented in the MESI log file [c28782045].

Findings identified during the imaging MQRM process were considered for data censoring. These exclusions are documented in the censoring log file [c32908066].

For subjects who re-started smoking during the observational period, all data collected from that timepoint onwards will be excluded from all analyses. These exclusions are documented in the iPD log file [c26595312].

Regarding timing of spirometry, all data collected at post-baseline visits which are not within 3 hours from the timing of Visit 2 and are outside the 6.00 a.m. and 12.00 a.m. interval will be excluded from analyses.

6.6.4 Diffusing capacity of the lungs for carbon monoxide

In case of use of restricted medication during the observational period (biologic antagonists or other investigational drugs), all DLCO data (see Section 5.3.1.3) collected from the first use of these medications onwards will be excluded from all analyses. Regarding concomitant medication and the restrictions stated in CSP Section 4.2.2.1, only respective data during the 15 day window will be excluded from analysis. These exclusions are documented in the conmed log file [c28419093].

If an exacerbation (or MESIs like pneumonia, pulmonary fibrosis, asthma-chronic pulmonary disease overlap syndrome) occurred or is not resolved 15 days prior to a visit with PFT testing, DLCO data from this visit will be excluded from the analysis. If a MESI is considered relevant to impact data from all follow up visits, all collected data from the MESI onset date onwards will be excluded from the analysis.These exclusions are documented in the MESI log file [c28782045].

Findings identified during the imaging MQRM process were considered for data censoring. These exclusions are documented in the censoring log file [c32908066].

For subjects who re-started smoking during the observational period, DLCO data collected from that timepoint onwards will be excluded from all analyses. These exclusions are documented in the iPD log file [c26595312].

Since most intra-session variability is technical, rather than physiological, the mean of acceptable DLCO measurements is reasonable to be reported. Moreover, there should be at least two acceptable measurements that meet the repeatability requirement of either being within 1 mmol/min/kPa of each other, or within 10% of the overall highest value. Therefore, in order to preserve data quality, all subjects with only one DLCO measurement should be set to missing. Following the rationale of MacIntyre et al (2005) [6], imputation rules, given below, will be implemented to ensure that all acceptable DLCO measurements adhere to the repeatability requirement criteria:

Assume $x1 \leq x2 \leq x3$ denote the single DLCO measurements. Then let

- $c0 = x3 * 10\%$
- $c12 = x2 - x1$
- $c23 = x3 - x2$
- $c13 = x3 - x1$
- x = DLCO value to be used.

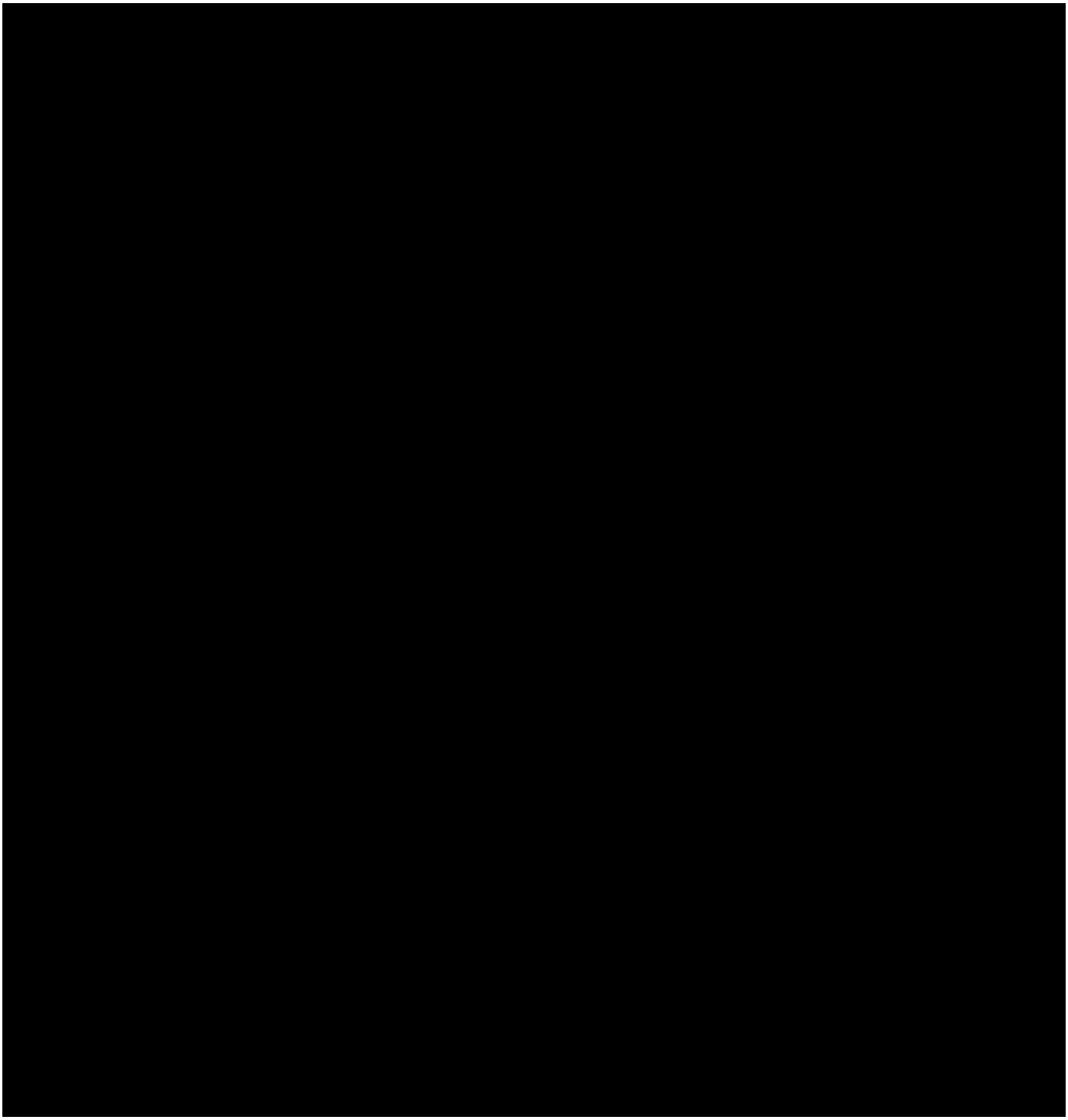
If ($c13 \leq c0$) or ($c13 \leq 1$ mmol/min/kPa), then $x = (x1 + x2 + x3) / 3$.

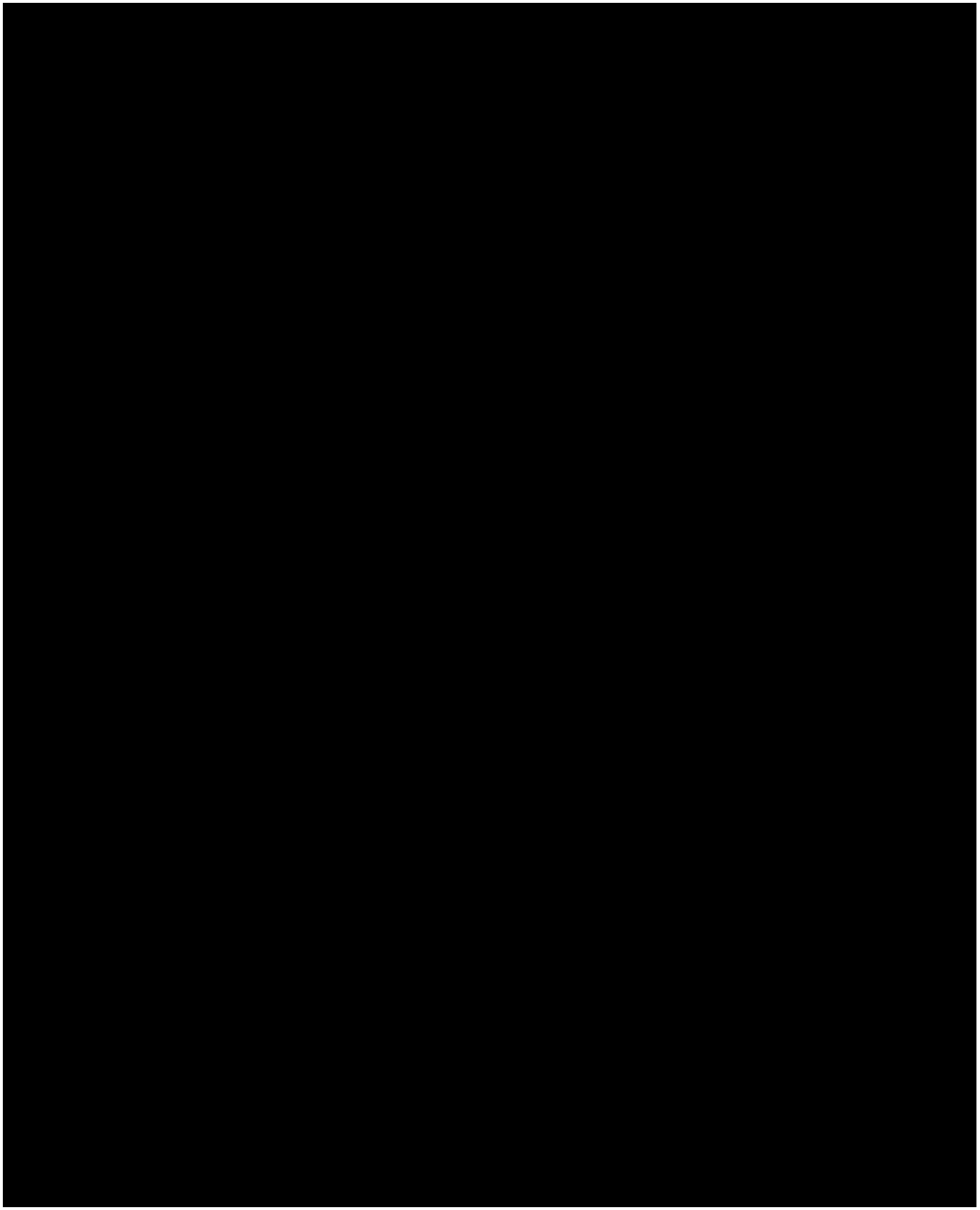
Else, if ($c23 \leq 1$ mmol/min/kPa) or ($c23 \leq c0$), then $x = (x2 + x3) / 2$.

Else, if (c12 ≤ 1 mmol/min/kPa), then x = (x1 + x2) / 2.

Else, x = missing.

If a DLCO measurement is excluded for the calculation of mean DLCO based on the above rules, the respective VA value will also be excluded from the calculation of the mean VA.





6.6.7 Safety

With regard to the safety analysis, no imputation of safety data is foreseen (observed case analysis) except for missing or incomplete AE dates. Missing or incomplete AE dates are imputed according to BI standards [7].

6.6.8 Symptom questionnaires

mMRC

- No imputation will be implemented for missing data.

CAT

- If responses to no more than two questions are missing, then missing scores for individual questions will be replaced by the mean score of the non-missing questions [8].
- If more than two questions are missing then the total score will not be calculated.

SGRQ

- Missing questionnaire responses will be handled according to the guidelines outlined in the SGRQ Manual [9]. Missing responses within patients' questionnaires will not be imputed, and will remain as is, with one exception:
    - Question 5 asks "how many severe or very unpleasant attacks of chest trouble" patients have had during the past 4 weeks, whilst Question 6 asks "how long did the worst attack of chest trouble last?"
    - It is possible that patients may answer Question 5 as 'No attacks' and then go on to state a length of time for the worst attack in Question 6. In this case, the response to Question 6 will be set to missing to be consistent with Question 5.
    - As stated below, the SGRQ guidelines for calculation of the Symptoms component allow for a maximum number of missing responses. However, due to the relationship between Questions 5 and 6, the response to Question 6 should be missing if Question 5 is answered as 'No attacks'. Therefore, a missing response to Question 6 will not be included in the count of missing responses for the Symptoms component in the following cases:
        - Questionnaires where the patient has deliberately not answered Question 6, due to answering Question 5 as 'No attacks', or
        - Question 6 has been set to missing
- If there are more than 2, 4, or 6 missed items in the Symptoms, Activity, or Impacts component, respectively, then the component score will be set to missing. A total score will not be calculated, unless a score exists for all three components (Symptoms, Activity, and Impacts).

For patients who re-started smoking during the observational period, all data collected from that timepoint onwards will be excluded from all analyses.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Definition of baseline

Analysis windows for all assessments during the study are given in the following tables. The date of the initial visit 2 will be used as study day 1 for the time windowing (including subjects with a repeated visit 2). If more than one value is available within one time window the one which is closest to the planned time/day is used for analysis. In case two values are equidistant from the planned time/day, then the last one will be picked.

Table 6.7: 1 Time windows for lung function assessment – Spirometry, pulse oximetry, lung diffusion capacity

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Observational period	Baseline	2	1	1	≤ 28
Observational period	Week 12	3	84	77 to ≤ 91	29 to ≤ 130
Observational period	Week 26	4	182	168 to ≤ 196	131 to ≤ 273
Observational period	Week 52	5	364	350 to ≤ 378	274 to ≤ 546
Observational period	Week 104	6	728	714 to ≤ 742	547 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

Table 6.7: 2 Time windows for lung function assessment - Body plethysmography

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Observational period	Baseline	2	1	1	≤ 28
Observational period	Week 12	3	84	77 to ≤ 91	29 to ≤ 130
Observational period	Week 26	4	182	168 to ≤ 196	131 to ≤ 273
Observational period	Week 52	5	364	350 to ≤ 378	274 to ≤ 546
Observational period	Week 104	6	728	714 to ≤ 742	547 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

Table 6.7: 3 Time windows for lung function assessment – BODE index

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Observational period	Baseline	2	1	1	≤ 28
Observational period	Week 104	6	728	714 to ≤ 742	29 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

Table 6.7: 4 Time windows for lung function assessment – 6-minute walk test

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Observational period	Baseline	2	1	1	≤ 28
Observational period	Week 104	6	728	714 to ≤ 742	29 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

Table 6.7: 5 Time windows for soluble biomarker assessment – blood and induced sputum

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Observational period	Baseline	2	1	1	≤ 28
Observational period	Week 12	3	84	77 to ≤ 91	29 to ≤ 130
Observational period	Week 26	4	182	168 to ≤ 196	131 to ≤ 273
Observational period	Week 52	5	364	350 to ≤ 378	274 to ≤ 546
Observational period	Week 104	6	728	714 to ≤ 742	547 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

Table 6.7: 6 Time windows for imaging biomarker assessment – CT

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Observational period	Baseline	2	1	1	≤ 28
Observational period	Week 52	5	364	350 to ≤ 378	29 to ≤ 546
Observational period	Week 104	6	728	714 to ≤ 742	547 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

Table 6.7: 7 Time windows for imaging biomarker assessment – MRI

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Observational period	Baseline	2	1	1	≤ 28
Observational period	Week 26	4	182	168 to ≤ 196	29 to ≤ 273
Observational period	Week 52	5	364	350 to ≤ 378	274 to ≤ 546
Observational period	Week 104	6	728	714 to ≤ 742	547 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

Table 6.7: 8 Time windows for symptom questionnaire – mMRC, CAT, SGRQ-COPD

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Observational period	Baseline	2[1]	1	1	≤ 28
Observational period	Week 52	5	364	350 to ≤ 378	29 to ≤ 546
Observational period	Week 104	6	728	714 to ≤ 742	547 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

[1] Visit 1 for mMRC (Screening)

Table 6.7: 9 Time windows for safety assessment – physical examination, vital signs

Interval	Label	Visit	planned day	Window [days]	Analysis Window [days]
Screening	Baseline	1	-28 to -1	1	≤ 28
Observational period	Week 52	5	364	350 to ≤ 378	29 to ≤ 546
Observational period	Week 104	6	728	714 to ≤ 742	547 to ≤ 910
Observational period	Week 156	7	1092	1078 to ≤ 1106	≥ 911

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow BI standards [10]. For End-Of-Text tables, the set of summary statistics is: N, Mean, SD, Min, Q1 (lower quartile), Median, Q3 (upper quartile) and Max. In descriptive statistics tables, all statistical parameters will be rounded to one additional digit than the raw individual value.

Tabulations of frequencies for categorical and ordinal data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). The category missing will be displayed only if there are actually missing values. Percentages will be rounded to one decimal place.

Subject sets for the planned analyses are displayed in Table 6.3: 2. Subject data listings (SDLs) will be based on the Observed subjects set.

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = Days / 7
- Months = (Days * 12) / 365.25
- Years = Days / 365.25

[redacted]

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be presented, using both the OBS and PPSBM subject analysis sets, for the following demographic and baseline characteristics, by diagnosis group and for all COPD GOLD groups combined (GOLD 1-3). A1ATD group will be presented separately. See Section 6.7 for definition of baseline measures.

Subjects who have not prematurely discontinued the study should be displayed as “Still in study”. Subjects who completed week 104 and didn’t consent for the 3rd year expansion of the observational period, they will be displayed as “Completers”.

Demographic data: Sex, ethnicity, race, age (years), age (categories), height [cm], weight [kg] and BMI [kg/m^2].

Disease characteristics:

- Smoking history in pack years
- Subgroups defined in Section 6.3
- Medical history for COPD (by type of medical disorder)
- Symptom questionnaires: defined in Section 5.3.4

- Spirometry: parameters listed in Section 5.3.1.1
- Body plethysmography: parameters listed in Section 5.3.1.2
- DLCO: parameters listed in Section 5.3.1.3
- SpO2 [%]
- BODE index
- 6 minute walk test: parameters listed in Section 5.3.7.3
- Soluble biomarkers: parameters listed in Section 5.3.2
- [redacted] biomarkers:
    - Qualitative and Quantitative CT: [redacted]

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive analysis is planned for this section of the report, using the PPSBM subject analysis set.

Concomitant medication taken at baseline or during the observation period will be summarised by World Health Organization-Drug Dictionary (WHO-DD) name and preferred term (PT), and presented by subject group.

Previous concomitant medication, i.e. those taken and stopped prior to entering the observation period, will be listed only.

Baseline conditions / concomitant diagnoses will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and PT, and presented by diagnosis group.

All data will be coded using the most recent versions of WHO-DD and MedDRA dictionaries.

7.3 TREATMENT COMPLIANCE

Not applicable.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis

Primary analysis will be performed on per protocol set – biomarker subjects (PPSBM).

Absolute change in lung density decline based on PD15 adjusted for lung volume (ALD) [g/L/year] (up to week 156)

The change from baseline over time for PD15 adjusted for lung volume (ALD) will be evaluated with a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM) approach with the fixed, categorical effects of subject groups (SG) at each visit. Visit (weeks) will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The statistical model will be as follows:

$$y_{ijk} = \tau_{jk} + e_{ik} \ , e_{ik} \overset{iid}{\sim} N(0, \sigma^2)$$

y_{ijk}= change from baseline for ALD for subject i in subject-group (SG) j at visit k, k = 5, 6, 7

τ_{jk}= the fixed effect subject-group (SG) j at visit k, j=0,…,4

The subject-group indicator is defined as:

$$SG = \begin{cases} 0, & \text{Ex} - \text{smoking control (reference category)} \\ 1, & \text{COPD GOLD 1} \\ 2, & \text{COPD GOLD 2} \\ 3, & \text{COPD GOLD 3} \\ 4, & \text{COPD} + \text{A1ATD} \end{cases}$$

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided α = 0.05 (two-sided 95% confidence intervals).

[redacted]

SAS procedure PROC MIXED is implemented for this analysis. SAS code can be found in Section 9.5.1.

Annual rate of lung function decline based on FEV1 [L/year] (up to week 156)

The continuous outcome measure FEV1 [L] will be analysed by performing a restricted maximum likelihood (REML) based approach using a random slope and intercept model. The analysis will include the fixed, categorical effect of subject-group indicator (SG, as specified above), and the fixed continuous effects of 'time' as well as the SG-by-time interactions. Random effects will be included for patient response for both time and intercept.

The statistical model will be as follows:

$$y_{ijk} = (\alpha + a_i + \tau_j) + (\gamma + g_i + \varphi_j)t_{ik} + e_{ik} \ ,$$

$$(a_i, g_i) \sim N_2(\mathbf{0}, \boldsymbol{\Sigma}), e_{ik} \overset{iid}{\sim} N(0, \sigma^2)$$

y_{ijk} = response variable (FEV1 [L]) for subject i in at visit k belonging to SG j,
α = mean patient intercept
a_i = random intercept effect for subject i, i=1,2,…
τ_j= intercept coefficient of the effect of subject-group j, j=0, 1, 2, 3, 4
γ = mean patient slope
g_i= random slope effect for subject i
φ_j= slope coefficient of the effect of SG j
t_{ik}= time of measurement k for subject i, k= 1, 2,… 7
e_{ik} = the random error associated with the kth visit of the ith subject. Errors are independent and normally distributed with mean 0 and variance σ^2, and uncorrelated with a_i and g_i.
$\boldsymbol{\Sigma}$= a 2x2 unstructured covariance matrix

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided α = 0.05 (two-sided 95% confidence intervals).The primary subject-group comparison of slopes will be assessed through the SG-by time interaction coefficient.

[redacted]

[redacted]

SAS procedure PROC MIXED is implemented for this analysis. SAS code can be found in Section 9.5.2.

Number of exacerbations during study (up to week 156)

This endpoint will be summarized descriptively by the following categories: 0 vs. 1 vs. ≥2.

Duration of exacerbations during study [days] (up to week 156)

This endpoint will be calculated by the sum of episodes during the study and will be summarized descriptively. Duration of exacerbations will be summarized for subjects with at least one exacerbation.

Occurrence of an at least moderate exacerbation during study (up to week 156)

This endpoint will be summarized by the number of patients with an at least moderate exacerbation during study falling into the following categories 0 vs. 1 vs. ≥2.

Occurrence of a severe exacerbation during study (up to week 156)

This endpoint will be summarized by the number of patients with a severe exacerbation during study falling into the following categories 0 vs. 1 vs. ≥2.

Definitions of severity of exacerbations can be found in Section 5.7.1.1 of the CSP.

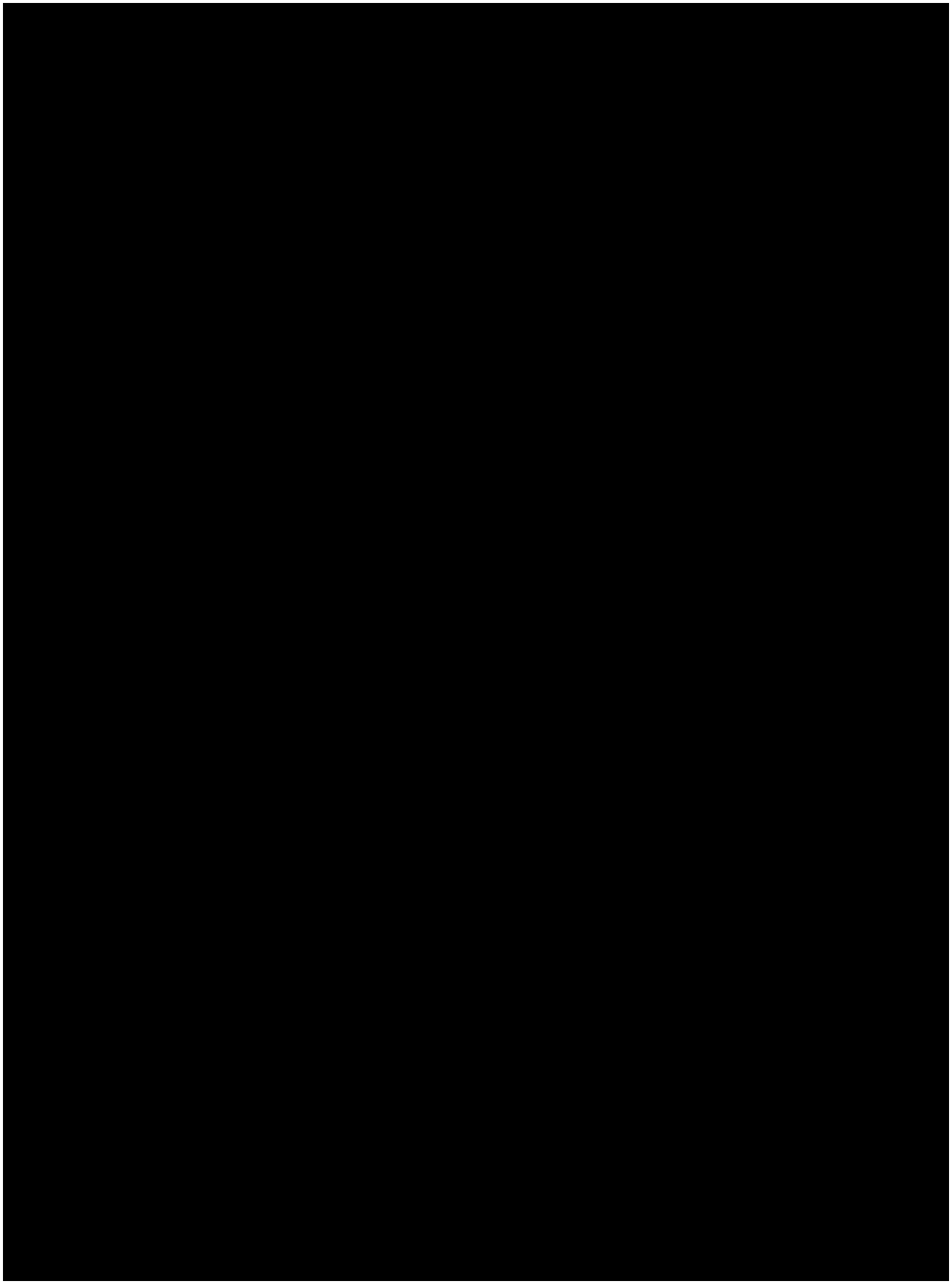
7.5 SECONDARY ENDPOINT(S)

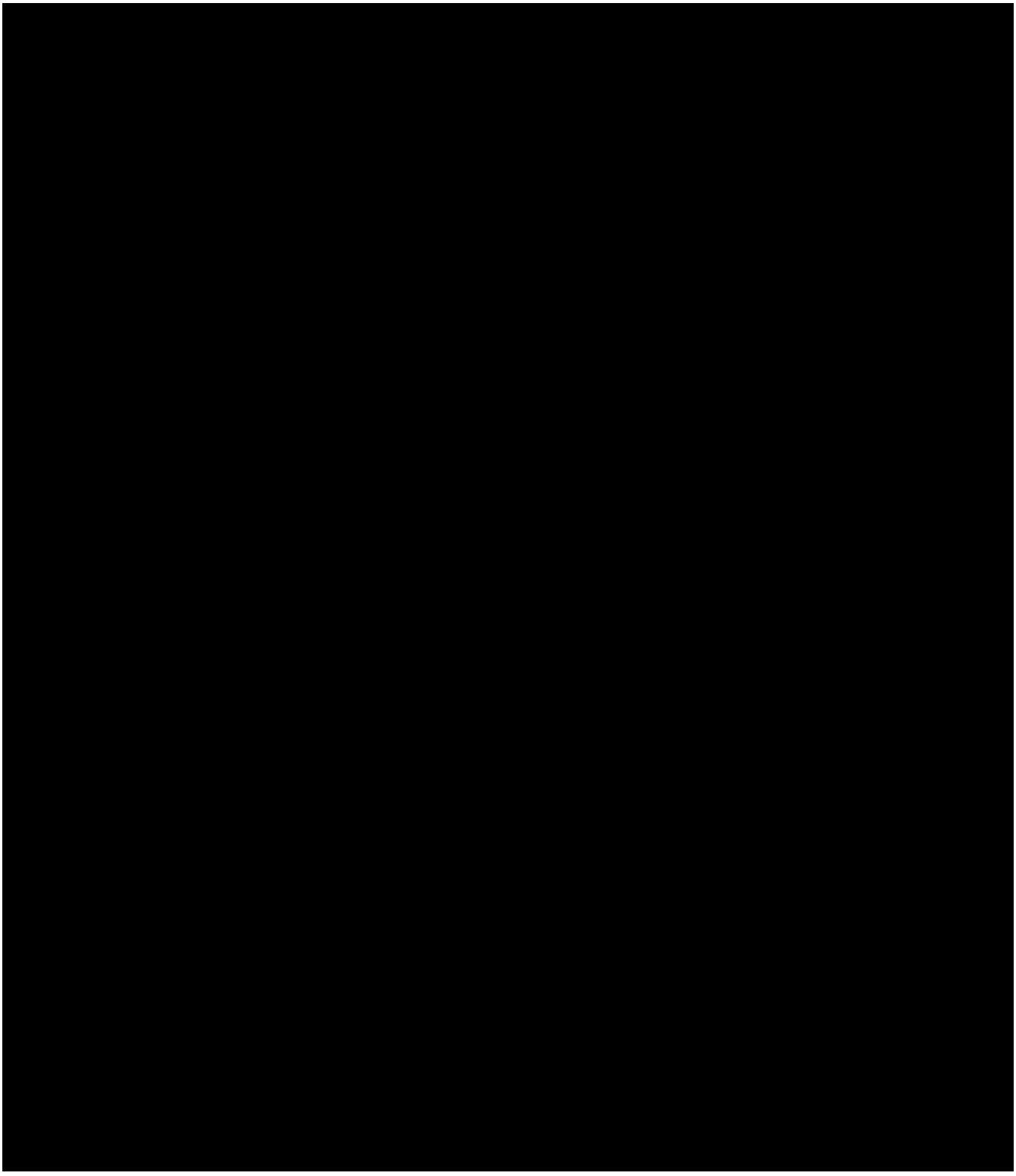
7.5.1 Key secondary endpoint(s)

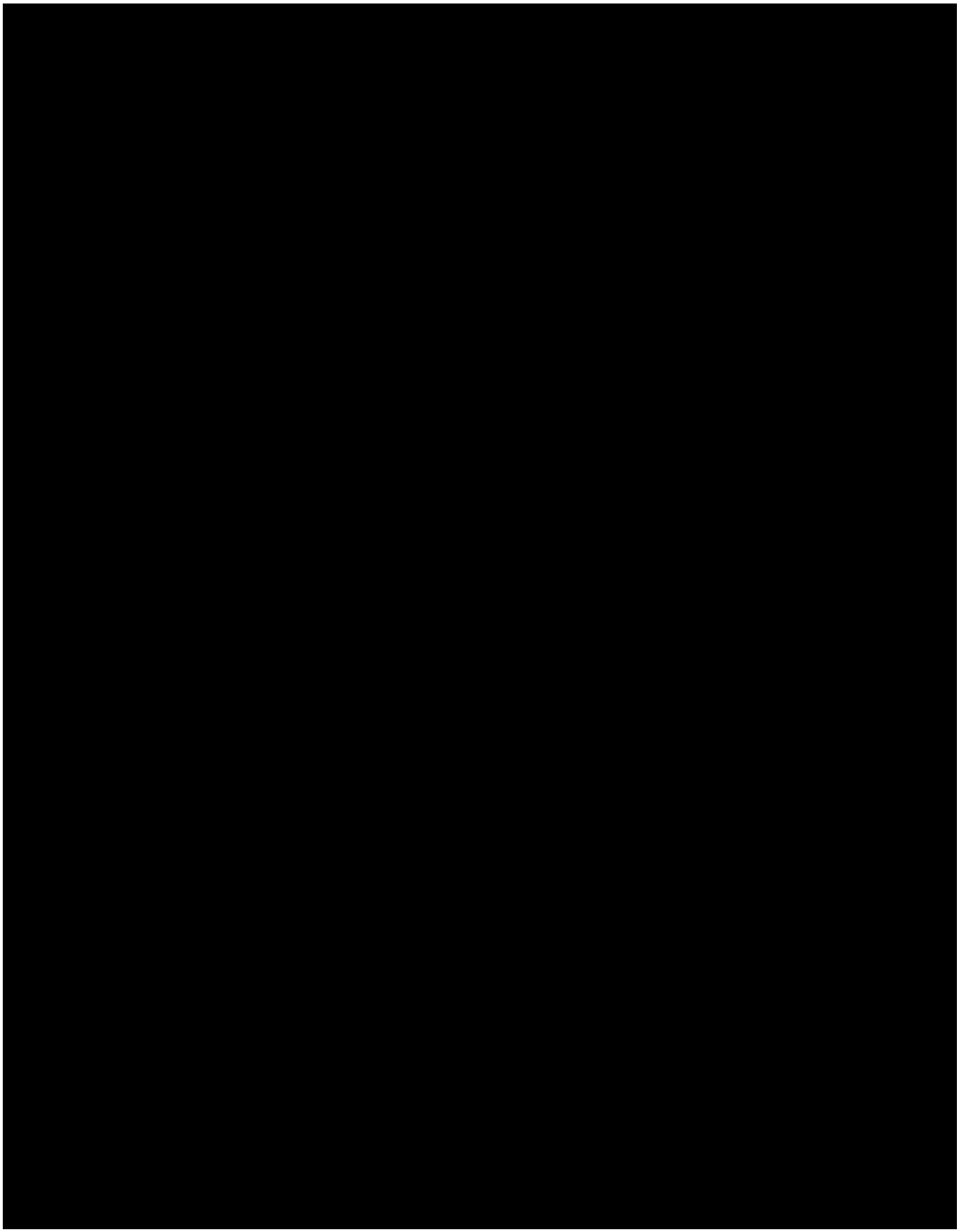
This section is not applicable as no key secondary assessment has been specified in the study.

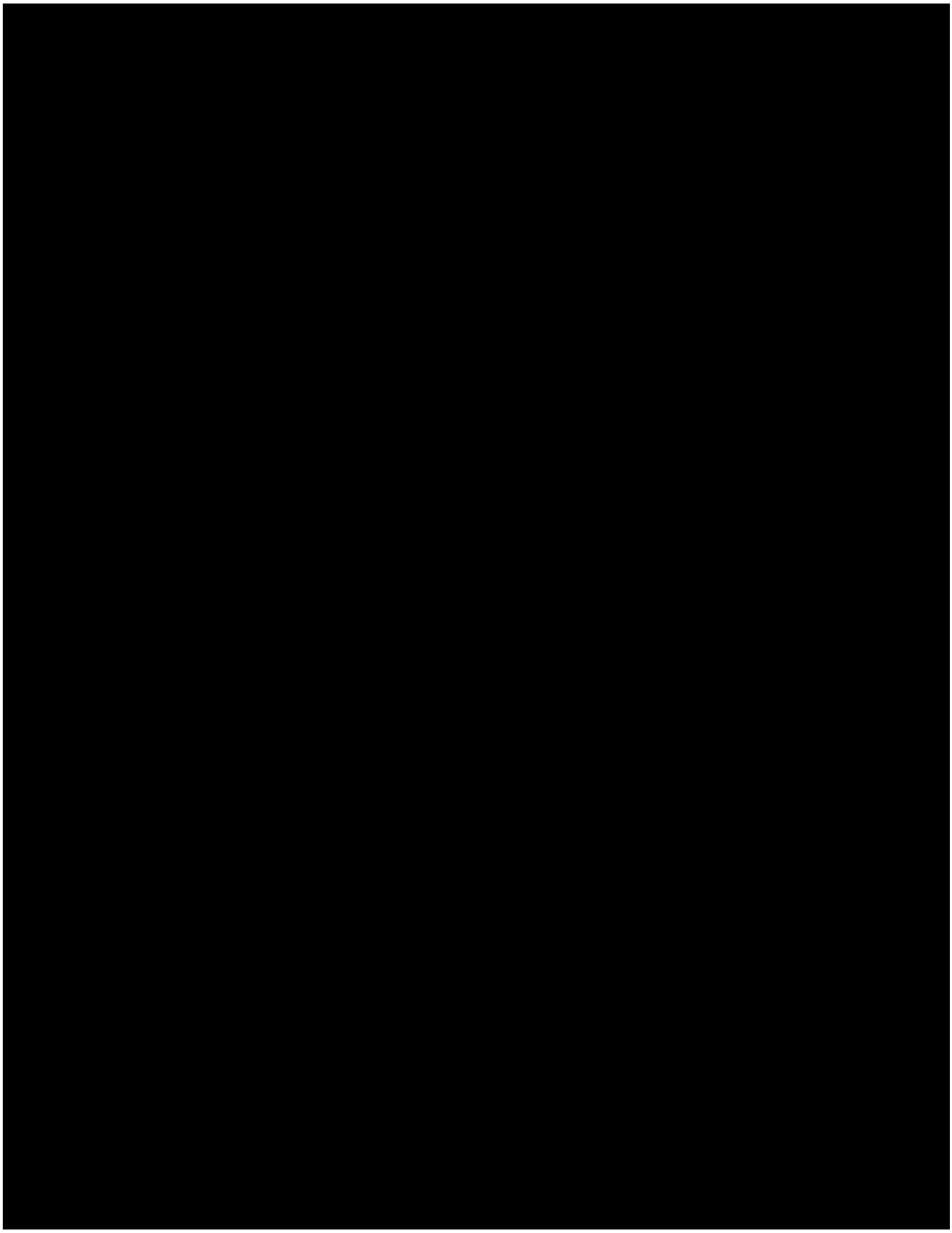
7.5.2 (Other) secondary endpoint(s)

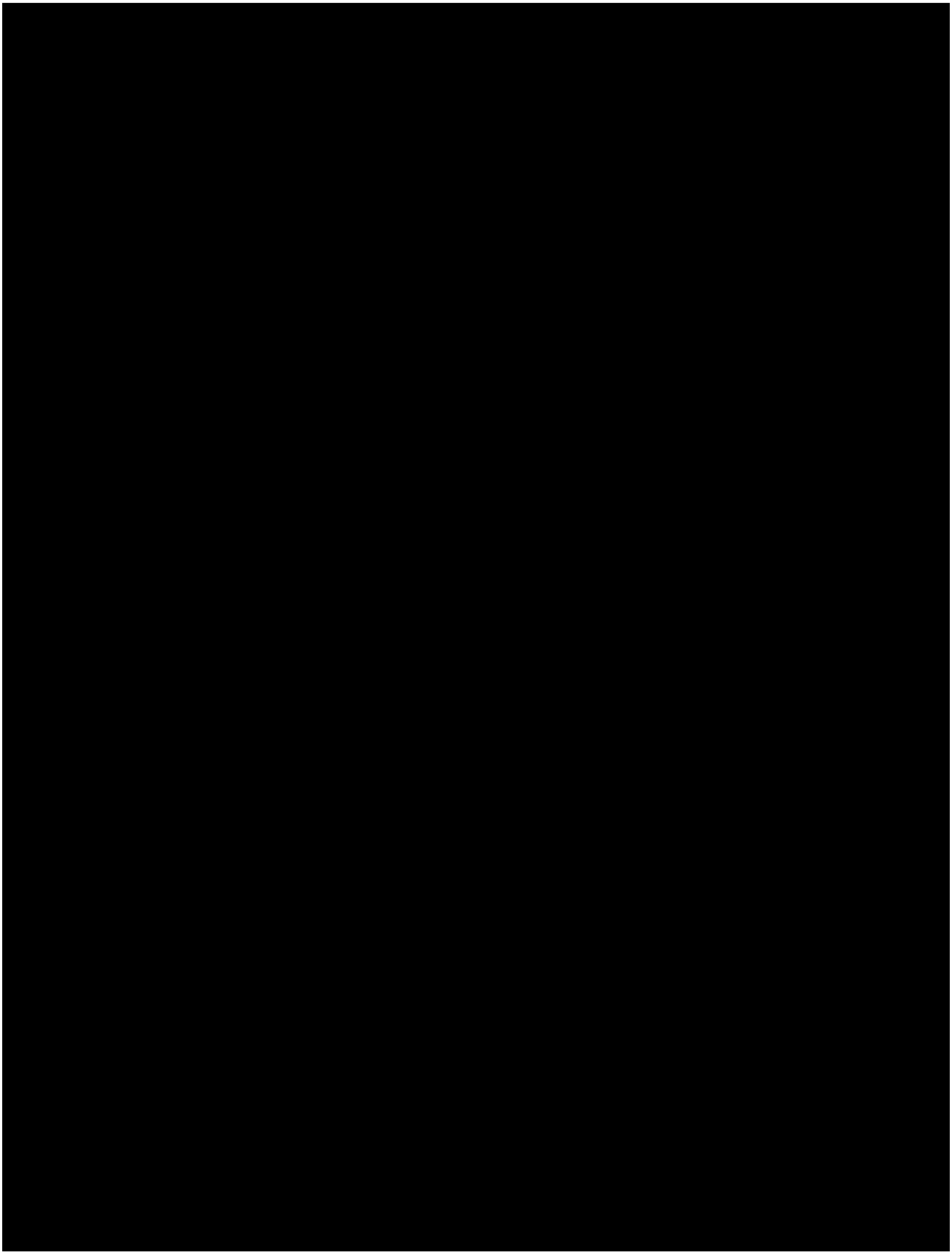
This section is not applicable as no secondary assessment has been specified in the study.











7.7 EXTENT OF EXPOSURE

Not applicable.

7.8 SAFETY ANALYSIS

If any AEs/SAEs are reported for screening failures, these will be summarised in the AE listing "Adverse event overall summary" and described in the Clinical Study Report (CSR) if considered related to the screening procedures.

7.8.1 Adverse events (procedure related)

Only procedure related AEs are recorded and analyses will be performed on the OBS subjects.

These events will be coded using the most recent version of MedDRA.

The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not the number of AEs.

For analysis, multiple AE occurrence data on the electronic case report form (eCRF) will be collapsed into one event provided that all of the following applies:

- All AE attributes are identical
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)

For further details on summarization of AE data, please refer to Analysis and Presentation of AE data from clinical trials ' [14] and "Handling of missing and incomplete AE dates" [7].

Other significant AEs will be reported and summarized according to ICH E3 [16] criterion. Thus, AEs classified as 'other significant' will include those non-serious adverse events with:

(i) 'action taken = discontinued from study', or

(ii) marked hematological and other lab abnormalities, or lead to significant concomitant therapy as identified by the Clinical Monitor / Investigator at an MQRM or a RPM.

An overall summary of adverse events will be presented by subject group.

The frequency of subjects with adverse events will be summarized by subject group, primary SOC and PT. Separate tables will be provided for subjects with serious adverse events and with other significant adverse events.

The SOCs will be sorted according to the standard sort order specified by the European Medicines Agency (EMA), PTs within SOC will be sorted by descending relative frequency.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs (procedure related) occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by primary SOC and PT. The frequency of subjects with SAEs will also be summarised.

7.8.2 Laboratory data

The analyses of laboratory data are descriptive in nature and are based on BI standards [15], where the process of standardisation and normalisation as well as standard analyses for safety laboratory data is described. The OBS will be used for this analysis. Clinically relevant abnormal values or changes in laboratory test results will be recorded as adverse event (if procedure related) or baseline condition in the eCRF.

7.8.3 Vital signs

Descriptive statistics by subject group over time including change from baseline will be performed for vital signs (blood pressure and pulse rate). The OBS will be used for this analysis. Clinically relevant changes in vital signs that are recorded as an AE in the eCRF will be analysed as planned in Section 7.8.1.

7.8.4 ECG

A standard 12-lead ECG is performed at screening, 52 weeks, 104 weeks and 156 weeks. The OBS will be used for this analysis. Any clinically relevant findings from this examination are recorded under baseline conditions or adverse events (if procedure related) in the eCRF. No separate tables/listings are planned for the report.

7.8.5 Others

A physical examination (body weight, body height, BMI) is performed at screening, 52 weeks, 104 weeks and 156 weeks. The OBS will be used for this analysis. Descriptive statistics for weight and/or BMI by subject group over time including change from baseline will be presented.

7.9 MEDICAL EVENTS OF SPECIAL INTEREST (MESIS)

Specific disorders related to the underlying COPD disease as defined in the CSP, Section 5.7, will be collected during the study. MESI are analysed per AE standards based on PPSBM subjects. The frequencies of these MESIs will be summarised by disorder and intensity following the same order as in the eCRF. A separate listing by subject group and disorder will be created including additional information of start/end date, outcome, provided therapy, and intensity of the event.

Further parameters relevant to exacerbations (see Section 5.3.6) will be summarized descriptively per subject group.

7.10 OTHER ASSESSMENTS

Pulse oximetry, BODE index and 6 minute walk test will be analysed descriptively.

7.11 ANALYSIS OF COVID-19 IMPACT

There is currently an outbreak of respiratory disease, COVID-19 worldwide which has impacted the conduct of this trial. This public health emergency has raised more difficulties for patients to meet protocol-specified procedures, e.g. adhering to protocol-mandated visits and laboratory/diagnostic testing. Site personnel or trial patients are also under the risk to get infection with COVID-19.

Consequently, there are unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public and individual health control measures. To assess the impact the following analyses are planned:

- Subjects with potentially protocol deviations (PDs) related to COVID-19 in the study will be documented in the Covid log file [c38560938].
- Frequency of the patient with missed relevant visits or early discontinued from study due to COVID-19 and related PDs will be listed and analysed descriptively.
- SARS-CoV-2 infection as well as AEs related to SARS-CoV-2 infection will be listed (if applicable).

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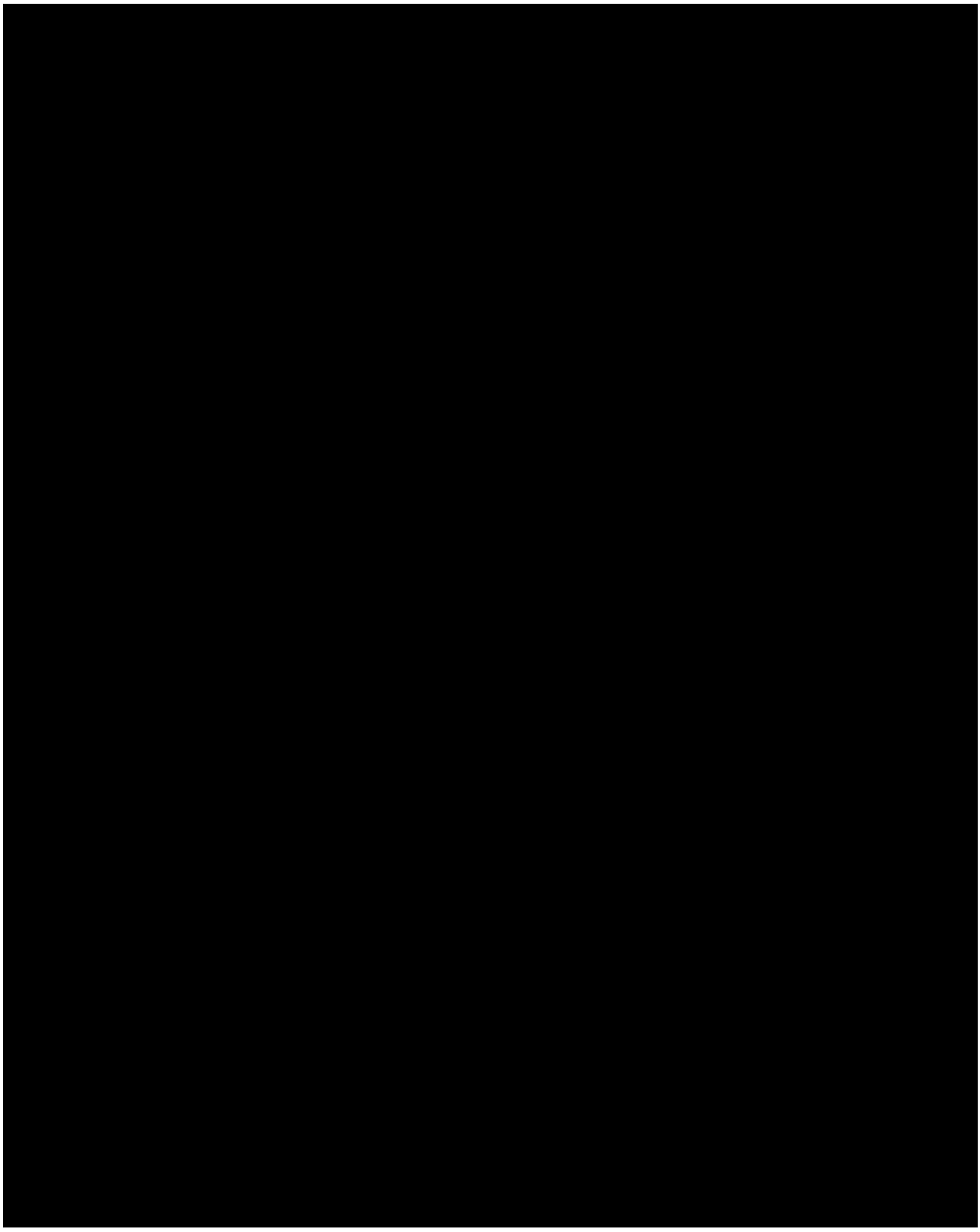
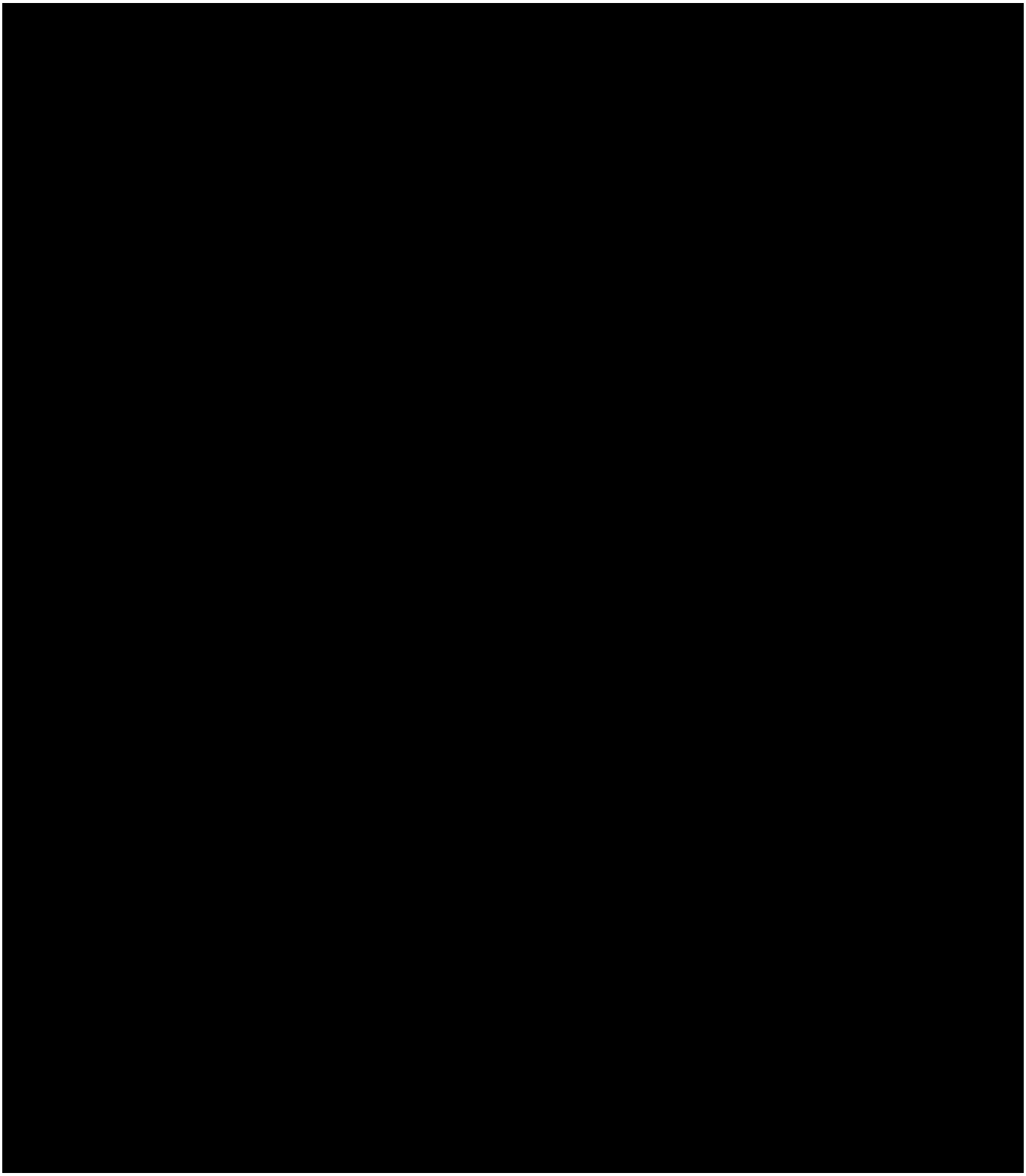
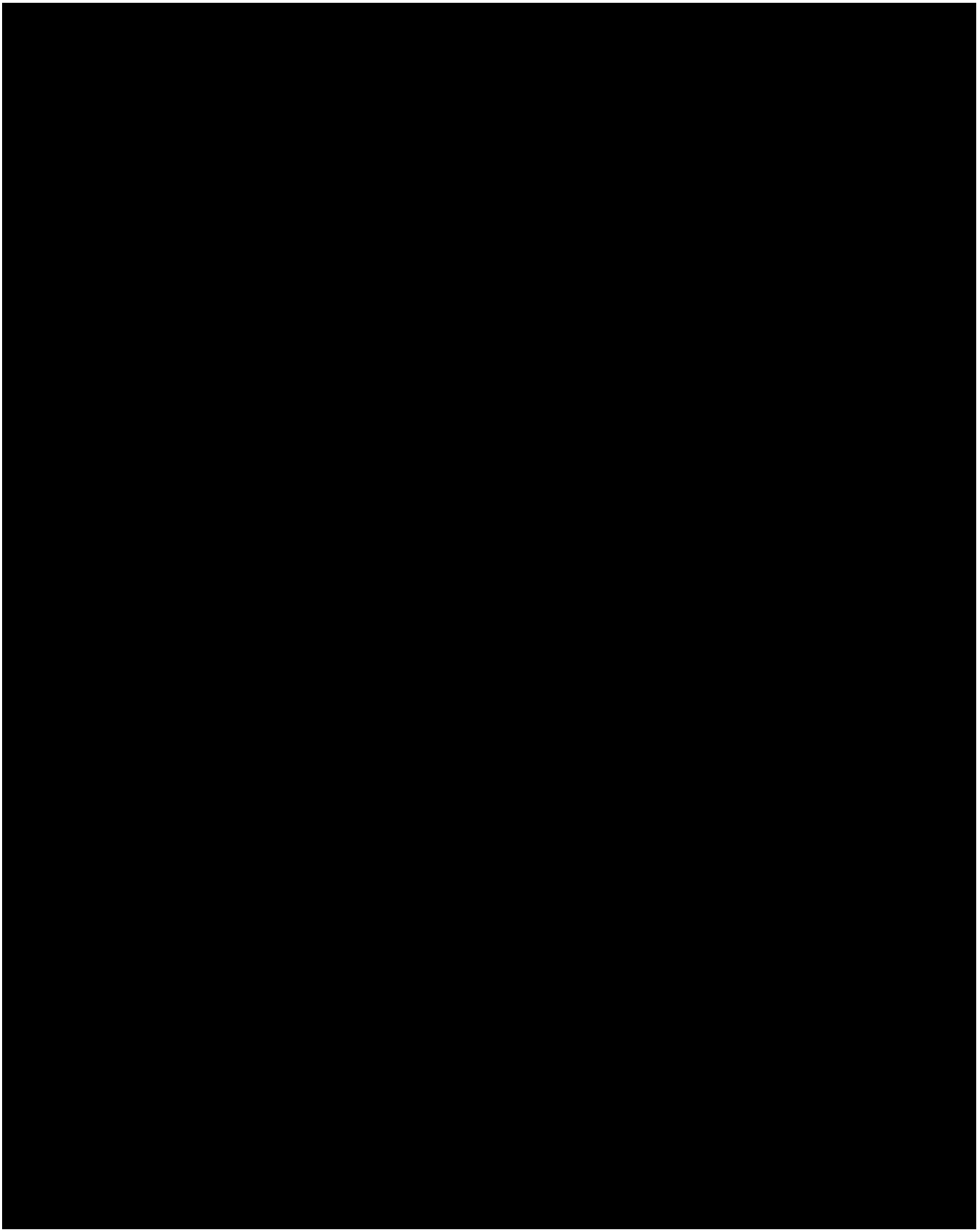
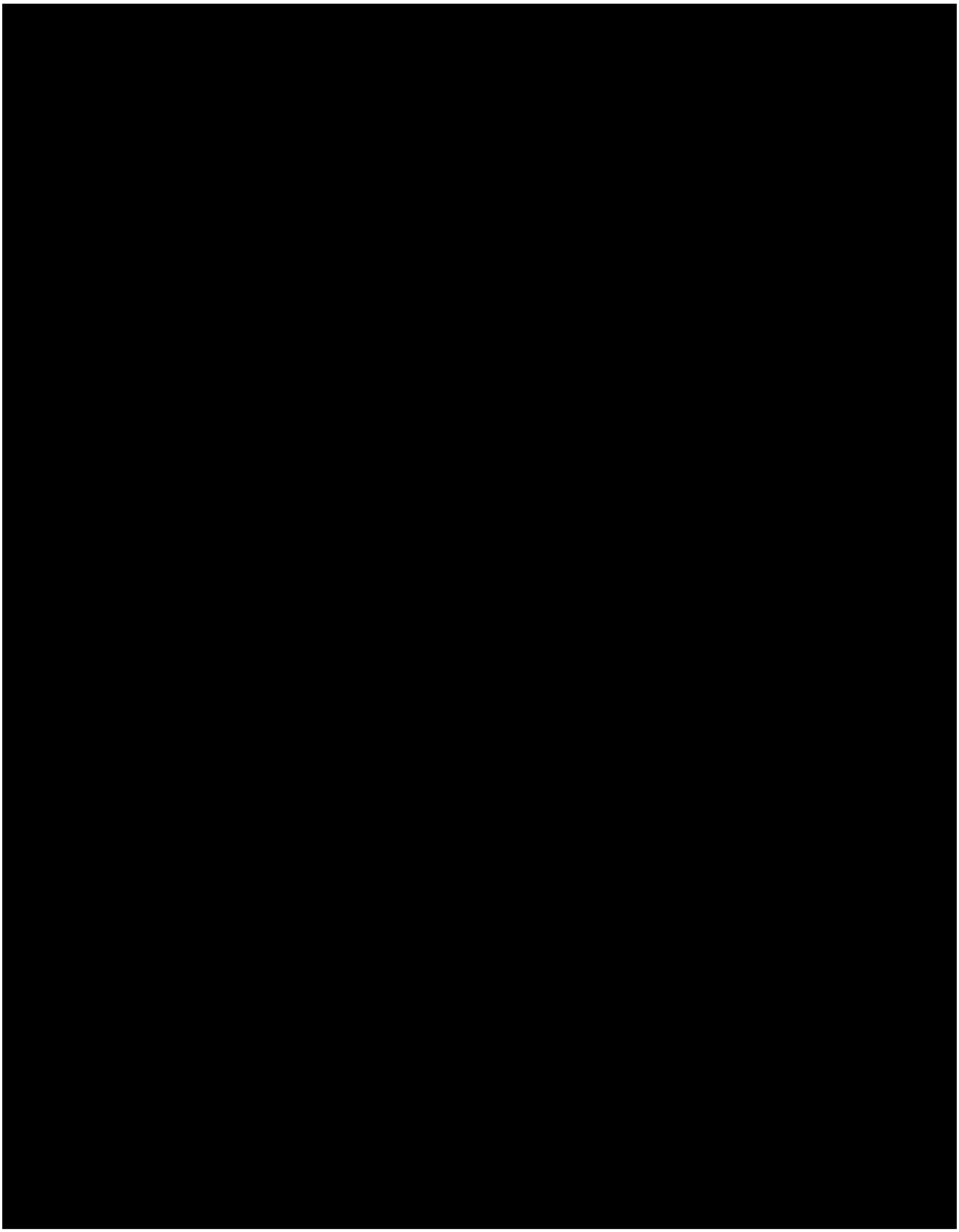
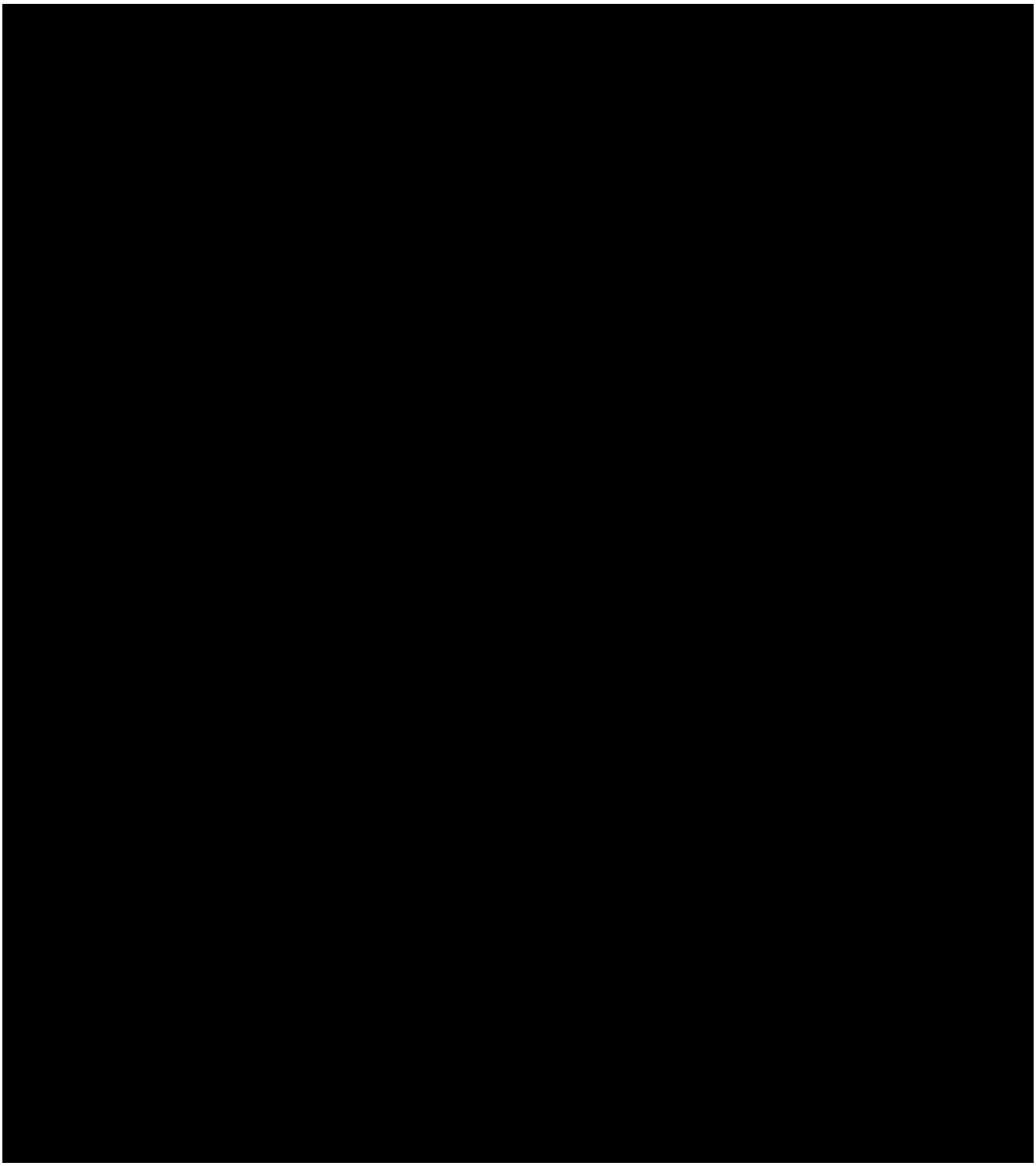
[14]	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; DMS for controlled documents.
[15]	*BI-KMED-BDS-HTG-0042*: " Handling, Display and Analysis of Laboratory Data ", current version, *BI-KMED-BDS-HTG-0042*.
[16]	*CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note for guidance on structure and content of clinical study reports, current version.
[17]	Lowe KE, Regan EA, Anzueto A, et al. COPDGene 2019: redefining the diagnosis of chronic obstructive pulmonary disease. Chronic Obstr Pulm Dis. 2019;6(5):384-399. [R20-2069]

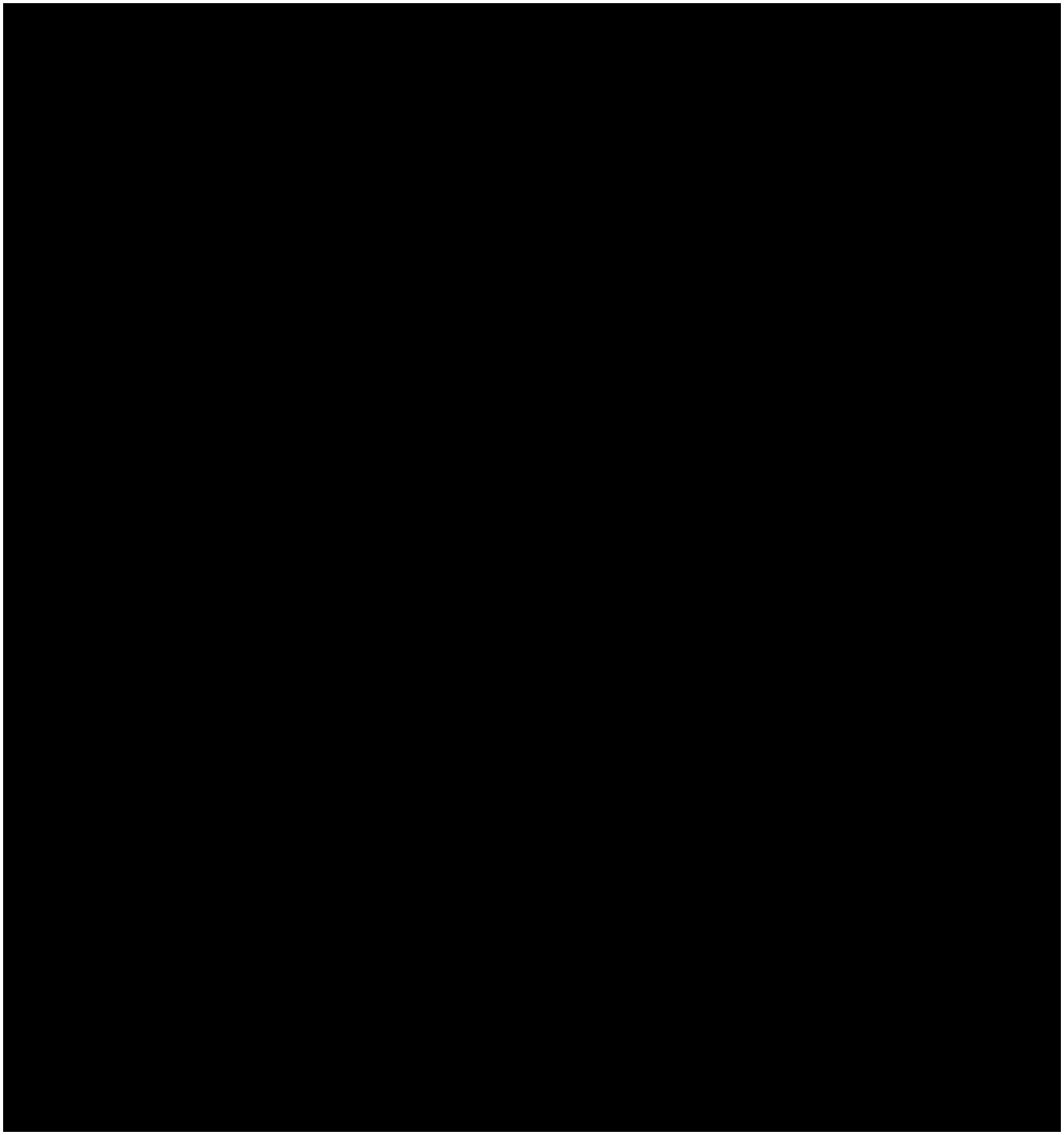


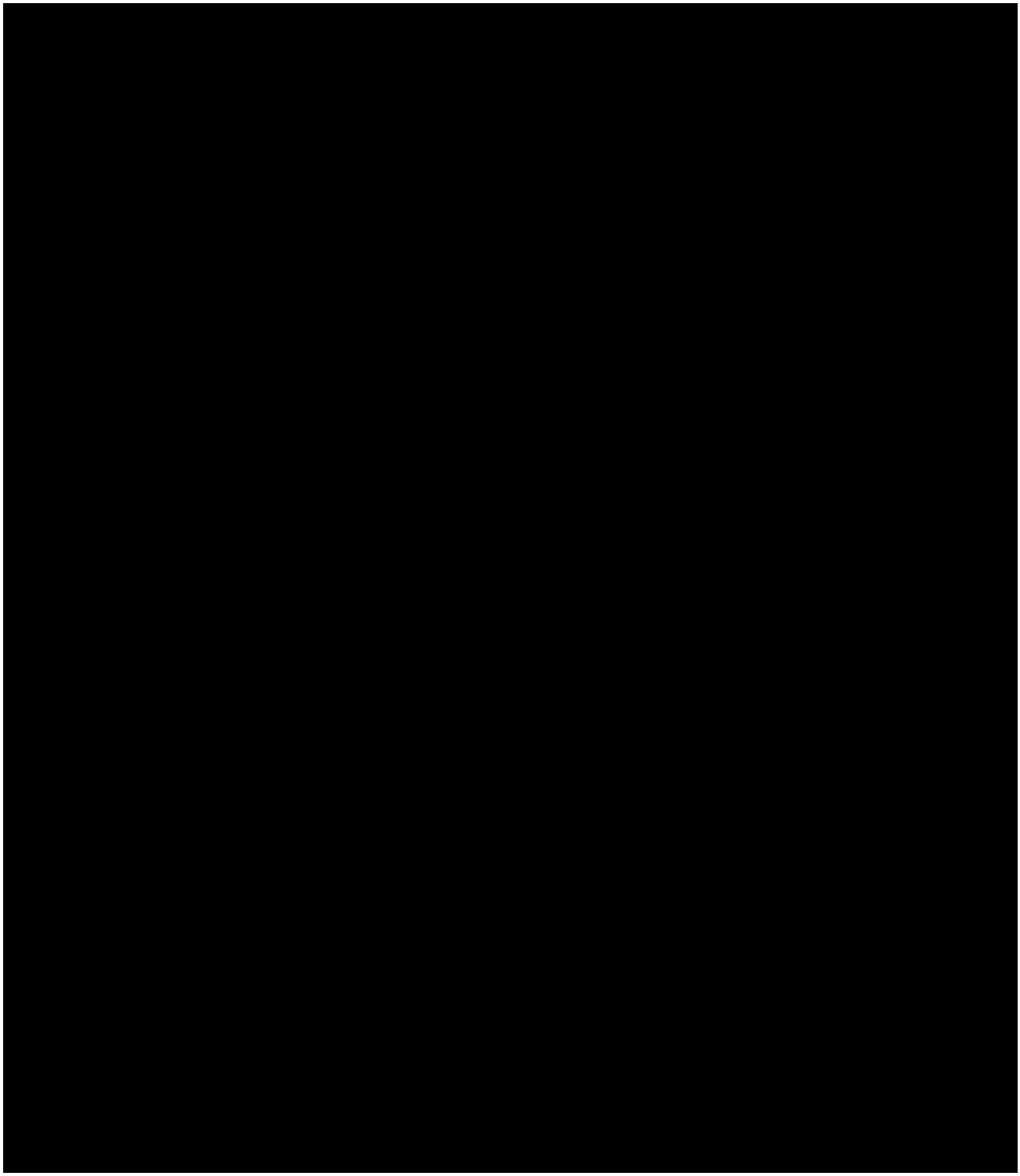


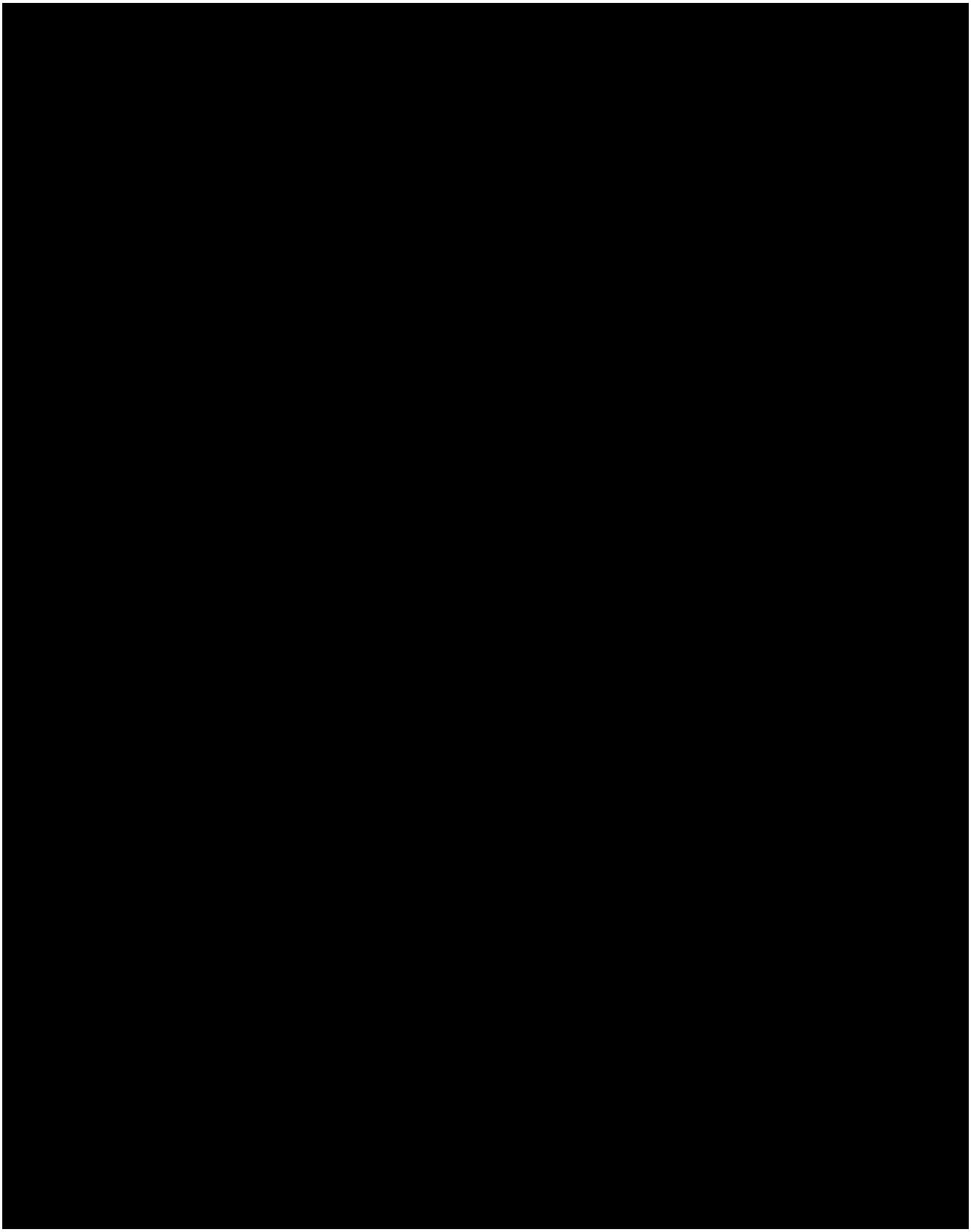












10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial Draft	**14-Dec-15**	[redacted]	N/A	This is the initial TSAP with necessary information for study conduct.
Version 2.0	**29-JUL-19**		All	This is the final TSAP describing the planned analyses that are required for the first interim analysis
Version 3.0	**02-OCT-20**		All	This is the final TSAP describing the planned analyses that are required for the second interim analysis
Version 4.0	**01-APR-2022**		All	This is the final TSAP describing the planned analyses that are required at the end of the study. Minor changes and additions were made for better comprehensibility, specification and adaption to current BI standards throughout all sections.
			Section 5 - 7	Primary endpoints were defined in more detail. FEF_{25-75} has been added to the lung function assessments. The list of soluble biomarkers that were analysed has been finalized. LM1 was removed as parameter for the quantification of lung mass. LM2 was renamed to LM. Medical events of special interest (description of endpoint, analysis) are described in a separate section. Two additional subgroup variables (COPDGene 2019

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
				[redacted] Multivariate analysis as well as descriptive and summary statistics were defined in more detail. A section on the analysis of COVID-19 impact was added. The numbering of the section headings has been adjusted due to the added sections.