STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double-blind, placebo-controlled, parallel-group, Proof-of-Concept (PoC) study to assess the efficacy, safety and tolerability of itepekimab, in participants with non-cystic fibrosis bronchiectasis**
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VERSION HISTORY

This is the original version of the statistical analysis plan (SAP).

This Statistical Analysis Plan (SAP) for study ACT18018 is based on the amended clinical trial protocol 04 dated 20-Jan-2025.

The first participant was randomized on 18-Mar-2024.

1 INTRODUCTION

This statistical analysis plan (SAP) provides a comprehensive and detailed description of statistical strategy and methodology to be used to analyze the data from the randomized, double-blind, placebo-controlled, parallel-group (3 groups), Proof-of-Concept (PoC) itepekimab/SAR440340 ACT18018 study. Major changes to the protocol-planned analyses are described in Section 3.9.

1.1 STUDY DESIGN

This Phase 2 study is a multinational, multicenter, randomized, double-blind, placebo-controlled trial with parallel groups (consisting of 3 groups) aimed at evaluating the efficacy, safety, and tolerability of two different dosing regimens of itepekimab in participants diagnosed with non-cystic fibrosis bronchiectasis (NCFB) who are receiving standard of care therapy, including bronchodilators, inhaled corticosteroidSNTs, mucolytics, and/or maintenance antibiotics.

All eligible patients will receive a subcutaneous administration of itepekimab at a dose of 300 mg every 2 weeks (Q2W), itepekimab 300 mg every 4 weeks (Q4W), or a matching placebo (1:1:1 randomization). Approximately 300 participants will be randomized in this study, and the treatment duration will be a minimum of 24 weeks and a maximum of 52 weeks. Following the treatment period, there will be a 20-week safety follow-up period. The variable treatment duration allows for maximizing data collection for the primary endpoint, which is the annualized rate of moderate or severe pulmonary exacerbations (PEs), in a time-efficient manner. Participants enrolled in the trial will receive treatment for up to a maximum of 52 weeks or until the last participant randomized completes a minimum treatment period of 24 weeks.

The randomization is stratified by geographical region, documented history of chronic obstructive pulmonary disease (COPD) and/or asthma (if asthma is resolved before 18 years of age and has not recurred, it will not be taken into consideration), and whether they are receiving maintenance macrolide antibiotic therapy at the start of the study. To ensure that the proportion of participants with a documented history of COPD and/or asthma does not exceed 20%, the enrollment of participants with a documented history of COPD and/or asthma in each stratification group will be closely monitored and controlled as follows:

- Documented history of either asthma or COPD: up to approximately 20% of participants.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB	• Annualized rate of moderate or severe PEs[a] over the treatment period

Objectives	Endpoints
Secondary	
• Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB	• Time to first moderate or severe PE over the treatment period **[Key secondary endpoint]** • Percentage of participants who are PE free over the treatment period • Annualized rate of severe PEs over the treatment period • Percentage of participants who are severe PE free over the treatment period • Time to first severe PE over the treatment period
• Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in NCFB	• Change From Baseline in Pre- and Post-bronchodilator FEV1 at Week 8 and Week 24
• Evaluate the efficacy of itepekimab compared with placebo on reduction in antibiotic use in NCFB	• Number of days of new and/or added (in participants with maintenance antibiotic use) antibiotic use
• Evaluate the efficacy of itepekimab compared with placebo on HRQoL and health status as assessed by QoL-B, and SGRQ in NCFB	• Change from Baseline in QOL-B Respiratory Symptoms Domain Score in Adult Participants at Week 24 • Change from baseline in SGRQ total score at Week 24 • Percentage of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24
• Evaluate the safety and tolerability of itepekimab in NCFB	• Incidence of TEAEs, AESIs, SAEs, and AEs leading to permanent study treatment discontinuation in the treatment-emergent period
• Evaluate the PK profile of itepekimab in NCFB	• Serum concentrations of itepekimab from baseline to end of study
• Evaluate immunogenicity to itepekimab in NCFB	• Incidence of treatment-emergent anti-itepekimab antibodies (ADA) responses throughout the study
Tertiary/Exploratory	
• Evaluate the effect of itepekimab compared with placebo on biomarkers in NCFB	• Change from baseline at Week 4[b], 24, and EOS in the following: - Blood proteinase 3, cathepsin G, CRP, fibrinogen, IL-6, IL-8, TNF-α, IFN-γ, IL-17A, IL-5, IL-13, IL-33, sST2, TARC, eotaxin-3, IgE, E-selectin, ICAM-1, VCAM-1, and neutrophil elastase - Blood eosinophils, neutrophils, and monocytes • Change from baseline at Week 4, Week 24-32 in the following: - Sputum (optional): IL-5, IL-13, IL-33, TARC, eotaxin-3, IgE, IL-6, IL-8, TNF-α, IL-17A, IFN-γ, eosinophil, neutrophil and macrophage count, neutrophil elastase, proteinase 3, cathepsin G, MMP-8, MMP-9, MUC5B, MUC5AC, and procalcitonin

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Objectives	Endpoints
• Evaluate the efficacy of itepekimab compared with placebo on FEV1 slope in NCFB	• Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4 weeks
• Evaluate the efficacy of itepekimab compared with placebo on healthcare utilization in NCFB	• Annualized number of days of healthcare resource utilization over the treatment period
• To characterize the effects of itepekimab on gene expression and to study genetic factors that may predict itepekimab safety/efficacy	• Pharmacogenomics analysis (optional) • Blood DNA sampling (optional) • Sputum RNA sampling (optional and selected sites only)
• Evaluate the efficacy of itepekimab compared with placebo on HRQoL and health status as assessed by SGRQ, QoL-B, and LCQ in NCFB	• Change from baseline in QoL-B Physical, Role, Emotional, and Social Functioning, Vitality, Health Perceptions and Treatment Burden Domain score in adult participants at Week 24 • Change from baseline in LCQ total score at Week 24
• Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB	• Annualized rate of all exacerbations (as recorded by Investigator) • Annualized rate of all exacerbations leading to prescription with antibiotics • Annualized rate of all exacerbations leading to prescription of antibiotics and/or systemic corticosteroids + meeting footnote a Part A criterion of a moderate exacerbation

Abbreviations: ADA = antidrug antibody; BD = bronchodilator(y); CRP = C-reactive protein; EOS = end of study; FEV1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life; ICAM-1 = intercellular adhesion molecule-1; IFN-γ = Interferon gamma; IgE = Immunoglobuline E; IL = interleukin; L = Liter; MMP = Matrix Metalloproteinase; MUC = mucin; NCFB = Non-cystic fibrosis bronchiectasis; PE = Pulmonary exacerbation; PK = pharmacokinetic(s); QOL-B = Quality-of-Life Questionnaire – Bronchiectasis; SGRQ = St. George's Respiratory Questionnaire; TARC = thymus and activation-regulated chemokine; TEAE = treatment-emergent adverse event; TNF-α = Tumor necrosis factor alpha; VCAM-1 = vascular cell adhesion molecule-1

a All worsening of respiratory symptoms leading to prescription of antibiotics (new, addition or change in) and/or systemic corticosteroids will be captured. Adjudication committee will determine if below criteria for moderate or severe exacerbation are met:

* Moderate PE in this study is defined as:

A) having 3 or more of the following symptoms for at least 48 hours

1. Increased cough
2. Increased sputum volume or change in sputum consistency
3. Increased sputum purulence
4. Increased breathlessness and/or decreased exercise tolerance
5. Fatigue and/or malaise
6. Haemoptysis

AND

B) A physician's decision to prescribe antibiotics (or addition of antibiotic or change in antibiotic).

* Severe PE as described above but resulting in intravenous antibiotics treatment, or hospitalization, or observation for >24 hours in emergency department/urgent care facility, or death.

Note: participants on chronic antibiotic therapy whose only change in therapy is dose or frequency adjustment in response to worsening of respiratory symptoms will not meet the definition of exacerbation.

b TARC, eotaxin-3, and IgE will not be analyzed at Week 4

Other exploratory endpoints including the PGIS, PGIC, EQ-5D-5L, SNOT-22 are described in the Section 3.7.1.4.

1.2.1 Estimands

Primary estimands defined for primary and key secondary efficacy endpoints are summarized in Table 2 and Table 3 below.

More details are provided in Section 3.

Table 2 - Summary of primary estimand for main endpoints

Endpoint	Estimands			
Category (estimand)	**Endpoint**	**Population**	**Intercurrent event(s) (ICEs) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB				
Primary endpoint (primary estimand: treatment policy)	Annualized rate of adjudicated moderate or severe Pulmonary Exacerbations (PEs) over the treatment period	ITT	• **The following ICEs may occur**: a) Early discontinuation of study treatment. b) Taking prohibited medications post randomization. c) Taking study treatment not as randomized (eg, dispensing error). d) Change in background therapy during the treatment period. It is noted that using new antibiotics to treat exacerbations is not considered an ICE as it is a criterion for PE definition, and it does not prevent continued study participation, nor exclude the possibility of additional PE events. The ICEs will be handled using treatment policy strategy as follows: a) Participants who discontinue IMP before their planned treatment duration will be asked and encouraged to return to the clinic for all remaining study visits; all PE events during the planned treatment period (between 24-52 weeks depending on participants' enrollment date) will be included in the analysis irrespective of study treatment adherence; the observation duration (used as offset variable in the analysis model) is equal to the planned treatment duration, except when a participant withdraws early from the study, in which case, the observation duration is from randomization to the last contact	**Below population-level summaries** will be derived using a negative binomial regression: • Estimated annualized rate of moderate or severe PEs and its 2-sided 90% confidence interval (CI) by treatment group. • The event risk ratio (RR) of each itepekimab regimen versus placebo, and the corresponding 2-sided 90% CI and p-value. The primary analysis model will include the total number of moderate or severe PE events that occur during the planned treatment period as the response variable, with treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), Pseudomonas aeruginosa (PA) chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), number of exacerbations in the prior year and maintenance macrolide antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. Log-transformed observation duration will be the offset variable. **Missing data handling for the primary estimand**: Although using the treatment policy strategy generally reduces the amount of missing data as compared to other strategies,

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) (ICEs) handling strategy**	**Population-level summary (Analysis and missing data handling)**
			date of the participant within the planned treatment duration. b) For participants taking prohibited medications all the data observed during their planned treatment period (as defined above) will be included in the analyses; the observation duration is defined in the same way as in the ICE a). c) If a participant takes study treatment not as randomized for any reason, the participant will be included in treatment group as initially randomized. d) For participants with change in background therapy, all the data observed during their planned treatment period (as defined above) will be included in the analyses; the observation duration is defined in the same way as in the ICE a).	missing data may nevertheless occur as a result of participants withdrawing from the study. To account for a shorter duration of follow-up of participants who withdraw from the study prior to their planned treatment duration, the primary analysis negative binomial model will include an offset term for the logarithm of observation duration. No further imputation will be performed for the unobserved PE events that may happen after study discontinuation and up to end of the planned treatment duration. **Sensitivity estimators**: Sensitivity analyses focusing on the assumptions about missing data will be performed to assess the robustness of the conclusion of the primary analysis using tipping point analysis and a pattern mixture model by multiple imputation. Details can be found in Section 3.1.3.
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB				
Key secondary endpoint (primary estimand: treatment policy)	Time to first moderate or severe PE over the treatment period	ITT	• The 4 ICEs specified above will be handled in the same way using treatment policy strategy. Operationally, regardless of treatment discontinuation, all participants will be followed-up according to the study procedures up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. That is, PE events and related data would be collected and reported over the entire planned treatment period for all study participants even if some participants may have discontinued the study treatment. Analytically, the time to first moderate or severe PE over the planned treatment period analysis is performed regardless of the occurrence of the ICEs and the timing of the ICE.	**Below population-level summaries** will be derived using a Cox regression model. • The hazard ratio of each itepekimab regimen versus placebo, and the corresponding 2-sided 90% CI and p-value. The model will include the time to the first event as the dependent variable, with treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), number of exacerbations in the prior year and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. The Kaplan-Meier method will be used to derive the probabilities that a

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) handling strategy	Population-level summary (Analysis and missing data handling)
			For participants without any PE events, time will be considered as censored at the end of their observation period, as defined in the primary endpoint primary estimand.	participant would experience an event up to specific time points for each treatment group. **Missing data handling**: For participants who discontinued the study early and without any PE events, time will be considered as censored at the end of their observation period. No imputation will be performed for the unobserved PE events that may happen after study discontinuation and up to end of the planned treatment duration.

Table 3 - Summary of primary estimand for other secondary endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) handling strategy	Population-level summary (Analysis and missing data handling)
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB				
Other secondary endpoints (Treatment policy)	Percentage of participants who are PE free over the treatment period	ITT	The ICEs, their handling, and the missing data handlantioing procedures are defined/described in the same way as those for the primary endpoint of annualized rate of moderate or severe PEs over the treatment period.	The percentage of participants who are PE free over the treatment period will be analyzed using a logistic regression model. The model will include treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (yes or No or Indeterminate), documented history of COPD and/or asthma (yes or no) strata, number of exacerbations in the prior year, and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. The odds ratio of being a responder comparing each itepekimab dose arm to placebo will be provided along with the corresponding 90% CI and p-value.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) (ICEs) handling strategy**	**Population-level summary (Analysis and missing data handling)**
				Missing data handling: No imputation will be performed for the unobserved PE events that may happen after study discontinuation and up to end of the planned treatment duration.
Other secondary endpoints (Treatment policy)	Annualized rate of severe PEs over the treatment period	ITT	The ICEs, their handling, and the missing data handling procedures are defined/described in the same way as those for the primary endpoint of annualized rate of moderate or severe PEs over the treatment period.	Same as those for the primary endpoint of annualized rate of moderate or severe PEs over the treatment period.
Other secondary endpoints (Treatment policy)	Percentage of participants who are severe PE free over the treatment period	ITT	The ICEs, their handling, and the missing data handling procedures are defined/described in the same way as those for the secondary endpoint of percentage of participants who are PE free over the treatment period.	Same as those for the secondary endpoint of percentage of participants who are PE free over the treatment period.
Other secondary endpoints (Treatment policy)	Time to first severe PE over the treatment period	ITT	The ICEs, their handling, and the missing data handling procedures are defined/described in the same way as those for the key secondary endpoint of time to first PE over the treatment period.	Same as those for the key secondary endpoint of time to first PE over the treatment period.
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in NCFB				
Other secondary endpoints: (Treatment policy)	Change From Baseline in Pre-bronchodilator FEV1 at Week 8 Change From Baseline in Pre-bronchodilator FEV1 at Week 24	ITT	The ICEs will be handled using **treatment policy strategy** as follows: a) Early discontinuation of study treatment for any reason before completing the planned treatment period: All pre- and post- BD FEV1 data collected during the planned treatment period will be included in the analysis irrespective of treatment adherence. b) Taking prohibited medications during the planned treatment period: All pre- and post- BD FEV1 data will be included in the analysis irrespective of use of prohibited medications. c) If a participant takes study treatment not as randomized for	The change from baseline for Pre- and Post-bronchodilator FEV1 endpoints will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline values up through Week 24 as response variables. The covariates to be included are treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) handling strategy	Population-level summary (Analysis and missing data handling)
	Change From Baseline in Post-bronchodilator FEV1 at Week 8 Change From Baseline in Post-bronchodilator FEV1 at Week 24		any reason, the participant will be included in treatment group as initially randomized (ITT principle). d) For participants with change in background therapy, all the data observed during the planned treatment period will be included in the analyses.	antibiotics) at baseline, visit, treatment by-visit interaction, the corresponding baseline value and baseline-by-visit interaction as covariates. Sex and height will be included as covariates. An unstructured correlation matrix will be used to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline will be derived from the mixed-effect model. Descriptive statistics including number of participants, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 90% CI and the p-value will be derived from the MMRM model for comparison of each itepekimab dose arm against placebo. **Missing data handling**: Participants that withdraw from the study prior to their planned treatment duration will have missing data between the last contact date to the end of the planned treatment period; in addition, some intermittently missing data are expected because of occasionally missing a study visit while continuing with the randomized treatment. For both types of missing data, the primary analysis MMRM model assumes that missing data are MAR, that is, that participants with missing data would have efficacy outcomes like those in similar participants in their treatment group who continue their randomized treatment through the time point at which data are missing, up to the end of their planned treatment period.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) (ICEs) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on reduction in acute antibiotic use in NCFB				
Other secondary endpoints: (Treatment policy)	Number of days of new and/or added (in participants with maintenance antibiotic use) acute antibiotic use to treat exacerbation	ITT	The ICEs will be handled using **treatment policy strategy** as follows: a) Early discontinuation of study treatment for any reason before completing the planned treatment period: All antibiotic medication data during the planned treatment period will be included in the analysis irrespective of treatment adherence. The observation duration is defined in the same way as those for the primary endpoint of annualized rate of moderate or severe PEs over the treatment period. b) Taking prohibited medications during the planned treatment period: All antibiotic medication data will be included in the analysis irrespective of use of prohibited medications. The observation duration is defined in the same way as those for the primary endpoint of annualized rate of moderate or severe PEs over the treatment period. c) If a participant takes study treatment not as randomized for any reason, the participant will be included in treatment group as initially randomized (ITT principle). d) For participants with change in background therapy, antibiotic medication data observed during the planned treatment period will be included in the analyses. The observation duration is defined in the same way as those for the primary endpoint of annualized rate of moderate or severe PEs over the treatment period.	The endpoint will be analyzed using the ANCOVA model. To account for the potential different treatment duration by study design, the response variable will be the % of days of new and/or added acute antibiotics used to treat exacerbation with the denominator as the treatment duration in days. The covariates to be included are treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline. Descriptive statistics including number of participants, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 90% CI and the p-value will be derived from the ANCOVA model for comparison of each itepekimab dose arm against placebo.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) (ICEs) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on HRQoL and health status as assessed by QoL-B, and SGRQ in NCFB	Change from Baseline in QOL-B Respiratory Symptoms Domain Score in Adult Participants at Week 24	ITT	The ICEs, their handling, and the missing data handling procedures are defined/described in the same way as those for the secondary endpoint of change from baseline in Pre- and Post-bronchodilator FEV1 at Week 24	The change from baseline for these continuous endpoints (QOL-B Respiratory Symptoms Domain Score in Adult Participants at Week 24 and SGRQ total score at Week 24) will be analyzed using the same approach as the secondary endpoint of change from baseline in Pre- and Post-bronchodilator FEV1 at Week 24, except for that sex and height will not be included as covariates. The same mixed-effect model with repeated measures (MMRM) will be applied except that Sex and height will be not included as covariates.
Other secondary endpoints: (Treatment policy)	Change from baseline in SGRQ total score at Week 24	ITT		**Missing data handling:** No imputation will be performed on missing scores
Other secondary endpoints: (Treatment policy)	Percentage of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24	ITT	The ICEs, their handling, and the missing data handling procedures are defined/described in the same way as those for the secondary endpoint of Percentage of participants who are PE free over the treatment period.	The percentage of participants with SGRQ improvement ≥4 points at Week 24, regardless of if the participant is still on treatment or not, will be analyzed using a logistic regression model. The model will include treatment group, age, region, baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, and baseline SGRQ total score as covariates. The odds ratio of being a responder comparing each itepekimab regimen to placebo will be provided along with the corresponding 90% CI and p-value. **Missing data handling:** Participants with SGRQ improvement <4points or missing SGRQ total score at Week 24 will be considered as non-responders.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 4 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Intent-to-treat (ITT) / Efficacy	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Exposed/Safety	All randomized participants who have taken at least 1 dose of study intervention, regardless of the amount of intervention administered. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All participants from the exposed population with at least one post-baseline PK result with adequate documentation of dosing and sampling dates and times. Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they actually received.
ADA	All participants from the exposed population treated with itepekimab with at least one post-baseline ADA result (positive, negative or inconclusive). Participants will be analyzed according to the intervention they actually received.

Abbreviations: ADA = anti-drug-antibody; ICF = informed consent form, IRT = interactive response technology; ITT = intent-to-treat; PK = pharmacokinetic

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the exposed population as randomized.

For any participant randomized more than once, only the data associated with the first randomization (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention (placebo and itepekimab) during the study, the intervention group for as-treated analyses will be the itepekimab Q4W group if only one dose of itepekimab was taken by error. If participants took both itepekimab Q4W and Q2W regimens by error, the intervention group assigned will be the itepekimab Q2W group. For participants randomized to itepekimab Q4W (or Q2W) and took itepekimab Q2W (or Q4W) by error, will be assigned to the intervention group the participant was randomized to.

3 STATISTICAL ANALYSES

3.1 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoint detailed in this section is the annualized rate of moderate or severe PEs over the treatment period.

3.1.1 Definition of endpoint(s)

The primary efficacy endpoint is the annualized rate of adjudicated moderate or severe PEs over the placebo-controlled treatment period.

Pulmonary exacerbations are recorded by the Investigator and characterized by a sudden worsening of symptoms. For this analysis, adjudicated moderate or severe exacerbation endpoints will be considered.

Moderate exacerbations will be recorded by the Investigator and are defined as acute worsening of respiratory symptoms leading to treatment with antibiotics or addition of antibiotics or change in antibiotics.

The adjudication committee will determine if this definition of all exacerbations is met for reported and suspected events.

A moderate PE in this study is defined as

A) having 3 or more of the following symptoms for at least 48 hours
    1. Increased cough
    2. Increased sputum volume or change in sputum consistency
    3. Increased sputum purulence
    4. Increased breathlessness and/or decreased exercise tolerance
    5. Fatigue and/or malaise
    6. Hemoptysis

AND

B) A physician’s decision to prescribe antibiotics (or addition of antibiotic or change in antibiotic).

A severe PE is defined as a PE as described above but resulting in one or more of the following:

a) intravenous antibiotic treatment
b) hospitalization
c) observation for >24 hours in emergency department/urgent care facility
d) resulting in death

For both moderate and severe events to be counted as 2 separate events, they must be separated by at least 14 days between any course of antibiotics or 14 days between discharge and new admission in case of hospitalization (severe events only). If the patient develops a severe PE after a moderate PE which recovers, then antibiotic treatment end date and hospitalization start date will be used to validate the 14 days in between rule. In the situation where a moderate PE event becomes a severe PE event, the exacerbation will be considered as severe, and the date of hospitalization will be used as event start date.

Subjects on chronic antibiotic therapy whose only change in therapy is dose or frequency adjustment in response to worsening of respiratory symptoms will not meet the definition of exacerbation.

Moderate or severe exacerbation events recorded in eCRF will go through a confirmatory adjudication by experts independent of sponsor for the evaluation. Only the adjudicated confirmed exacerbation events will be used for analysis.

Participants who discontinue IMP before their planned end of treatment duration, are taking prohibited medications, are taking study treatment not as randomized for any reason or with change in background therapy will be asked and encouraged to return to the clinic for all remaining study visits; all PE events during the planned treatment period (between 24-52 week depending on participants' enrollment date) will be included in the analysis irrespective of study treatment adherence; the observation duration (used as offset variable in the analysis model) is equal to the planned treatment duration, except when a participant withdraws early from the study, in which case, the observation duration is from randomization to the last contact date of the participant within the planned treatment duration.

3.1.2 Main analytical approach

The primary endpoint will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: Annualized rate of adjudicated moderate or severe Pulmonary Exacerbations over the placebo-controlled treatment period.
- Treatment condition: itepekimab 300 mg SC Q4W and itepekimab 300 mg SC Q2W will be compared to placebo, on top of background therapy.
- Analysis population: ITT population
- Intercurrent events (ICEs):

The following ICEs may occur:

a) Early discontinuation of study treatment.

b) Taking prohibited medications post randomization.

c) Taking study treatment not as randomized (eg, dispensing error).

d) Change in background therapy, during the treatment period.

All four ICEs will be handled with treatment policy strategy. As defined in Table 2, all moderate or severe PEs events during the planned treatment period will be included in the analysis, and the observation duration will be equal to the planned treatment duration. Participants who permanently discontinue IMP will be asked and encouraged to return to the clinic for all remaining study visits, and all off-treatment moderate or severe PEs during the planned treatment period will be included in the primary analysis, regardless of adherence to IMP or background controller therapy or use of prohibited medications. Similarly, if a participant withdraws from the study prior to the end of the planned treatment period, all observed moderate or severe PEs events up to the last contact date will be included in the analysis, and in this case the observation duration will be from randomization to the last contact date within the planned treatment period. When determining the observation duration for the efficacy endpoints, the last contact date is defined as the EOS or premature EOS date, or the last visit date, whichever occurs later.

- The statistical hypotheses for comparing itepekimab against placebo on the primary endpoint of annualized rate of moderate to severe PEs during the treatment period are as follows:
    - Null hypothesis: $r_{itepekimab}/r_{placebo} = 1$
    - Alternative hypothesis: $r_{itepekimab}/r_{placebo} \neq 1$

  Where $r_{itepekimab}$ represents exacerbation rate for itepekimab 300 mg Q2W or Q4W, $r_{placebo}$ represents exacerbation rate for placebo.

- Population-level summary:

  The annualized rate of moderate or severe PEs will be analyzed using a negative binomial regression. The primary analysis model will include the total number of moderate or severe PE events that occur during the planned treatment period as the response variable, with treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), Pseudomonas aeruginosa (PA) chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (Yes or No), number of exacerbations in the prior year, and maintenance macrolide antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. A positive PA carrier status is defined by the isolation of PA in randomization/baseline sputum culture (positive or negative). If no PA sputum culture was obtained at randomization/baseline, the outcome is indeterminate. Log-transformed observation duration will be the offset variable. Parameters will be estimated using the maximum likelihood method with the Newton-Raphson algorithm. The estimated annualized event rate for each treatment group and its CIs will be derived from the

negative binomial model. The event risk ratio (RR) of each itepekimab regimen versus placebo, and the corresponding 2-sided CI (90% and 95%) and p-value will also be provided.

- Missing data handling:

  Although using the treatment policy strategy generally reduces the amount of missing data as compared to other strategies, missing data may nevertheless occur as a result of participants withdrawing from the study. To account for a shorter duration of follow-up of participants who withdraw from the study prior to their planned treatment duration, the primary analysis negative binomial model will include an offset term for the logarithm of follow-up duration. No further imputation will be performed for the unobserved PE events that may happen after study discontinuation and up to end of the planned treatment duration.

3.1.3 **Sensitivity analyses**

Sensitivity analyses for missing data in the primary endpoint

If participants withdraw from the study before completing the planned treatment duration and did not reach the end of planned treatment period in the follow-up period after premature EOT, exacerbation events that may occur after study discontinuation will not be observed. These participants are considered as participants with missing data on exacerbation. Participants who prematurely discontinued study treatment but reached the end of planned treatment period in the follow-up period after premature EOT will be censored at the end of planned treatment period for time to event analyses. The number of participants with missing data and reasons for and timing of study withdrawals will be summarized by treatment group. Summary statistics of selected demographic and baseline disease characteristics will be provided for participants with missing data and participants with complete data separately. Graphical summaries of the dropout patterns, such as Kaplan-Meier plots of time to study discontinuation with different reasons of discontinuation may be provided to examine if the missing data patterns are different between treatment groups. In addition, the following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model.

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

  For each participant with missing data of exacerbation events due to discontinue from study prior to the end of the planned treatment period , individual bi-weekly event probability will be estimated using observed data with adjustment of the treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥ 300 cells/mm^3), Pseudomonas aeruginosa (PA) chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (Yes or No), number of exacerbations in the prior year, and maintenance macrolide antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. The total number of moderate or severe events (on bi-weekly basis) will be calculated based on data imputed using multiple imputation.

- Tipping point analysis

  For each participant with missing data of exacerbation events due to discontinue from study prior to the end of the planned treatment period, the bi-weekly event will be imputed in a similar fashion as PMM-MI based on various odds values. If the participant is on itepekimab, the predicted odds will be increased; if the participant is on placebo, the predicted odds will be decreased. The adjusted rate will then be used to impute the number of events that would occur during the missing observation period. A sequence of increasing/decreasing ratio will be used to generate different imputed datasets until p-value becomes >0.05.

  For each of the above methods, a negative binomial model will be fitted using each of the complete datasets composed of observed and imputed data, including the total number of observed and imputed events over the planned treatment period as the response variable, with the treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), Pseudomonas aeruginosa (PA) chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (Yes or No), number of exacerbations in the prior year, and maintenance macrolide antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. Log transformed observation duration will be the offset variable for patients who complete the planned treatment period, and log transformed planned treatment duration will be the offset variable for participants who discontinue the study before the end of their planned treatment period. SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the analysis with each dataset using Rubin's formula.

3.1.4 Supplementary analyses

Supplementary analyses on additional estimands will be performed.

3.1.4.1 Supplementary estimand 1 (while-on-treatment)

This supplementary estimand for the primary endpoint will be a while-on-treatment estimand. The moderate or severe PEs events observed during the actual treatment period will be included:

- For participants who completed their planned treatment period, the actual on-treatment period is from first administration of IMP to the EOT visit, or to the initialization of prohibited medication, or to the change in background therapy (new antibiotics used more than 60 days will be considered), whichever is earlier.
- For participants who did not complete their planned treatment period, the actual on-treatment period is from first administration of IMP to the last administration of IMP+ 14 days, or to the initialization of prohibited medication or the change in background therapy, whichever is earlier.

A negative binomial model with the same set of covariates as specified in the primary analysis will be used. This model will include moderate or severe pulmonary exacerbation events occurring during the actual treatment period as the response variable and the log transformed

duration of the actual on-treatment period will be the offset variable. This approach defines the estimand to evaluate the efficacy of itepekimab while on treatment.

3.1.4.2 Supplementary estimand 2 (Composite variable strategy)

For this supplementary estimand, the ICEs will be handled as follows:

- For participants who discontinued the study treatment prematurely due to lack of efficacy and adverse event, or taking prohibited medications post randomization, the primary endpoint will be assessed based on assessments up to the discontinuation of the study treatment, or initiation of prohibited medication, whichever is earlier; the observation duration will be from randomization to the treatment discontinuation date, or the initiation date of prohibited medication, whichever is earlier.
- For participants who took study treatment not as randomized (eg, dispensing error) or changed in background therapy during the treatment period, the ICEs will be handled with treatment policy. All moderate or severe PEs events during the planned treatment period will be included in the analysis, and the observation duration will be equal to the planned treatment duration, regardless of adherence to randomized treatment arm or background controller therapy.

3.1.4.3 Supplementary analysis on subpopulation without major or critical IC/EC

Another supplementary analysis will be performed for the primary endpoint on the subpopulation that has no major or critical inclusion/exclusion criteria as per protocol. The annualized rate of moderate or severe PEs will be analyzed using the same negative binomial regression approach for this subpopulation. The same set of covariates as specified in the main analysis will be included in the model.

3.2 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of double-blind IMP. For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

Unless otherwise specified, all efficacy analyses will be performed by treatment group and in the ITT/efficacy population. In addition, for the summary of baseline values and demographics characteristics, the randomized population will be used as appropriate.

Observation period

The observation period will be divided into 4 segments:

- The **pre-treatment** period is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period (i.e., to the end of 20-week safety follow-up period). The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP +14 days.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment -emergent period.

The on-study period is defined as the time from enrollment until the end of the study defined as the last scheduled visit for those who completed the study (after follow-up period completion) and the end-of-study date collected on the electronic case report form (e-CRF) page "Completion of End of Study" for those who did not complete the study.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are efficacy secondary endpoints. Other secondary endpoints analyses are defined in Section 3.6.1 (AE, SAE), Section 3.6.2.1 (laboratory abnormalities), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity).

3.3.1 Key/Confirmatory secondary endpoint(s)

The key secondary endpoint detailed in this section is the time to first moderate or severe PE over the treatment period.

3.3.1.1 Definition of endpoint(s)

The definition of pulmonary exacerbations is detailed in the Section 3.1.1.

Time to first adjudicated moderate or severe PE is defined as the onset date of the first moderate or severe PE during the observation period - randomization date + 1. If the participants did not experience any moderate to severe PE events, the event time will be considered as censored at the end of the observation period. The observation period is defined in the same way as for the primary endpoint. All off-treatment moderate or severe PE during the planned treatment period will be included in the analysis.

3.3.1.2 Main analytical approach

The key secondary endpoint will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: Time to first adjudicated moderate or severe PE over the treatment period.
- Treatment condition: itepekimab 300 mg Q2W and itepekimab 300 mg Q4W will be compared to matching placebo, on top of the background therapy.
- Analysis population: ITT population.
- Intercurrent events (ICEs):

  The following ICEs may occur:

  a) Early discontinuation of study treatment.

  b) Taking prohibited medications post randomization.

  c) Taking study treatment not as randomized (eg, dispensing error).

  d) Change in background therapy, during the treatment period.

  It is noted that using new antibiotics to treat an exacerbation is not considered an ICE as it is a criterion for PE definition, and it does not prevent continued study participation, nor exclude the possibility of additional PE events.

  The ICEs will be handled using treatment policy strategy as follows:

  Operationally, regardless of treatment discontinuation, all participants will be followed-up according to the study procedures up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. That is, PE events and related data would be collected and reported

  over the entire planned treatment period for all study participants even if some participants may have discontinued the study treatment. Analytically, the time to first moderate or severe PE over the planned treatment period analysis is performed regardless of the occurrence of the ICEs or when do the ICEs occur. For participants without any PE events, event time will be considered as censored at the end of their observation period, as defined in the primary endpoint primary estimand.
- Population-level summary:

  The time to first moderate or severe PE will be analyzed using a Cox regression model. The model will include the time to the first event as the dependent variable, with treatment group, age, region, baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3), PA chronic colonization status (yes or no or indeterminate), documented history of COPD and/or asthma strata (yes or no), number of exacerbations in the prior year, and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates.

  The hazard ratio will be estimated for comparison of each itepekimab regimen to placebo.

  The Kaplan-Meier method will be used to derive the probabilities that a participant would experience an event up to specific time points for each treatment group.

In addition, a mean cumulation function (MCF) of the number of moderate or severe PE events over time will be calculated and plotted.

3.3.2 Other secondary endpoint(s)

For other secondary endpoints listed in this section, the ICEs and missing data assumption and handling for other secondary endpoints are specified in Table 3. The estimand for all other endpoints is the treatment policy estimand.

In addition to the below endpoints, additional analysis will be provided for the annualized rate of investigator reported moderate or severe exacerbation events and the annualized rate of the investigator reported severe exacerbation events. The same statistical model and missing data handling of the primary estimand will be used, except for that the response variable will be the investigator reported events. No sensitivity analysis or supplementary analysis will be performed for investigator reported exacerbation analyses.

3.3.2.1 Annualized rate of adjudicated severe PEs over the treatment period

Event rate will be analyzed similar to the primary endpoint of "Annualized rate of adjudicated moderate or severe PEs over the treatment period", but only adjudicated severe PE events will be taken into consideration. No sensitivity or supplementary analysis will be performed for this endpoint.

3.3.2.2 Time to first severe PE over the treatment period

Time to event will be analyzed similar to the key secondary endpoint of "time to first moderate or severe PE over the treatment period", but only severe PE events will be taken into consideration. No sensitivity or supplementary analysis will be performed for this endpoint. In addition, a mean cumulation function (MCF) of the number of severe PE events over time will be calculated and plotted.

3.3.2.3 Percentage of participants who are adjudicated PE free over the planned treatment period

The percentage of participants who are PE free over the treatment period will be analyzed using a logistic regression model. The model will include treatment group, age, region, baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3), PA chronic colonization status (yes or No or Indeterminate), documented history of COPD and/or asthma (yes or no) strata, number of exacerbations in the prior year, and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. The odds ratio of being a responder comparing each itepekimab dose arm to placebo will be provided along with the corresponding 90% CI and p-value.

3.3.2.4 Percentage of participants who are severe adjudicated PE free over the planned treatment period

The analysis model for percentage of participants who are severe PE free over the treatment period is identical to the analysis of the percentage of participants who are PE free over the treatment period, but only severe PE events will be taken into consideration.

3.3.2.5 Change from baseline in pre-BD FEV1 at Week 8 and Week 24

The change from baseline for continuous endpoints will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline values up through Week 24 as response variables. The covariates to be included are treatment group, age, region, sex, height, baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, visit, treatment by-visit interaction, Pre-BD FEV1 baseline value and Pre-BD FEV1 baseline-by-visit interaction.

Participants who discontinue IMP before the end of planned treatment period (between 24-52 weeks depending on participants' enrollment date) will be asked and encouraged to return to the clinic for all remaining study visits and the additional off treatment values measured up through the end of planned treatment period will be included in the analysis. For participants who withdraw from the study before the end of planned treatment period, values will be missing after study discontinuation or last contact. No imputation will be performed for missing values in this analysis.

An unstructured correlation matrix will be used to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline will be derived from the mixed-effect model. Descriptive statistics including number of participants, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 90% CI and the p-value will be derived from the MMRM model for comparison of each itepekimab dose arm against placebo.

A supplementary analysis will be performed for the change from baseline to W24 in pre-BD FEV1 endpoint. The ICEs will be handled as follows:

- ICEs of early discontinuation of study treatment due to lack of efficacy or adverse events, and ICEs of taking prohibited medications will be handled with the composite variable strategy. For participants who prematurely discontinued the study treatment due to lack of efficacy or adverse events, or taking prohibited medications, data will be censored after the treatment discontinuation or prohibited medication initialization, and will be replaced by the worst postbaseline value on or before the time of discontinuation or initialization of prohibited medication. For participants whose postbaseline values are all missing, the baseline will be used to impute.
- Other ICEs will be handled with treatment policy. Participants who prematurely discontinue IMP due to reasons other than lack of efficacy or adverse event will be asked and encouraged

to return to the clinic for all remaining study visits and the additional off treatment values measured up through the end of planned treatment period will be included in the analysis.

Mean difference and 2-sided 90% CI between each active arm and placebo will be estimated from ANCOVA with treatment group, age, region, sex, height, baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, visit, treatment by-visit interaction, Pre-BD FEV1 baseline value and Pre-BD FEV1 baseline-by-visit interaction as covariates.

Another supplementary analysis will be performed for the change from baseline to W24 in pre-BD FEV1 endpoint for the subpopulation that has an Obstructive disease (identified by a ratio post-BD FEV1/FVC < 0.7).

A mixed-effect model with repeated measures (MMRM) approach with the same set of covariates as specified above will be performed on this subpopulation.

3.3.2.6 Change from baseline in post-BD FEV1 at Week 8 and Week 24

The analysis model for post-BD FEV1 is identical to the analysis of the pre-BD FEV1, except that the baseline post-BD FEV1 will be included as a covariate instead of baseline pre-BD FEV1.

The same sensitive analyses than for pre-BD FEV1 will be provided.

3.3.2.7 Change from baseline in Quality-of-Life Questionnaire Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score in Adult Participants at Week 24

The QOL-B provides a broad and detailed measure of quality of life overall, which encompasses all aspects of the condition (see Section 5.8). The QOL-B yields 8 domain scores (Physical Functioning, Role Functioning, Vitality, Emotional Functioning, Social Functioning, Treatment Burden, Health Perceptions and Respiratory Symptoms). The Respiratory symptoms domain includes 9 questions (from 29 to 37 of the QOL-B Questionnaire).

See Section 5.9 for the scoring algorithm and handling of missed items.

The analysis model for QOL-B is identical to the analysis of the pre-BD FEV1, except that the baseline QOL-B will be included as a covariate instead of baseline pre-BD FEV1, and that sex and height will not be included as covariates.

3.3.2.8 Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24

St. George's Respiratory Questionnaire (SGRQ) is a 50-item PRO instrument developed to measure the health status of participants with airflow obstruction diseases (see Section 5.6). The questionnaire is divided into two parts: part one consists of eight items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part two consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition.

The SGRQ yields a total score and three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score ranges from 0 to 100; 100 represents the worst possible health status and 0 indicates the best possible health status (minimal clinically important difference: −4 units (1). Likewise, the domain scores range from 0–100, with greater scores indicative of greater impairment. See Section 5.7 for the scoring algorithm and handling of missed items.

This questionnaire is assessed at baseline and at Weeks 8, 24, 40 and 52.

Change from baseline in SGRQ total score and the three domain scores at Week 24 will be analyzed using the MMRM approach described for the analysis of pre-BD FEV1. For change from baseline in SGRQ total score and the three domain scores at Week 24, the model will include all SGRQ scores (total or the three domain scores, respectively) measured up through to Week 24, regardless of whether the participant is on treatment or not when the endpoint is measured. Participants who discontinue IMP prior to the end of the planned treatment period will be asked and encouraged to return to the clinic for all remaining study visits. No imputation will be performed on missing values.

The model covariates will be treatment group, age, region, baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, visit, treatment-by-visit interaction, baseline SGRQ total score or the three domain scores score, and baseline SGRQ total score or the three domain scores-by-visit interaction. The missing questionnaire items are handled as specified in Section 5.7; no further imputation will be performed on missing scores. Difference in LS means, the corresponding 90% CI, and p-value will be provided for the comparison of each itepekimab regimen versus placebo.

Figures of change from baseline over time for SGRQ total score and the three domain scores by treatment group will be generated.

3.3.2.9 Number of days of new and/or added (in participants with maintenance antibiotic use) acute antibiotic use to treat exacerbation

The endpoint will be analyzed using ANCOVA model. To account for the potential different treatment duration by study design, the response variable will be the % of days of new and/or added acute antibiotics used to treat exacerbation with the denominator as the treatment duration in days. Systemic antibiotics (CMROUTE = ‘INTRAMUSCULAR OR’, ‘INTRAOSSEOUS, ‘INTRAPULMONARY’ or ‘INTRAVASCULAR’, ‘INTRAVENOUS’, ‘INTRAVENOUS DRIP’, ‘ORAL’, ‘ORAL GAVAGE’ or ‘RESPIRATORY’) used less than 60 days to treat a NCFB exacerbation (cmrestrt='NCFBexacerbation' OR CMCENO contains 'NCFB') will be considered. New suppressive antibiotics will be not included in this analysis. The covariates to be included are treatment group, age, region, baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline.

Descriptive statistics including number of participants, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 90% CI and the p-value will be derived from the ANCOVA model for comparison of each itepekimab dose arm against placebo.

3.3.2.10 Percentage of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24

The percentage of participants with SGRQ improvement ≥4 points at Week 24, regardless of if the participant is still on treatment or not, will be analyzed using a logistic regression model. The model will include treatment group, age, region, baseline eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, and baseline SGRQ total score as covariates. Participants with SGRQ improvement <4 points or missing SGRQ total score at Week 24 will be considered as non-responders. The odds ratio of being a responder comparing each itepekimab regimen to placebo will be provided along with the corresponding 90% CI and p-value. Descriptive statistics including number and percentage of responders by visit will also be provided. Cumulative distribution function (CDF) of change from baseline in SGRQ at Week 24 will be presented by treatment group.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

3.4.1 Definition of endpoint(s)

- Annualized number of days of healthcare resource utilization over the placebo-controlled treatment period
- Annualized rate of all exacerbation (as recorded by Investigator)
- Annualized rate of all adjudicated exacerbations leading to prescription with antibiotics
- Annualized rate of all adjudicated exacerbations leading to prescription of antibiotics and/or systemic corticosteroids + meeting footnote a Part A criterion of a moderate exacerbation
- Time to first days of healthcare resource utilization
- Time to first exacerbation (as recorded by Investigator)
- Time to first exacerbation leading to prescription with antibiotics
- Time to first exacerbation leading to prescription of antibiotics and/or systemic corticosteroids + meeting footnote a Part A criterion of a moderate exacerbation
- Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4 weeks
- Change from baseline in pre-BD FVC at Week 8 and Week 24
- Change from baseline in post-BD FVC at Week 8 and Week 24
- Change from Baseline in Quality-of-life Questionnaire - Bronchiectasis (QoL-B) Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden Domain score in Adult participants at Week 24
- Change from baseline in LCQ total score at Week 24

The Leicester Cough Questionnaire is a validated PRO questionnaire evaluating cough on quality of life in subjects with NCFB (See Appendix 10).

The LCQ comprises 19 items and takes 5 to 10 minutes to complete. Each item assesses symptoms or the impact of symptoms over the last 2 weeks on a seven-point Likert scale. Scores in 3 domains (Physical, Psychological and Social) are calculated as a mean of available item scores for each domain (range 1 to 7). A total score (range 3 to 21) is also calculated by adding the domain scores together. Higher scores indicate better QOL.

3.4.2 Main analytical approach

- Descriptive summary of annualized number of ER and hospital days related to moderate or severe PEs will be provided.
- All definition of annualized rate of exacerbation or acute pulmonary worsening will be analyzed using the same negative binomial regression approach described for the analysis of the primary endpoint annualized rate of moderate or severe PEs over the placebo-controlled treatment period. Additional analysis will be performed on the investigator reported event associated to each annualized rate of adjudicated exacerbation definition in the study.
- All time to event will be analyzed similar to the key secondary endpoint of "time to first moderate or severe PE over the treatment period". A mean cumulation function (MCF) will be calculated and plotted for each time to event endpoint.
- Rate of change in post-BD FEV1 (L/yr) (post-BD FEV1 slope) after a period of initial bronchodilator effect (4 weeks), during which a rapid increase in post-BD FEV1 is expected for all active treatment arms, will be analyzed.

Descriptive statistics including number of participants, mean, standard error of the individual post BD FEV1 slopes will be provided based on the individual post-BD FEV1 slope. It will be derived as the slope of a linear regression model with the post-BD FEV1 (L) at each visit after Week 4 (up to the planned treatment period) as the response variable and the time (continuous variable) as the independent variable for each participant.
Formal statistical inferences including estimated post-BD FEV1 slopes for each treatment group, 90% CIs, and p-values on the slope differences between active treatment groups and placebo will be derived from a mixed-effects model with repeated post-BD FEV1 measured during the treatment period after Week 4 (up to the planned treatment period) as the response variable, age, sex, baseline height (continuous variable), region, baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, treatment group, time (continuous variable) and treatment-by-time interaction and baseline post-BD FEV1 (continuous variable) as covariates. Intercept and time since randomization are random effects in the model. Estimated from the linear mixed-effects model, least squares (LS) means, difference in LS means and the corresponding 90% confidence intervals (CI) will also be provided.

- Change from baseline in pre-BD FVC and in post-BD FVC will be analyzed using the same model than the pre-BD FEV1 and post-BD FEV1 respectively except that the baseline FVC corresponding will be included as a covariate instead of baseline FEV1.
- Change from Baseline in LCQ total score and Quality-of-life Questionnaire - Bronchiectasis (QoL-B) domain scores will be analyzed using the MMRM approach described for the analysis of pre-BD FEV1. The model will include records up though Week 24, regardless of whether the participant is on treatment or not when the endpoint is measured. No imputation will be performed on missing values.

  The model covariates will be treatment group, baseline eosinophil, region, PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction. No imputation will be performed on missing values. Difference in LS means, the corresponding 90% CI, and p-value will be provided for the comparison of each itepekimab regimen versus placebo.

Other tertiary endpoints analyses are defined in Section 3.6.1 (AE, SAE), Section 3.6.2.1 (laboratory abnormalities), and Section 3.7 : Section 3.7.1.1 (PK), Section 3.7.1.2 (immunogenicity) and Section 3.7.1.4 (Other quality of life analyses).

3.4.3 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 14 days, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

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

- >0 and ≤8 weeks
- >8 and ≤16 weeks
- >16 and ≤24 weeks
- >24 and ≤32 weeks
- >32 and ≤40 weeks
- >40 and ≤48 weeks
- >48 and <52 weeks – 3 days

- ≥52 weeks – 3 days

Additionally, the cumulative duration of treatment exposure (expressed in participant-years) will be provided.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the number of administration/days as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.Cases of overdose (defined as at least twice the intended dose during an interval of less than 8 days) will constitute serious adverse events and will be listed as such.

3.5 MULTIPLICITY ISSUES

No adjustments for multiplicity are planned for this Phase 2 study.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided separately.

3.6.1 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened or became serious during the treatment-emergent period

- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 5.

Table 5 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
SMQ/CMQ and PT	By decreasing frequency of SMQs/CMQs and PTs[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the itepekimab 300 mg Q2W intervention group
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any treatment emergent SAE
- Any treatment emergent AESI
- TEAE leading to death
- Any TEAE leading to permanent intervention discontinuation

The AE summaries of Table 6 will be generated with number (%) of participants experiencing at least one event.

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
	Primary SOC, HLGT, HLT and PT
	PT
	Primary and secondary SOC and PT
Common TEAE (≥5% in any group)	Primary SOC and PT
Common TEAE (≥2% in any group)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent intervention discontinuation	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Pre-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment SAE	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent [full] intervention discontinuation

Analysis of deaths

In addition to the analyses of deaths included in Table 6 the number (%) of participants in the following categories will be provided:

- Number (%) of participants who died by study period (TEAE, on-study and post-treatment periods) summarized on the safety population by treatment received.
- Deaths in non-randomized or randomized but not treated participants

Cardiovascular assessment

The CV adjudication committee will adjudicate each event as: a CV event, a non-CV event, not an event to be considered for adjudication, or not possible to adjudicate.

The number and percentage (%) of participants with any treatment-emergent event selected for adjudication will be summarized by primary SOC and PT.

All events submitted for cardiovascular adjudication will be listed and summarized, including the final classification results. A swimmer plot including all events classified as cardiovascular,

including cardiovascular death, will also be provided. The number and percentage (%) of participants experiencing a treatment-emergent adjudicated event will be summarized within each treatment group.

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 7 and tabulated by treatment group. Number (%) of participants experiencing at least one event will be provided for each event of interest. The risk difference (asymptotic 90% CI with continuity correction) will be computed for the itepekimab dose versus placebo. Tables will be sorted as indicated in Table 7.

Table 7 - Selections for AESIs and other AEs of interest

AE Grouping	Selection
AESI	
Significant ALT elevation	eCRF AECAT = 'ALT increase' is checked and AESI = 'Y.'
Anaphylactic reaction	Anaphylactic or systemic allergic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other, and to IMP administration for final determination of an anaphylactic reaction or not.
systemic allergic reaction requiring treatment (medically reviewed)	SMQ hypersensitivity (20000214) narrow search and with [AECONTRT =Yes (Corrective treatment/therapy=Yes) OR action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review for selection of relevant systemic allergic events.
Severe injection site reactions (ISRs) that last longer than 24 hours	AE category = "Injection Site Reaction" and AESI = "Y"
Serious infection	Primary SOC = 'Infections and infestations' and with serious status and AESI='Y'.
Infection requires parenteral (IV, IM, SC) antimicrobial therapy	AE category = "Infection Event" and AESI = 'Y' and eCRF Infection Event Form question "Have any parenteral treatment (IV, Intramuscular, SC) been given for this event?" = "Y"
Infection requires oral antimicrobial therapy for longer than 2 weeks	eCRF Infection Event Form FAMEDYN= 'Y' and AESI = 'Y' and duration is 15 days or more.
Parasitic infection	eCRF Infection Event Form Infection Type = 'Parasitic' and AESI = 'Y'.
Opportunistic infection	eCRF Infection Event Form FAOPYN= 'Y' and AESI = 'Y'.
Malignancy	Sub-SMQ (20000091)– Malignant or unspecified tumors and AESI= 'Y'
Pregnancy	Primary SOC = 'Pregnancy, puerperium and perinatal conditions' or PT in (Aborted pregnancy, False negative pregnancy test, Pregnancy test positive, Pregnancy test urine positive, Ectopic pregnancy termination)
Symptomatic overdose with IMP/NIMP	Symptomatic Overdose is answered Yes, with Overdose of IMP/NIMP answered Yes on AE eCRF.
Other selected AE Grouping	
Injection site reaction	HLT = 'Injection site reactions'

The list of terms may be adjusted according to MedDRA version changes

The following summaries will be provided:

All treatment-emergent adverse events, by selected standardized MedDRA query (SMQ) and PT or by laboratory values (as in ALT elevation), showing the number (%) of participants with at least 1 PT, sorted by decreasing incidence of PTs within each SMQ in the 300 q2w treatment group.

For the overview of AESI and other selected AE groupings,

- Number (%) of participants with any specific TEAE
- Number (%) of participants with any specific serious AE (regardless of treatment emergent status)
- Number (%) of participants with any specific treatment emergent serious AE
- Number (%) of participants with any specific AE leading to death
- Number (%) of participants with any specific treatment emergent AE leading to death
- Number (%) of participants with any specific TEAE leading to permanent study intervention discontinuation
- Number (%) of participants with any specific TEAE related to IMP reported by investigator
- Number (%) of participants with any specific TEAE by maximum intensity, corrective treatment, and final outcome
- Number of any specific TEAE adjusted by the exposure duration (per 100 person-years)
- Number (%) of participants with injection site reactions by the related injection.
- Number (%) of participants with different number of injection site reactions.

3.6.2 Additional safety assessments

3.6.2.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variablesand vital signs variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, red blood cell count, platelet count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose (fasting), total cholesterol, total protein, albumin, creatine phosphokinase, C-reactive protein
  - Electrolytes: sodium, potassium, bicarbonate

  - Renal function: creatinine, blood urea nitrogen (BUN)
  - Liver function: alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT), aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by local dipstick, specific gravity
  - Vital signs: pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg), weight (kg), respiratory rate (breaths per full minute), Body temperature (degrees Celsius) and height (cm; screening only).

Quantitative analyses

For all laboratory variables and vital signs above, descriptive statistics for results and changes from baseline will be provided for baseline and each post baseline time point. For each analysis window, the last value during the on-treatment period will be used. Summary statistics will include number of participants, mean, standard deviation, median, Q1, Q3, minimum, and maximum. These analyses will be performed using central measurements only (when available) for laboratory variables.

For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to PCSA

The percentage of participants who had at least one incidence of PCSA at any time during the TEAE period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables and vital signs, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

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

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury:

- Time to onset of the initial alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) during the treatment-emergent period will be analyzed using Kaplan-Meier method.
- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ ULN in case of missing baseline) before last IMP dose, Returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

Itepekimab concentrations in serum at Visit 2 (Day 1, or Baseline), Week 4, Week 8, Week 24, Week 52 (and/or EOT/ETD Visit) and Week 72/ EOS Visit will be provided.

Itepekimab concentrations in serum will be summarized by the intervention group on the PK population using the following descriptive statistics: mean, geometric mean, standard deviation, coefficient of variation, minimum, median and maximum. If date and/or time of the drug injection and/or sampling is missing, the concentration will not be taken into account.

Concentrations below the lower limit of quantification (LLOQ) will be set to zero for pre-dose samples (Week 0). Other concentrations below LLOQ will be replaced by LLOQ/2. Values will be expressed in the tables with no more than three significant figures.

3.7.1.2 Immunogenicity analyses

Anti-drug antibody (ADA) blood samples will be collected at Visit 2 (Day 1, or Baseline), Week 8, Week 24, Week 52 (and/or EOT/ETD Visit), and follow up at Week 72/EOS Visit. For

patients who discontinue early from the treatment, ADA samples will be collected at EOT and EOS. If an SAE or AESI (anaphylaxis, systemic hypersensitivity reaction, and severe ISR lasting more than 24 hours) occurs in a participant, additional blood samples may be collected for determination of functional itepekimab concentration (PK), and/or ADA assessment at or near the onset of the event. For China, these assessments can be considered optional.

At each sample time point, the result of an analyzed sample in the antidrug antibody (ADA) assay will be categorized as either positive or negative.

The ADA status of each patient will be classified as one of the following:

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

The ADA category of each positive patient is classified as:

- **Treatment-emergent response:** defined as a positive response in the ADA assay post first dose when baseline results are negative or missing. A treatment-emergent response is further classified as persistent, indeterminate or transient:
  - **Persistent response:** treatment-emergent ADA response detected at 2 or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time) with no ADA negative samples in between.
  - **Indeterminate response:** treatment-emergent response when only the last collected sample is positive.
  - **Transient response:** a treatment-emergent response that is not persistent or indeterminate.
- **Treatment-boosted response:** defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive.

  Maximum Titer categories

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

    High (Titer >10000)

  The following summaries will be provided based on ADA population:

  <u>Baseline summary:</u>

- Number (%) of participants with pre-existing immunoreactivity ADA response, or a positive response in the ADA assay at baseline

  - Summary statistics (including number, median, Q1, Q3, minimum and maximum) of titer for participants with pre-existing immunoreactivity ADA response, or a positive response

- Number (%) of participants with a negative response in the ADA assay at baseline

Post-baseline summary:

- Number (%) of participants with pre-existing immunoreactivity
- Number (%) of participants with negative responses at all time points
- Number (%) of ADA positive participants
- Number (%) of participants with treatment-emergent ADA response
  - The summary statistics (including number, median, Q1, Q3, minimum, and maximum) of the peak post-baseline titer for treatment-emergent ADA-positive participants
  - Number (%) of participants with persistent response
  - Number (%) of participants with indeterminate response
  - Number (%) of participants with transient response
- Number (%) of participants with treatment-boosted ADA response
  - The summary statistics (including number, median, Q1, Q3, minimum, and maximum) of the peak post-baseline titer for treatment-boosted ADA-positive participants
- Listing of all ADA titer levels will be provided for participants with treatment-emergent and treatment-boosted responses.

  The impact of positive immune response on PD, PK, safety, and efficacy variables may be further explored, depending on ADA incidence.

3.7.1.3 Bronchiectasis Severity Index (BSI)

Bronchiectasis severity index is a scoring system based on a combination of clinical, radiological and microbiological features that can be used to assess subjects' NCFB severity. The BSI can be predictive of mortality and hospital admissions and be predictive of exacerbations and QOL giving a broad assessment of disease severity.

The BSI score will be calculated only at Baseline in order to estimate disease severity. The BSI score calculation is described in Appendix 13 (Section 5.14) and will be entered into the eCRF directly.

Severity Score (calculated from results of the above criteria) :

- 0- 4 Mild Bronchiectasis
- 5 – 8 Moderate Bronchiectasis

- 9 + Severe Bronchiectasis

3.7.1.4 Other quality of life analyses

3.7.1.4.1 Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS)

The PGIC (Appendix 10) is a 1-item questionnaire that asks the participant to provide the overall self-assessment of change in their bronchiectasis symptoms on a 7-point scale, compared to just before the participant started taking the study treatment. Response choices are 1 = "Very much better", 2 = "Much better", 3 = "A little better", 4 = "No change", 5 = "A little worse", 6 = "Much worse", 7 = "Very much worse". PGIC will be assessed at Visit 5 (Week 8), Visit 9 (Week 24), Visit 13 (Week 40), Visit 16 (Week 52) and/or the EOT/ETD visit.

The PGIS (Appendix 10) is a 1-item questionnaire that asks participants to provide the overall self-assessment of their bronchiectasis symptom severity on a 4-point scale for the past week. Response choices for both items are 1 = "None", 2 = "Mild", 3 = "Moderate", 4 = "Severe". PGIS will be assessed at Visit 2 (Week 0), Visit 5 (Week 8), Visit 9 (Week 24), Visit 13 (Week 40), Visit 16 (Week 52) and/or the EOT/ETD visit.

PGIC and PGIS of Bronchiectasis at Week 24 and Week 52 will be summarized descriptively.

3.7.1.4.2 EuroQol 5-Dimension 5-Level Quality-of-Life Questionnaire

The European quality of life-5D scale (EQ-5D) (Appendix 11) is a standardized HRQoL questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (2) EQ-5D is designed for self-completion by participants. The EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ VAS. The EQ-5D comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. EQ-5D-5L health status will be converted into a single index value according to the new crosswalk algorithm developed by Hernandez Alava et al (3) and using the UK value set. The EQ VAS records the respondent's self-rated health on a vertical VAS. The EQ VAS 'thermometer' has endpoints of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. EQ-5D self-reported VAS data generates information on the self-perceived overall health-related quality of life. EQ-5D will be assessed at Visit 2 (Week 0), Week 24 and Week 52 and/or the EOT/ETD visit.

Change from baseline in EQ-5D-5L single index score and EQ VAS at Week 24 will be analyzed using the MMRM approach described for the analysis of pre-BD FEV1. The model will include records up though Week 24, regardless of whether the participant is on treatment or not when the endpoint is measured. No imputation will be performed on missing values.

The model covariates will be treatment group, baseline eosinophil, region, PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction. No imputation will be performed on missing values. Difference in LS means, the corresponding 90% CI, and p-value will be provided for the comparison of each itepekimab regimen versus placebo.

Descriptive statistics including number of subjects, mean, median, SD, minimum, maximum will be provided by treatment groups for the value and change from baseline at each visit (baseline, Week 24 and Week 52) for the quantitative variables of EQ-5D-5L single index score and EQ VAS. No missing data will be imputed.

3.7.1.4.3 SNOT-22 Questionnaire

The SNOT-22 is a PRO questionnaire (Appendix 12) designed to assess the impact of CRS on patients' Health-Related Quality of Life (HRQoL) (4). SNOT-22 has 22 items covering symptoms social/emotional impact, productivity, and sleep consequences of CRS. The recall period is past 2 weeks. Each item is rated on a 6-point Likert scale response option, ranging from 0 ('No problem') to 5 ('Problem as bad as it can be'). A global score ranging from 0 to 110 is calculated by summing the responses to all items; higher score indicates greater rhinosinusitis-related health burden. The questionnaire is an easy, valid, and reliable tool (4).

Change from baseline in global SNOT-22 score and domain scores at Week 24 will be analyzed using the MMRM approach described for the analysis of pre-BD FEV1. The model will include records up though Week 24, regardless of whether the participant is on treatment or not when the endpoint is measured. No imputation will be performed on missing values.

The model covariates will be treatment group, baseline eosinophil, region, PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction. No imputation will be performed on missing values. Difference in LS means, the corresponding 90% CI, and p-value will be provided for the comparison of each itepekimab regimen versus placebo.

Descriptive statistics including number of subjects, mean, median, SD, minimum, maximum will be provided by treatment groups for the value and change from baseline at each visit (baseline, Week 24 and Week 52) for the quantitative variable of global SNOT-22 score and domain scores. No missing data will be imputed.

A supplementary analysis will be performed for the change from baseline to W24 in global SNOT-22 score and domain scores endpoints for the subpopulation that has Chronic Rhinosinusitis (CRS) based on the SNOT-22 questionnaire (identified by a SNOT-22 >20).

A mixed-effect model with repeated measures (MMRM) approach with the same set of covariates as specified above will be performed on patients with CRS.

3.7.1.5 Biomarker analyses

- The pharmacodynamic (PD) effects of itepekimab in participants with bronchiectasis will be assessed through changes in blood biomarkers, including CRP, fibrinogen, IL-6, IL-8, TNF-α, IFN-γ, IL-17A, IL-5, IL-13, IL-33, TARC, eotaxin-3, IgE. Analyses will be conducted for the participants from the safety population who have biomarker measurements available at baseline and at least one post-baseline visit and within predefined subgroups, such as age groups, comorbid conditions, and racial/ethnic subpopulations. Analysis will be stepwise and depending upon outcome some analyses may be skipped.
- The PD effects of itepekimab in participants with bronchiectasis will also be assessed through changes in sputum biomarkers. Sputum will be collected at baseline, Weeks 4, and Week 24. If sputum sample is not successfully collected at Week 24, it can be collected up to Week 32. Samples for analysis of sputum markers will be collected, which may include sputum proteins IL-5, IL-13, IgE, IL-6, IL-8, TNF-α, IL-17A, IFN-γ, neutrophil elastase, proteinase 3, and cathepsin G and/or cells (eg, eosinophils, neutrophils and macrophages). Analysis will be stepwise and depending upon outcome some analyses may be skipped.

3.7.1.5.1 Descriptive Analysis

Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) will be calculated for blood biomarkers at baseline, Weeks 4, 24 and Week 72/EOS and for sputum biomarker at baseline, Weeks 4, and Week 24-32. Baseline values will be the last value collected prior to the first IMP administration. Summary plots (mean +/- standard error of the mean) on values at each visit for absolute changes from baseline and percent changes from baseline will be provided for biomarker listed above by treatment group.

For optional endpoints (for participano be mergedts who signed the optional pharmacogenetic/pharmacogenomic informed consent), whole sputum messenger RNA for sequencing (RNAseq) or whole transcriptome will be collected at Visits 2, 4 and 9 and stored for future analysis. Exploratory analysis of sputum RNA samples will be addressed in a separate document.

3.7.2 Subgroup analyses

Subgroup analyses of the primary efficacy endpoint (annualized rate of moderate or severe PEs over the treatment period) and key secondary efficacy endpoint (Time to first moderate or severe PEs) will be performed to assess the homogeneity of the treatment effect across the following subgroups (categories with fewer than 15 participants may be combined with other categories):

- Age group (<40, 40 to <70, ≥70)
- Gender (Male, Female)
- Baseline weight categories (<70, ≥70-<90, ≥90 kg)
- Baseline body mass index (BMI) level (<25, ≥25-<30, ≥30 kg/m2)

- Race (White, Non-white; Note: missing race will be excluded from the subgroup analysis.)
- Ethnicity (Hispanic, Not Hispanic)
- Region (Asian, Latin America, East Europe, Western countries)
- Inhalation Background therapy (Yes, No)
- BSI based Pseudomonas aeruginosa (PA) chronic colonization status (Yes, No)
- Sputum culture Colonization Status (Not Colonized, Chronic Colonization)
- Documented history of COPD and/or asthma strata from eCRF (No, Only COPD, Only ASTHMA, COPD and ASTHMA)
- Documented history of CRS (Yes, No)
- Maintenance antibiotic therapy strata (macrolide antibiotics, non-macrolide antibiotics, no antibiotics)
- Baseline blood eosinophil (<150, 150 to <300, ≥300 cells/mm^3; <300, ≥300 cells/mm^3)
- Number of moderate or severe PE exacerbation events within one year prior to screening visit (0 to 2, 3 or More)
- History of at least one severe PE events within one year prior to screening (Yes, No)
- Baseline SGRQ score (< median, ≥ median)
- BSI Score (Mild, Moderate, Severe)
- Baseline mMRC Breathlessness Score (1-3, 4-5)
- Post-BD FEV1/FVC ratio (<0.7, ≥0.7)
- Post-BD FEV1 percent predicted (<30, 30 to 49, 50 to 80, >80)
- Reversibility (<12% or <200ml, ≥12% and ≥200ml according to ERS/ATS 1991 criteria) and (<10%, ≥10% according to ERS/ATS 2022 criteria)
- BSI based Radiological Severity (<3 Lobes Involved, 3 or More Lobes or Cystic Changes)
- Etiology of Bronchiectasis (Idiopathic, post infection, COPD, ABPA/asthma, ciliary disorders (PCD/ciliary dysfunction), other)
- Pre-BD FVC percent predicted (<80%, ≥80%)

For the primary endpoint, the treatment effects for these subgroups will be provided using the same model as for the primary analysis. Rate ratio between treatment and control and the corresponding 90% CI will be provided within each subgroup. Treatment-by-subgroup interaction and its p-value will be derived by a negative binomial regression model. The model will include treatment group, age, region, baseline eosinophil (<300 cells/µL or ≥300 cells/µL), number of moderate or severe PEs in previous year at baseline (0 versus ≥1), Pseudomonas aeruginosa (PA) chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (Yes or No), maintenance macrolide antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics), subgroup (if different from the aforementioned

covariates) and subgroup-by-treatment interaction as covariates. Log transformed observation duration will be the offset variable. Forest plots will also be provided.

3.8 INTERIM ANALYSES

No interim analysis is planned.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the SAP compared to the protocol.

Major statistical changes in the SAP or in the protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
04	20-Jan-2025	Added supplementary estimand for the primary endpoint, that handles the ICE b) Taking prohibited medications post randomization and d) Change in background therapy, during the treatment period differently from the primary estimand: Instead of using treatment policy, only data before the initiation of the prohibited medication or start of antibiotic maintenance therapy will be included in the analysis. The observation duration will also be capped at the time of initiation of prohibited medication or the start of antibiotic maintenance therapy.	Taking prohibited medication or start of antibiotic maintenance therapy may bring bias to the analysis.
		Change the covariate screening eosinophil (<300 cells/mm3 or ≥300 cells/mm3) to baseline eosinophil (<300 cells/mm3 or ≥300 cells/mm3) in all statistical models.	Given the fact that there might be multiple eosinophil measurements during the screening period, it is decided that the baseline eosinophil count should be used in the model. Baseline record is defined as the last available measurement on or prior to the day of first IMP.

4 SAMPLE SIZE DETERMINATION

The sample size calculation is based on a comparison between itepekimab 300 mg SC Q2W or Q4W versus placebo with regard to annualized rate of moderate-to-severe PEs over the 52-week treatment period. Taking into account the objectives of the study, the following assumptions were made:

- Average of [redacted] moderate-to-severe PEs per year in the placebo group of this study population.
- The number of moderate-to-severe PEs follows a negative binomial distribution with dispersion parameter [redacted] for all the groups.
- Participants will be treated with a minimum of 24 weeks and a maximum of 52 weeks depending on their study entry times. The monthly patient accruals are assumed to be 1, 4, 5, 15, 25, 40, 60, 60, 60, and 30. The enrollment period is approximately 10 months.
- 5% loss on the average treatment duration per participant to account for the shortened treatment duration due to early study discontinuation.
- Participants are randomized to the treatment group and the placebo group with a 1:1:1 ratio.

With these assumptions and 100 participants per group (300 participants in total), the study will yield a 75% power to detect a 40% relative rate reduction in the annualized rate of moderate-to-severe PE for itepekimab 300 mg q2w or q4w versus placebo, with a 2-sided alpha of 0.1. The minimum detectable rate reduction is around [redacted].

If the observed treatment effects on itepekimab 300 mg q2w and q4w are similar, the 2 itepekimab doses will be combined to get a more accurate estimate of the treatment effect. The study has an 84% power to detect a 40% relative rate reduction in the annualized rate of PEs for itepekimab 2 combined doses versus placebo with a 2-sided alpha of 0.1. The minimum detectable rate reduction is around [redacted].

Based on the accrual and drop-out assumptions, the average treatment duration per participant is estimated to be approximately [redacted] years. Due to the variable treatment period study design, participants will have different follow-up times depending on their enrollment times, and the power will depend on the actual accrual rates and the drop-out rates. These rates will be closely monitored. If the accrual rate is significantly faster than projected and/or the drop-out rate is higher than expected, the minimum treatment period (ie, 24 weeks) may be extended to achieve the desired amount of total exposure. The maximum treatment period of 52 weeks will not be changed.

5 CHANGED.SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE: adverse event
AESIs: adverse events of special interest
ALT: alanine aminotransferase
BMI: body mass index
CI: confidence interval
COPD: chronic obstructive
e-CRF: electronic case report form
EQ-5D: European quality of life-5D scale
HLT: high level term
LLT: lower-level term
MedDRA: medical dictionary for regulatory activities
MMRM: mixed-effect model with repeated measures
NCFB: non-cystic fibrosis bronchiectasis
Non-cystic fibrosis bronchiectasis: NCFB
PA: Pseudomonas aeruginosa , Pseudomonas aeruginosa, Pseudomonas aeruginosa, Pseudomonas aeruginosa, Pseudomonas aeruginosa
PCSA: potentially clinically significant abnormality
PE: pulmonary exacerbation
PGIC: Patient Global Impression of Change
PGIS: Patient Global Impression of Severity
PRO: patient reported outcome
PT: preferred term
SAE: serious adverse event
SAP: Statistical analysis plan
SD: standard deviation
SGRQ: St. George's Respiratory Questionnaire
SOC: system organ class
TEAE: treatment-emergent adverse event
WHO-DD: World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants still on study intervention
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation
- Participants who completed the study period as per protocol
- Participants who did not complete the study period as per protocol and main reason for study discontinuation
- Vital status at last study contact

The number (%) of exposed and not randomized participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, randomized, with permanent intervention discontinuation and with early study discontinuation will be provided by country and site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population.

Note that data from patients with deviations will not be excluded from the ITT population for efficacy or safety analyses.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (18 to <40, 40 to <70, ≥70)
- Gender (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Japanese, Not Reported, Unknown)

- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- region (APAC-EMEA: China, Israel, Japan, Taiwan and Turkey; EU: Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Spain and United Kingdom, Americas: Argentina, Brazil, Canada, Chile and United States)
- Body weight group as quantitative variable and in categories (<70, ≥70-<90, ≥90 kg)
- Height as quantitative
- Body mass index as quantitative variable and in categories (<15, ≥15-<25, ≥25-<30, ≥30 kg/m^2)
- Smoking status at screening (Never, Current, Former)
- Tobacco Consumption for Former Smoker (cigarettes/day)
- Electronic Cigarette Use Status at Screening (Never, Current, Former)
- Nicotine Consumption for Former Electronic Cigarette User (mg/day)
- PA chronic colonization status (Yes, No, Intermediate)

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by intervention group:

- Age at diagnosis of NCFB (years)
- Age at diagnosis of NCFB Categories (<18, 18 to <40, 40 to <70, ≥70)
- Documented history of COPD and/or asthma status (Yes, No)
- Duration of NCFB at randomization (years)
- Time since last pulmonary exacerbation at randomization (months)
- Number of moderate or severe pulmonary exacerbations experienced in the past one year before screening visit (quantitative variable and qualitative variable: 0, 1, 2, 3, ≥4)
- Number of moderate or severe Exacerbations that Required Hospitalization or Urgent Medical Care (quantitative)
- Number of severe pulmonary exacerbations experienced in the in the past one year before screening visit (quantitative variable and qualitative variable: 0, 1, 2, 3, ≥4)
- Baseline controller therapy (Yes (Double, Triple), No)
- Any medication for NCFB During the Previous 30 Days (Yes, No)
- Maintenance macrolide antibiotic therapy use (Macrolide antibiotics, Non-macrolide antibiotics, No antibiotic)
- Bronchiectasis Severity Score BSI (Mild, Moderate, Severe)
- Mucous clearance regimen (Yes, No)

Primary efficacy parameter at baseline as quantitative variable and in categories:

- Pre-BD FEV1 (L)
- Post-BD FEV1 (L)
- Pre-BD FEV1 percent predicted (%)
- Post-BD FEV1 percent predicted (%)
- FEV1 reversibility as quantitative variable (%) and in categories ((<12% or <200ml, ≥12% and ≥200ml) and (<10%, ≥10%))
- Pre-BD FVC (L)
- Post-BD FVC (L)
- Pre-BD FVC percent predicted (%)
- Post-BD FVC percent predicted (%)
- Pre-BD FEV1/FVC ratio as quantitative variable (%) and in categories (<0.7, ≥0.7)
- Post-BD FEV1/FVC ratio as quantitative variable (%) and in categories (<0.7, ≥0.7)
- Pre-BD forced expiratory flow (FEF) 25-75
- Post-BD forced expiratory flow (FEF) 25-75
- QOL-B Respiratory Symptoms Score
- SGRQ total score
- SNOT-22 Total Score
- PGIS Score
- EQ-5D-5L score
- EQ VAS score
- LCQ score

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the participant. Medical and surgical history will be coded to a PT, HLT, HLGT, and associated primary SOC using the MedDRA version in effect at Sanofi at the time of database lock.

Etiology of NCFB will be summarized separately, including:

- Comorbidities (Yes, Ongoing for each): idiopathic NCFB, Post Infective NCFB, COPD, Autoimmnue, Immunodeficiency, Asthma, Severe Asthma, ABPA (Allergic BronchoPulmonary Aspergillosis), Ciliary Dysfunction, IBD (Inflammatory Bowel Disease), Aspiration, PCD (Primary Ciliary Dyskinesia), Congenital Malformations,

Connective Tissue Disease, Alpha-Antitrypsin Deficiency, Cystic Fibrosis, Hypogammaglobulinemia, Common Variable Immunedeficiency, Mannose-Binding Lectin Deficiency, Pulmonary Fibrosis.

Prior or concomitant medications

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

Prior medications are those the participant used prior to first IMP intake.

- Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any treatments received by the participant concomitantly to the IMP, from the first administration of IMP to the last administration of IMP + 154 days
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the randomized population, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence in itepekimab 300 mg q2w group. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

For efficacy analysis, Table 8 presents the prohibited medications and procedures.

Table 8 - Selected prohibited medications and procedures that may impact efficacy

Medication/Procedure	Identification
Immunosuppressant drugs (Antineoplastic and immunomodulating agents)	**CDGsn00186**
Corticosteroids NARROW	**CDGsn00010 + duration more than 2 weeks + systemic routes**
Live/attenuated vaccines	**CDG40355**
BCG vaccine	**CDG00725**
Anti-infectives Narrow	**CDGsn00876 + duration more than 4 weeks**
Long Acting Beta Agonists (LABA)	**CDGsn00514**
Long Acting Muscarinic Antagonists (LAMA)	CDG20005
Immunoglobulin E inhibitors	**CDG00486**

Medication/Procedure	Identification
Anti-IL5/IL5R mAb	**CDG20156**
DUPILUMAB_mono_and_multi_ingredients	**CDG20153**
Anti-thymic stromal lymphopoietin (TSLP) agents	**CDG40187**
Cell depletion agents	**CDG10236**
JANUS-ASSOCIATED KINASE (JAK) INHIBITORS	**CDG40096**
Macrolides Narrow	**CDGsn00893 + duration more than 4 weeks (Stable use allowed)**
Phosphodiesterase type 4 inhibitors Narrow	**CDGsn00122 + duration more than 4 weeks (Stable use allowed)**
XANTHINES_AND_XANTHINE DERIVATIVES	**CDG00262 + duration more than 2 weeks**
Leukotriene receptor antagonists for obstructive airway diseases Narrow	**CDGsn00522 + duration more than 4 weeks (Stable use allowed)**
Antibacterials Narrow	**CDGsn00892 + duration more than 4 weeks (Stable use allowed)**
Dipeptidyl peptidase 1 (DPP-1) inhibitors	**CDG40256**
RESLIZUMAB_mono_and_multi_ingredients	**CDG40244**
Anti-inflammatory drugs Narrow	**CDGsn00280**
Allergens Narrow	**CDGsn00276**
Anti-IL-6	**CDG00582**
Anti-IL-17	**CDG10444**
Anti-IL-23	**CDG10445**
Anti-IL-12	**CDG40103**
Methylxanthines	**CDG00262**
Anti-IL4 mAb	**CDG40192**

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, PK and ADA variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window. If there is no scheduled measurement within the visit window, the unscheduled measurement that is closest to the target date will be used (in case of tie select the latest).

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the value at the latest time of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 8 - Analyses window definition for efficacy endpoints - Treatment period

		Time windows							
Scheduled visit	**Targeted study day**	**Pre-BD FEV1**	**Post-BD FEV1**	**SGRQ**	**PGIC**	**PGIS**	**QOL-B**	**EQ-5D-5L/LCQ/ SNOT22**	**HRU**
Visit 1 (W-5 to W-3)	-35								
Week 0 (Visit 2)	1	-21-1	-21-1	≤1		≤1	≤1	≤1	≤1
Week 2 (Visit 3)	15								
Week 4 (Visit 4)	29	2-42	2-42						
Week 8 (Visit 5)	57	43-112	43-112	2-112	2-112	2-112	2-112		2-112
Week 12 (Visit 6)	85								
Week 16 (Visit 7)	113								
Week 24 (Visit 9)	169	113-224	113-224	113-224	113-224	113-224	113-224	2 - 266	113-224
Week 32 (Visit 11)	225								
Week 36 (Visit 12)	253								
Week 40 (Visit 13)	281	225-322	225-322	225-322	225-322	225-322	225-322		225-322
Week 48 (Visit 15)	337								
Week 52 (EOT)	365	323-379	323-379	> 322	>322	>322	>322	>266	>322
Week 72 (EOS)	505	>379	>379						

BD = Bronchodilator, FEV1 = Forced Expiratory Volume in 1st second, SNOT-22 = 22-item Sino-nasal Outcome Test, EQ-5D-5L = EuroQol 5-dimension 5-level quality-of-life Questionnaire, PGI = participant Global Impression, QOL-B = Quality-Of-Life-Bronchiectasis, SGRQ = St. George's Respiratory Questionnaire, LCQ = Leicester Cough Questionnaire, HRU = Healthcare Resource Utilization.

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed). For patients who withdrawn from the study treatment early, measurements taken at pEOT and after are also mapped to the analysis windows. In addition, and to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study treatment visits and participate in all safety follow-up assessments according to the visit schedule with a ±5-day window.

Table 9 - Analyses window definition for safety endpoints - Treatment period

		Time windows						
Scheduled visit	Targeted study day	Vital signs	Routine urine cotinine dipstick test	Hematology	clinical chemistry, urinalysis	ECG	Anabasine urine test	Physical examination
Visit 1 (W-5 to W-3)	-35	-35- -21	-35- -21	-35- -21	-35- -21	-35- -21	-35- -21	-35- -21
Week 0 (Visit 2)	1	-21-1	-21-1	-21-1	-21-1	-21-1		-21-1
Week 2 (Visit 3)	15							2-21
Week 4 (Visit 4)	29		2-42	2-42	2-42			22-42
Week 8 (Visit 5)	57	2-112	43-84	43-84	43-112			43-84
Week 12 (Visit 6)	85							
Week 16 (Visit 7)	113		85-140	85-140				85-140
Week 24 (Visit 9)	169	113-266	141-196	141-196	113-196	2 - 266	-21 - 266	141-196
Week 32 (Visit 11)	225		197-252	197-252	197-294			197-252
Week 36 (Visit 12)	253							
Week 40 (Visit 13)	281		253-308	253-308				253-308
Week 48 (Visit 15)	337		309-350	309-350				309-350
Week 52 (EOT)	365	267-379	351-379	351-379	295-379	267-379	267-379	351-379
Week 72 (EOS)	505	>379	>379	>379	>379	>379	>379	>379

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed). For patients who withdrawn from the study treatment early, measurements taken at pEOT and after are also mapped to the analysis windows. In addition, and to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study treatment visits and participate in all safety follow-up assessments according to the visit schedule with a ±5-day window.

Table 10 - Analyses window definition for PK/PD endpoints - Treatment period

		Time windows					
Scheduled visit	Targeted study day	Itepekimab concentration in serum	Anti-drug antibody	Blood eosinophils and neutrophils	Total IL-33	Whole blood RNA	Serum/plasma for archival samples
Visit 1 (W-5 to W-3)	-35						
Week 0 (Visit 2)	1	-21-1	≤1	≤1	≤1	≤1	≤1
Week 2 (Visit 3)	15						
Week 4 (Visit 4)	29	2-42		2-98	2-98	2-98	2-98
Week 8 (Visit 5)	57	43-112	2-112				
Week 12 (Visit 6)	85						
Week 16 (Visit 7)	113						
Week 24 (Visit 9)	169	113-266	113-266	99-266	99-379	99-379	99-266

		Time windows					
Scheduled visit	**Targeted study day**	**Itepekimab concentration in serum**	**Anti-drug antibody**	**Blood eosinophils and neutrophils**	**Total IL-33**	**Whole blood RNA**	**Serum/plasma for archival samples**
Week 32 (Visit 11)	225						
Week 36 (Visit 12)	253						
Week 40 (Visit 13)	281						
Week 48 (Visit 15)	337						
Week 52 (EOT)	365	267-379	267-379	267-379			267-379
Week 72 (EOS)	505	>379	>379	>379			>379

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed). For patients who withdrawn from the study treatment early, measurements taken at pEOT and after are also mapped to the analysis windows In addition, and to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study treatment visits and participate in all safety follow-up assessments according to the visit schedule with a ±5-day window

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and ADA will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

Missing data

Handling of medication with missing/partial dates

If a medication start date is partially missing, missing month is imputed with January and missing day is imputed as the first day of the month. If medication end date is partially missing, missing month is imputed with December and missing day is imputed as the last day of the month. If a medication date is missing, it will be considered as prior and concomitant medication. These data imputation is for categorization of prior/concomitant medication purpose only and will not be used in listings.

Handling of AEs with missing/partial date of onset

If the partial AE onset date information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment emergent. No imputation of AE end dates will be performed. These data imputation is for categorization of prior/concomitant medication purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

5.5 APPENDIX 5 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

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

5.6 APPENDIX 6 ST GEORGE'S RESPIRATORY QUESTIONANAIRE FOR COPD PATIENTS (SGRQ)

[redacted]

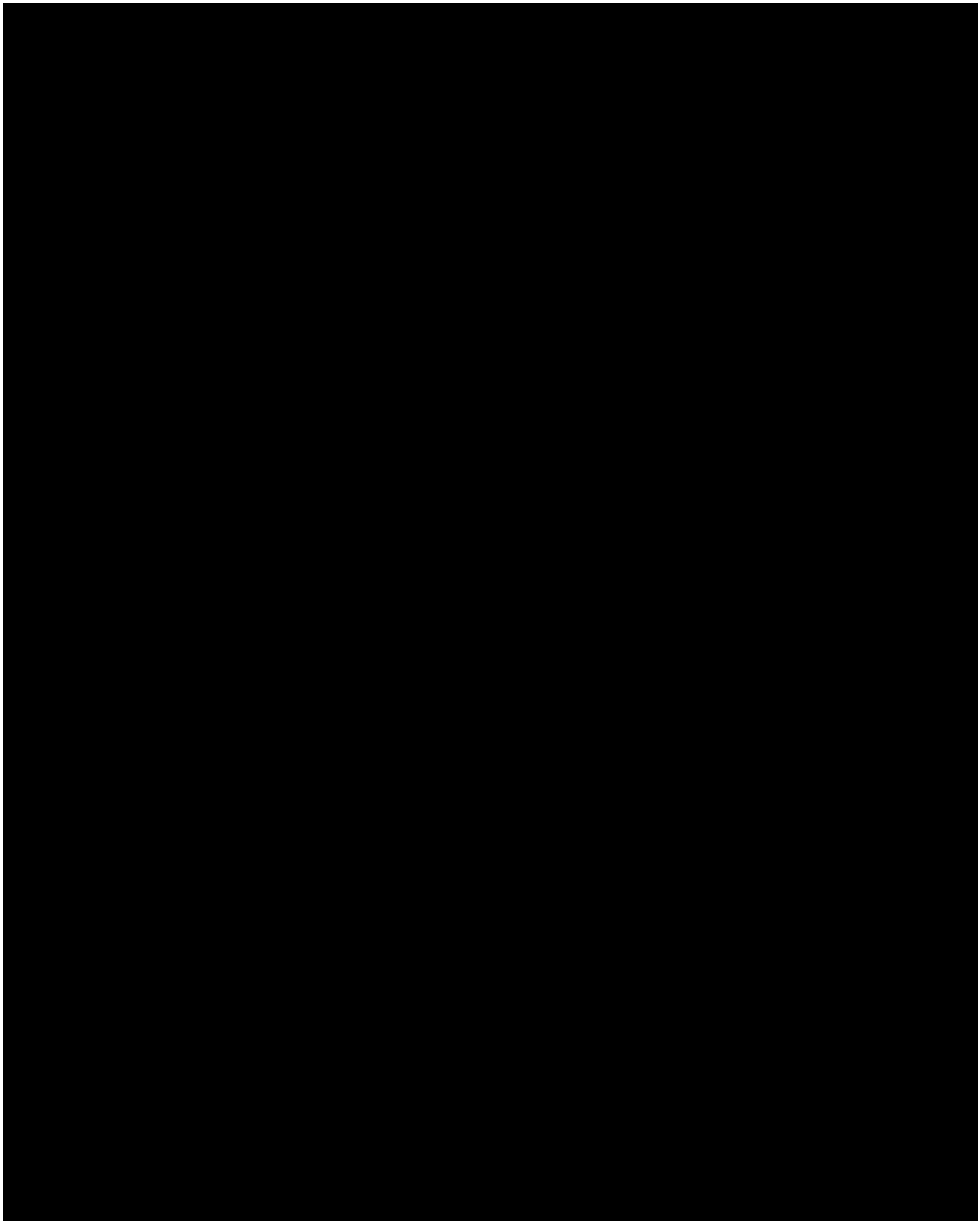
Copyright reserved
P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

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UK/ English (original) version 1

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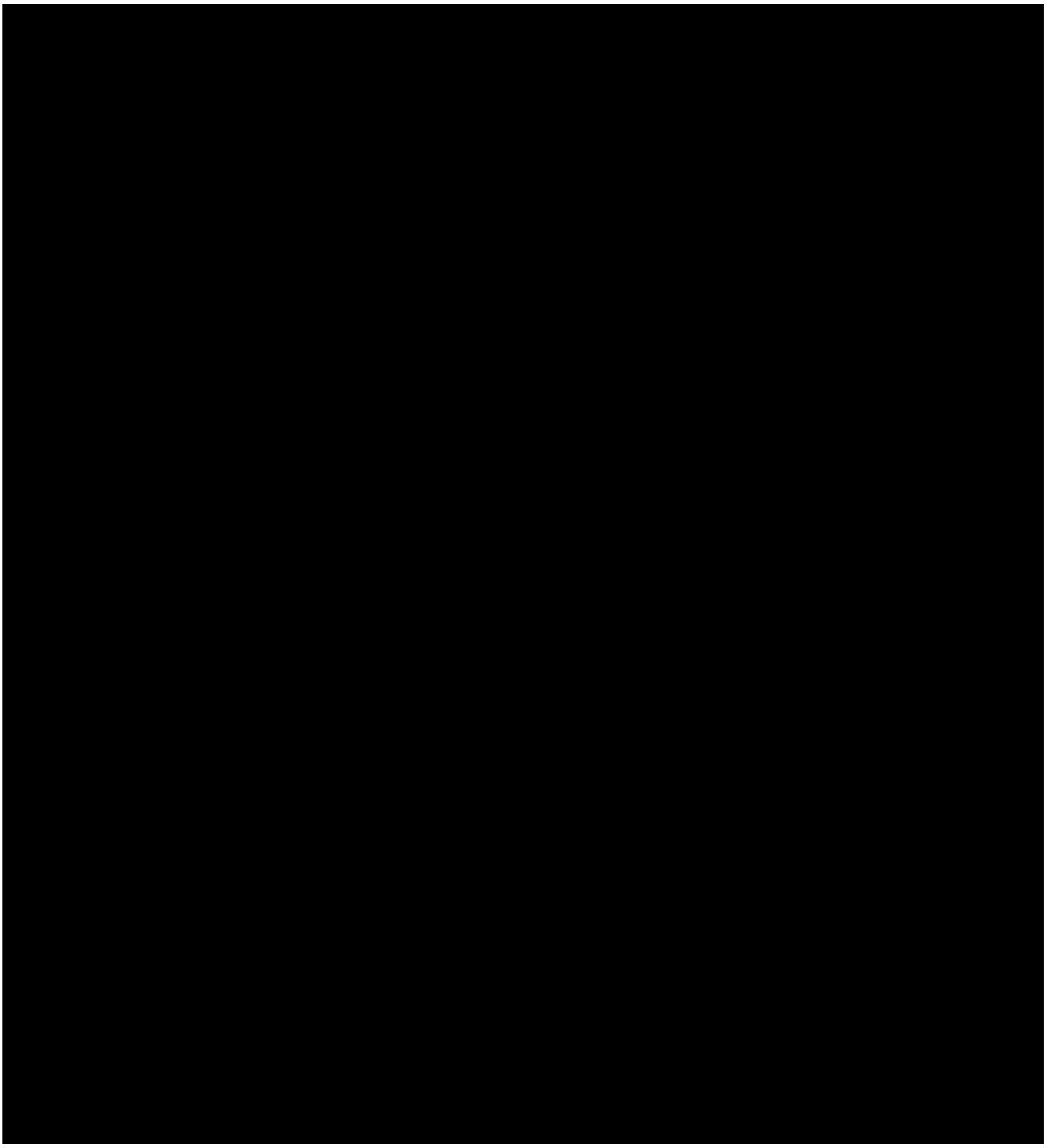


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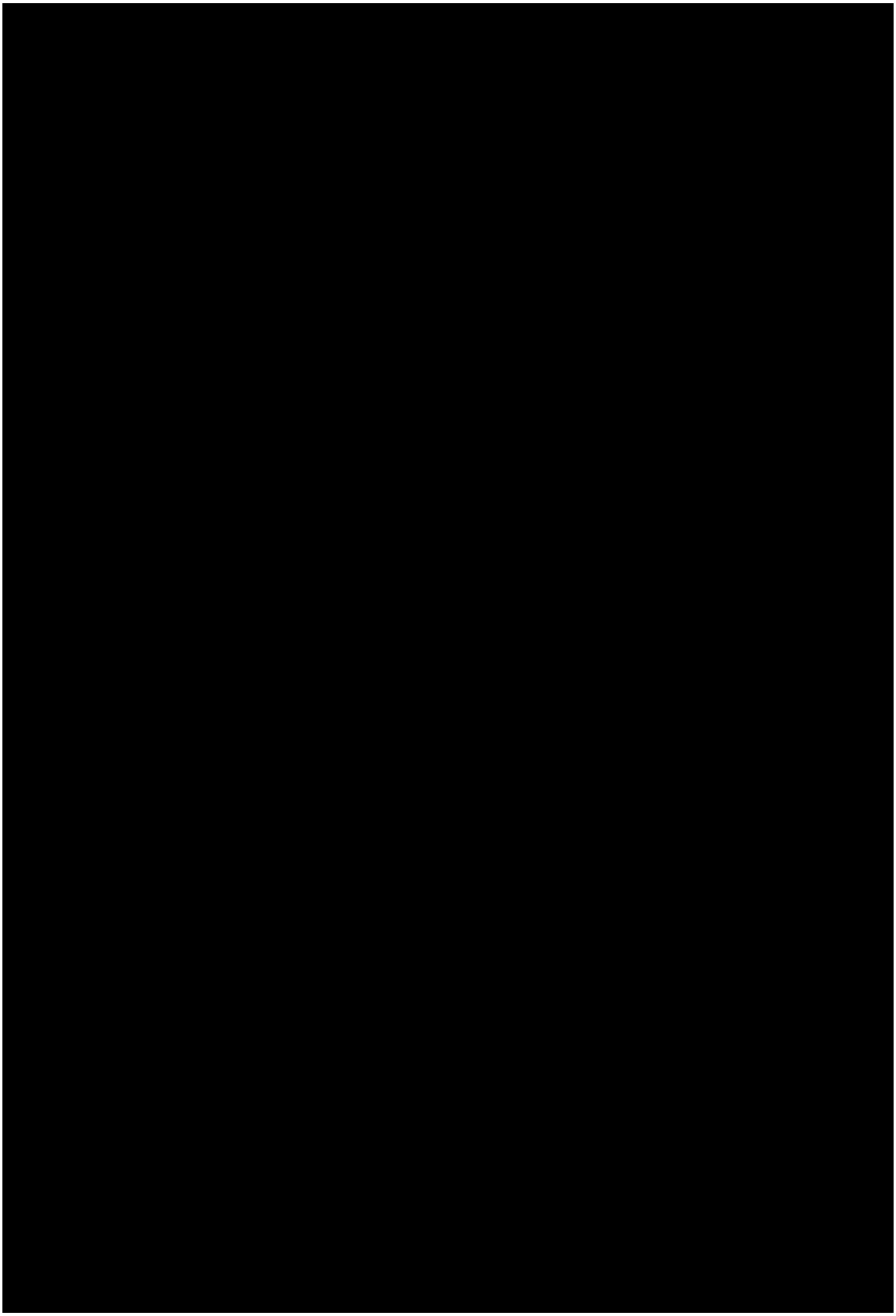
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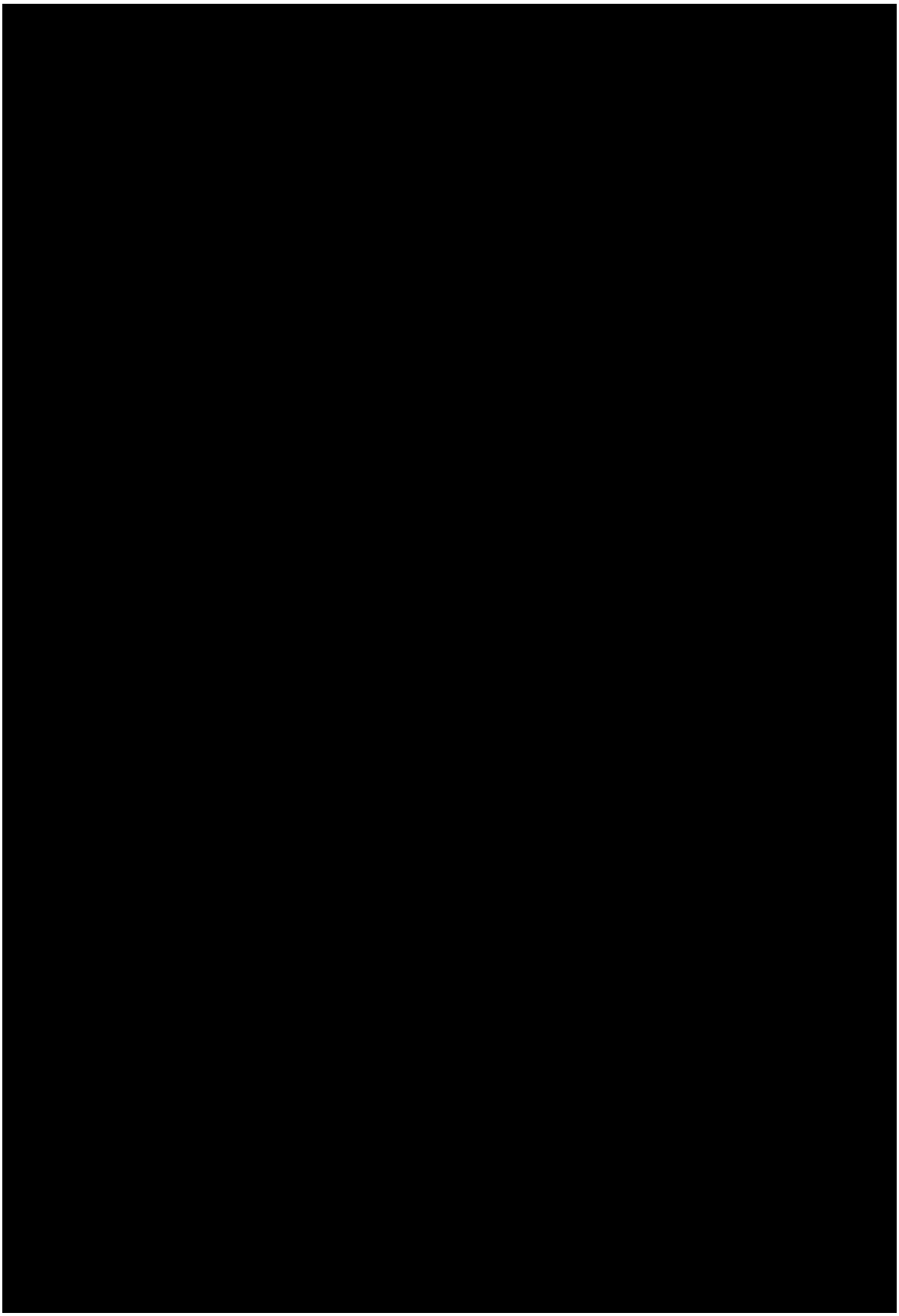
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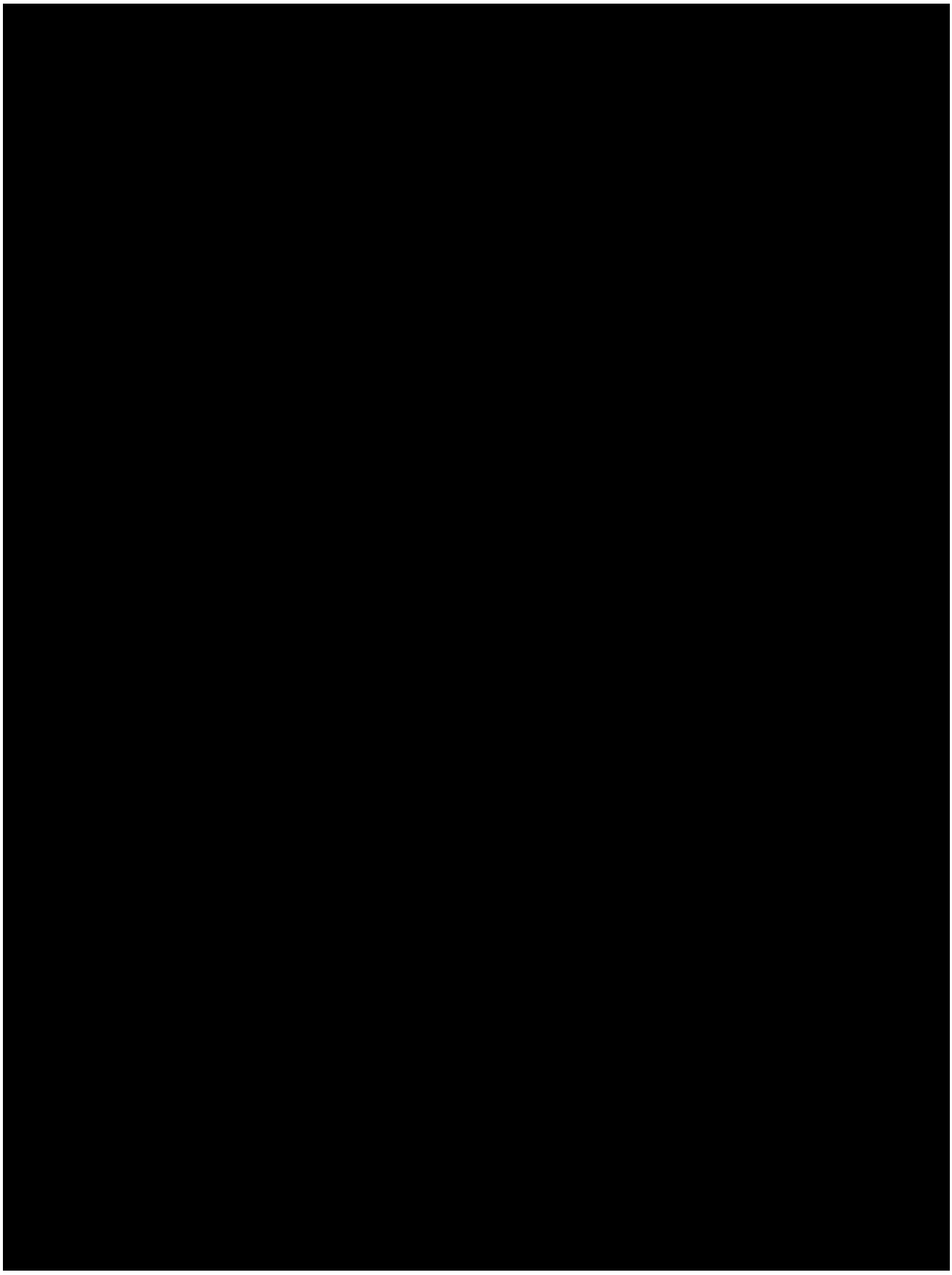


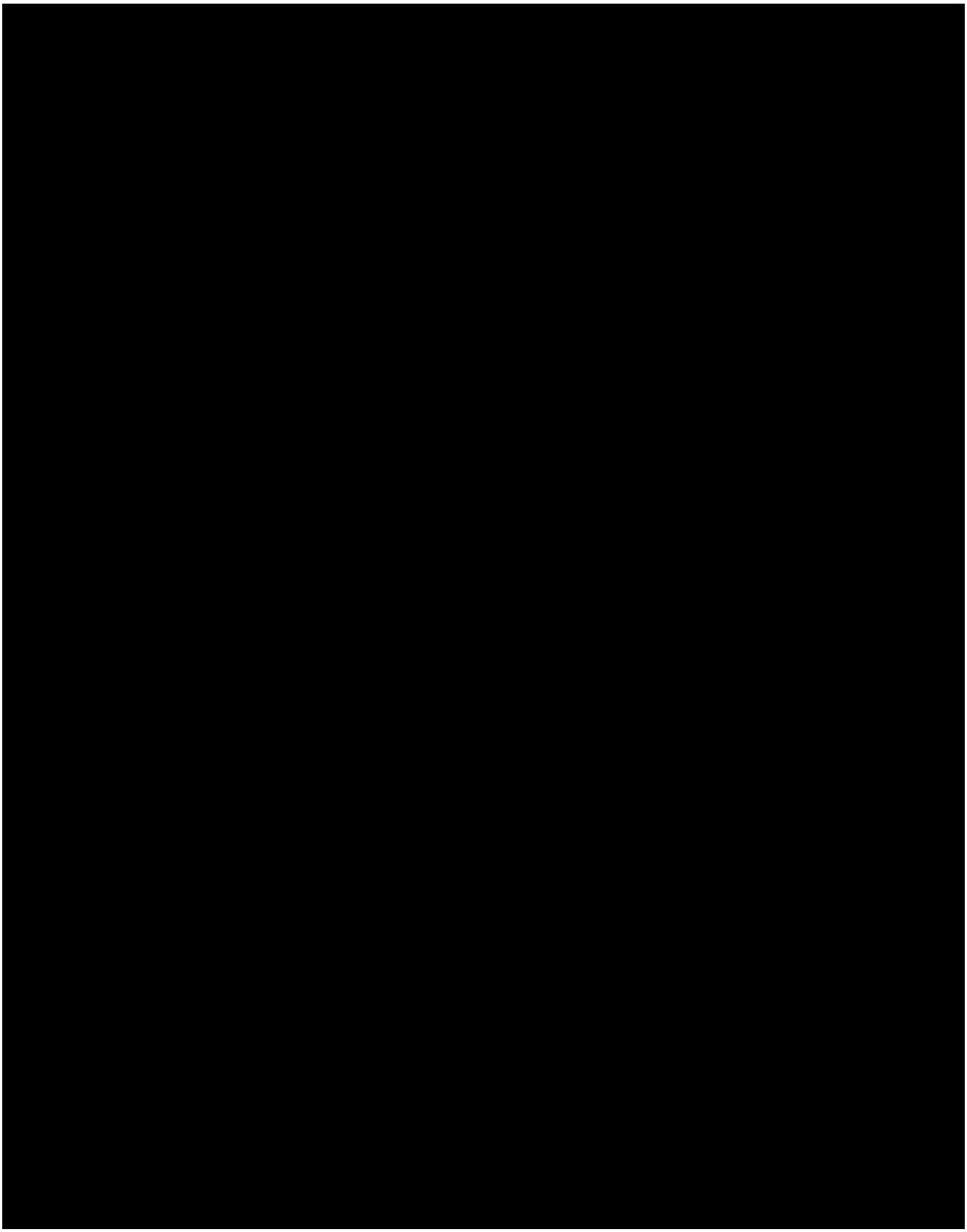


5.7 APPENDIX 7 SGRQ SCORING ALGORITHM



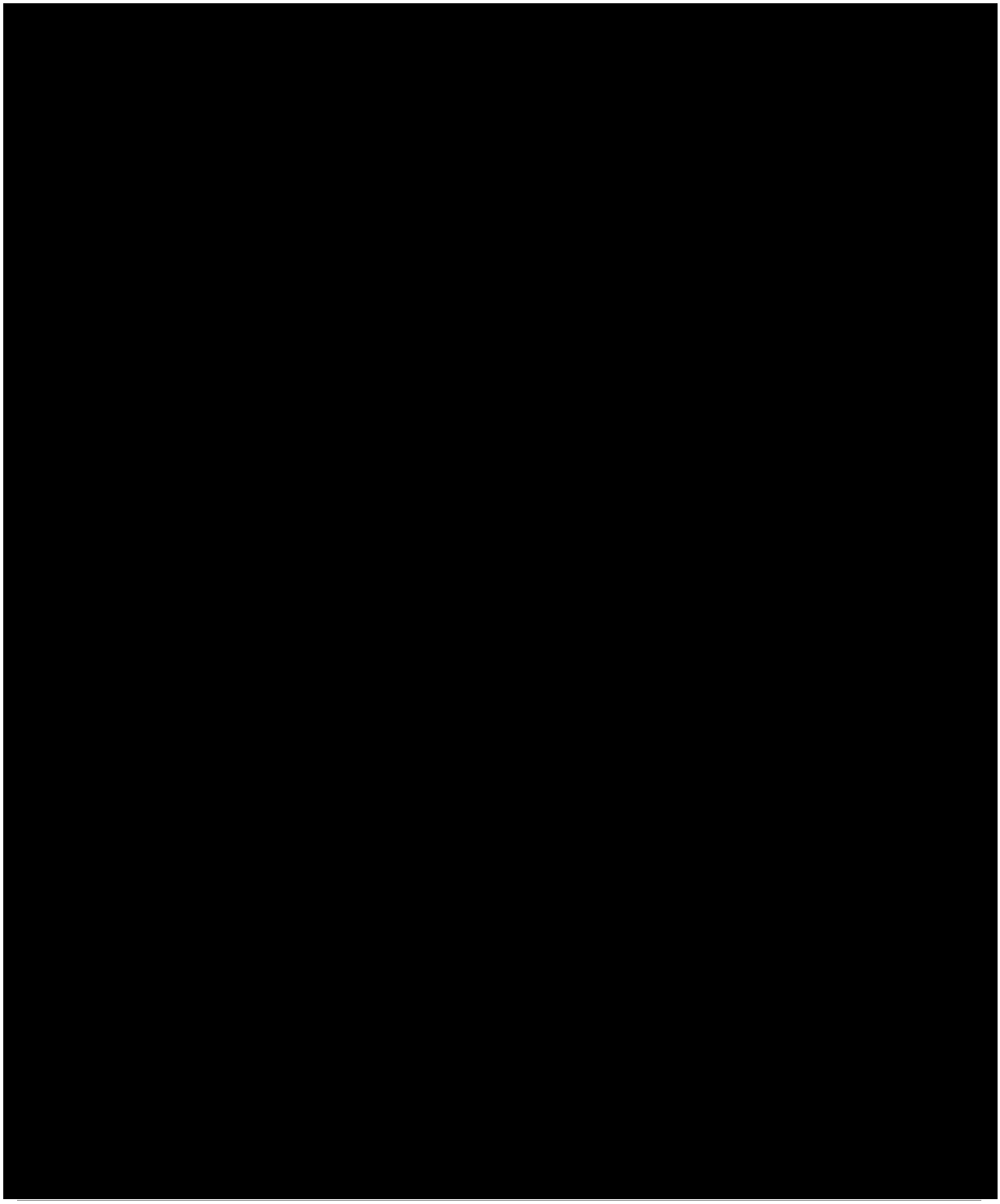








5.8 APPENDIX 8 QOL-B QUESTIONNAIRE



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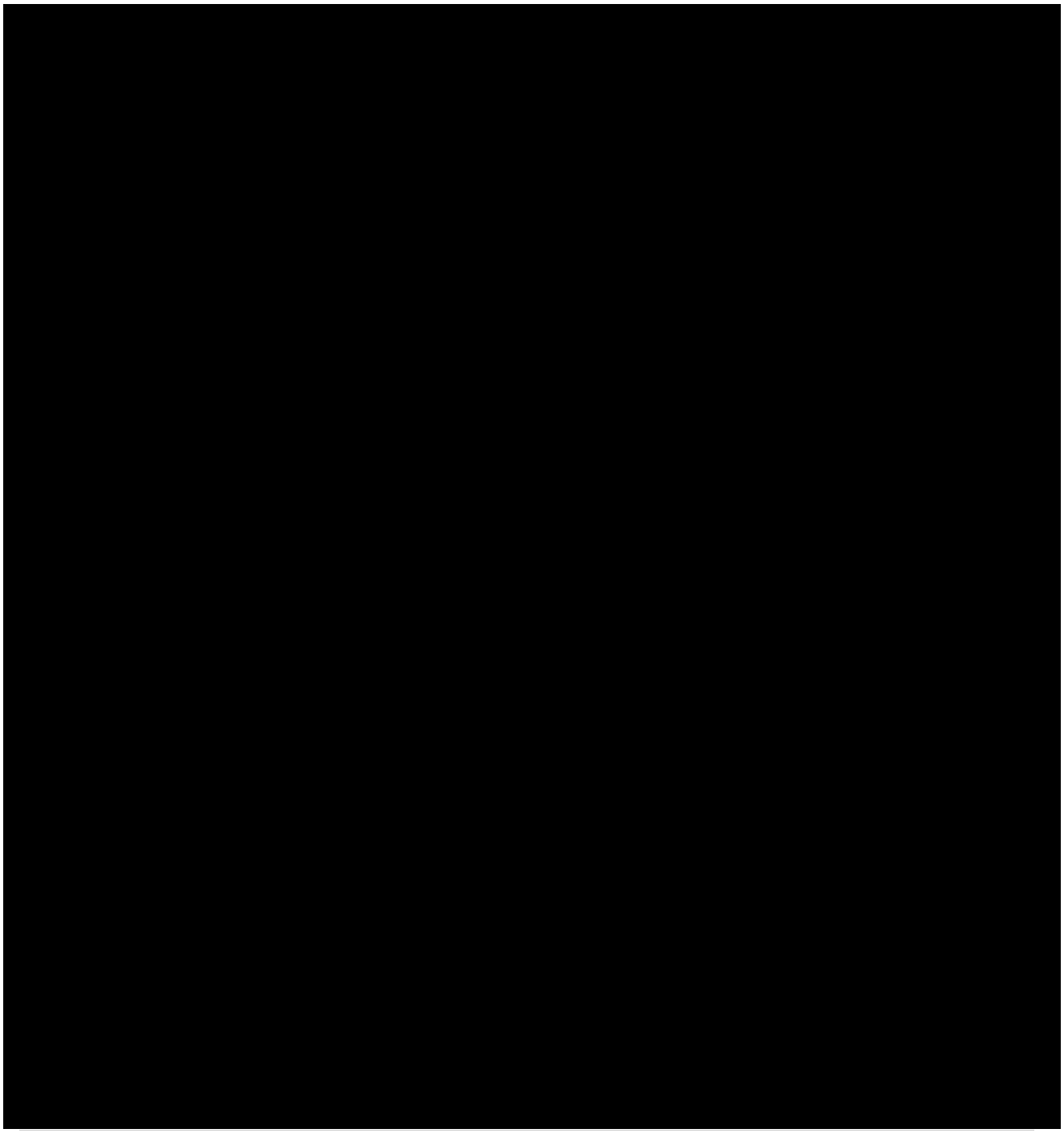
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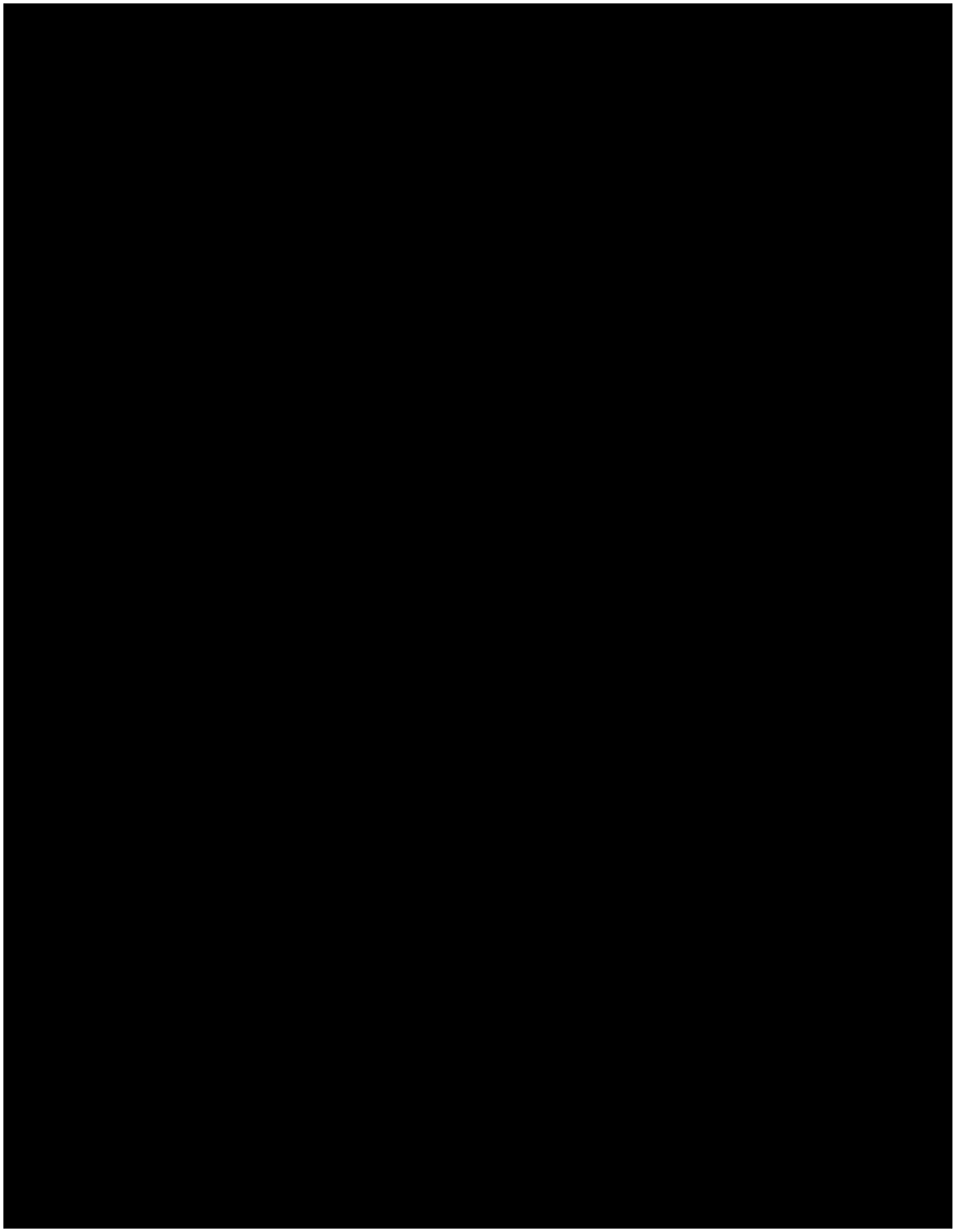
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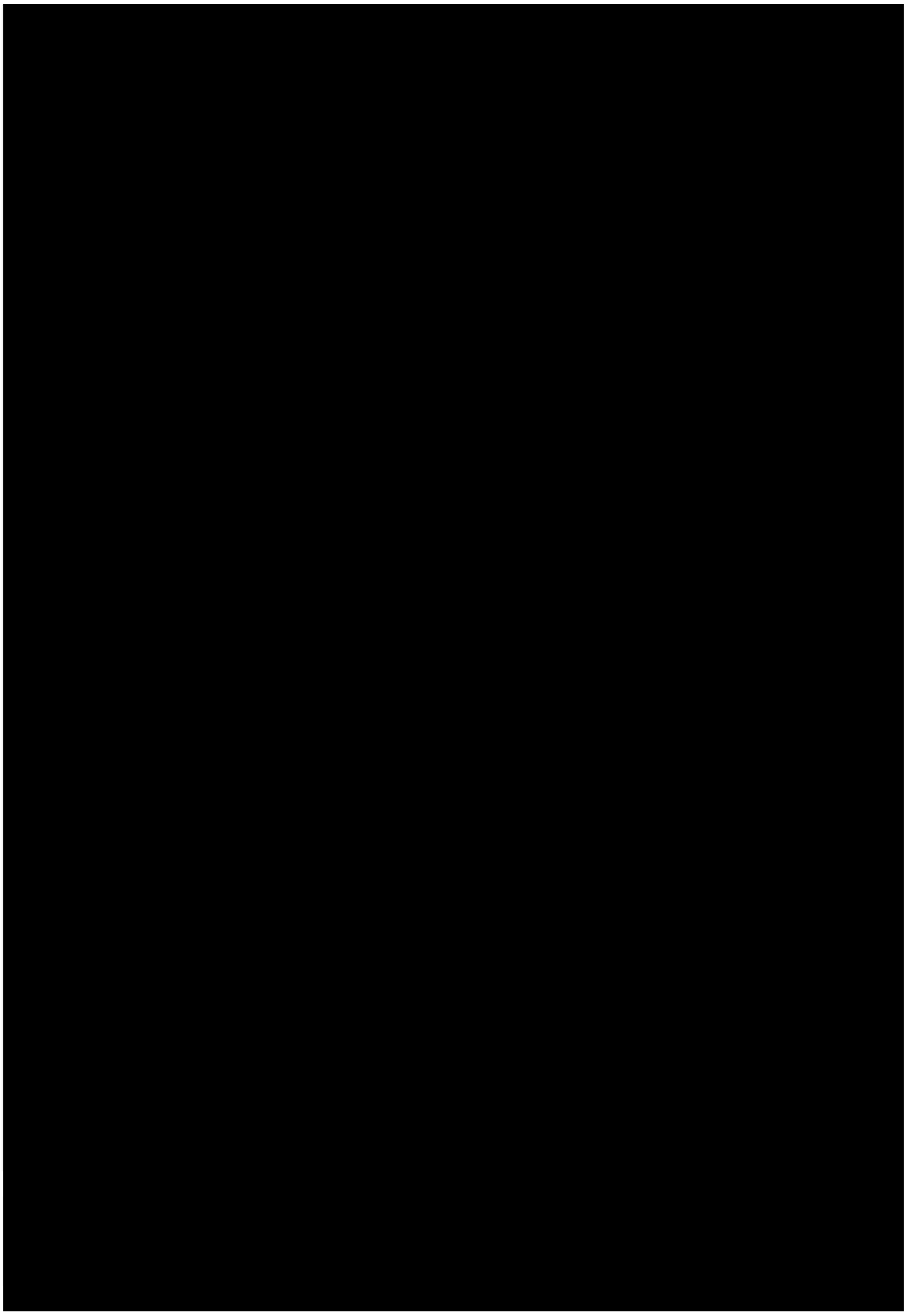
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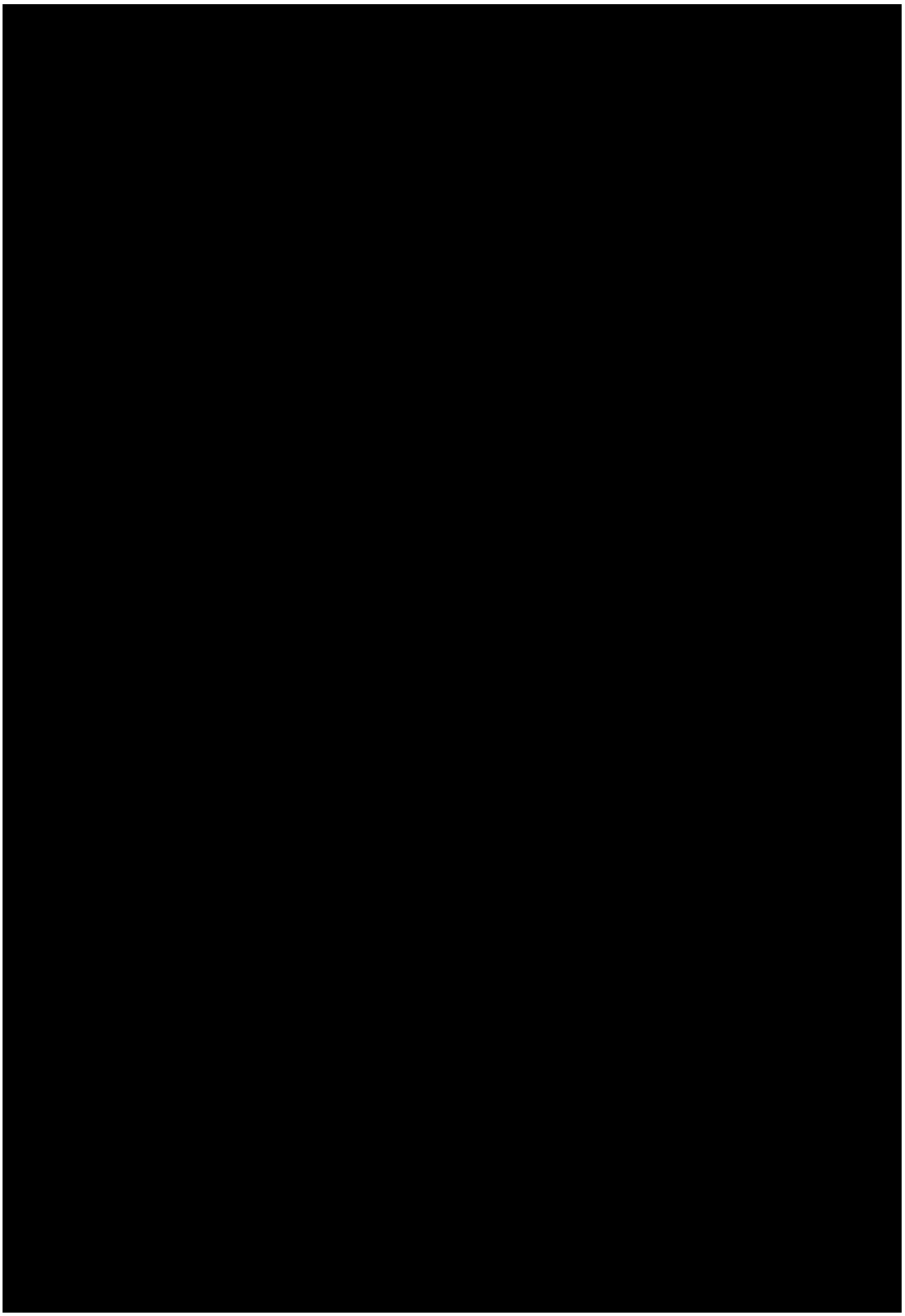


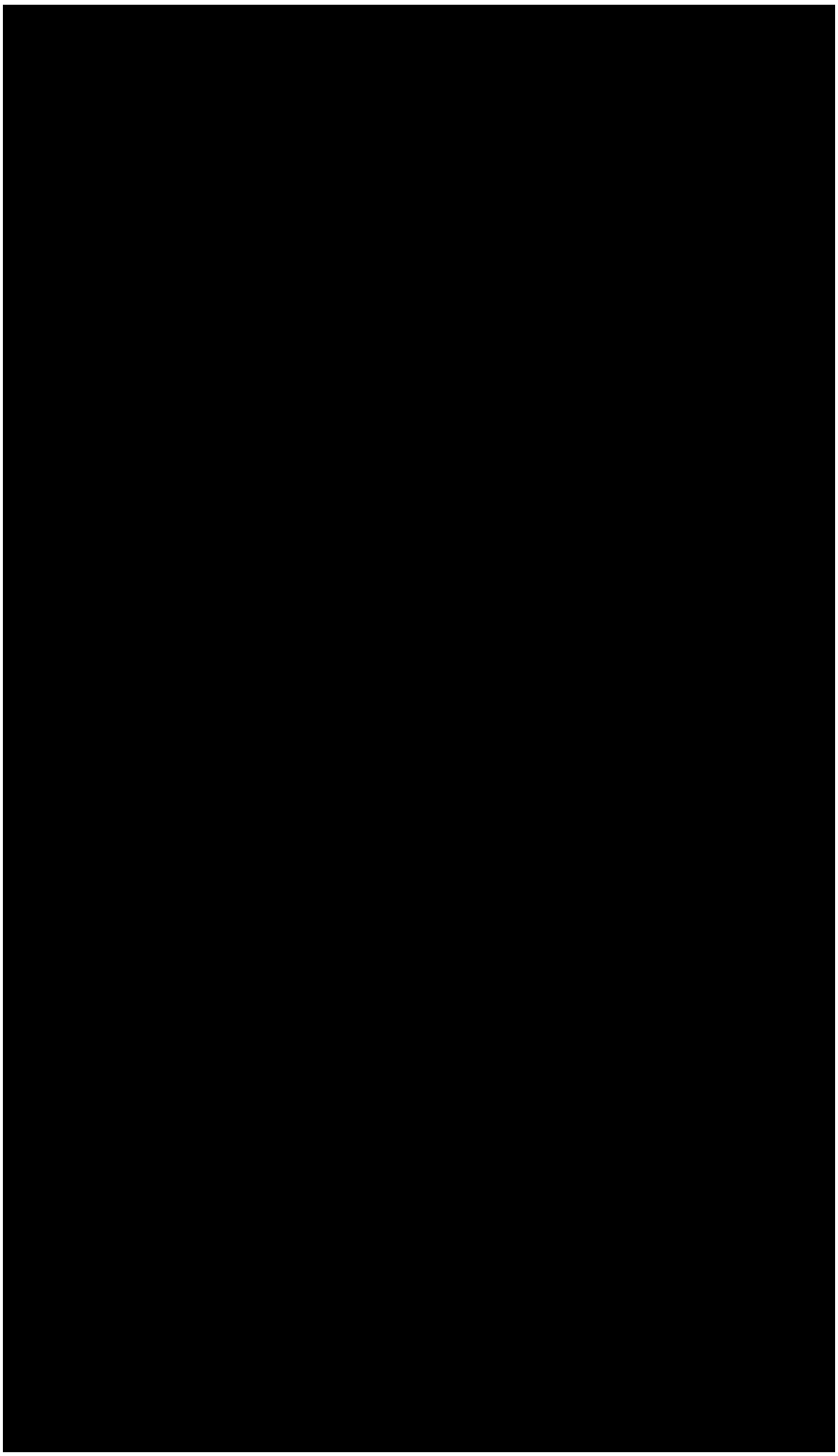
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5.9 APPENDIX 9 QOL-B SCORING ALGORITHM



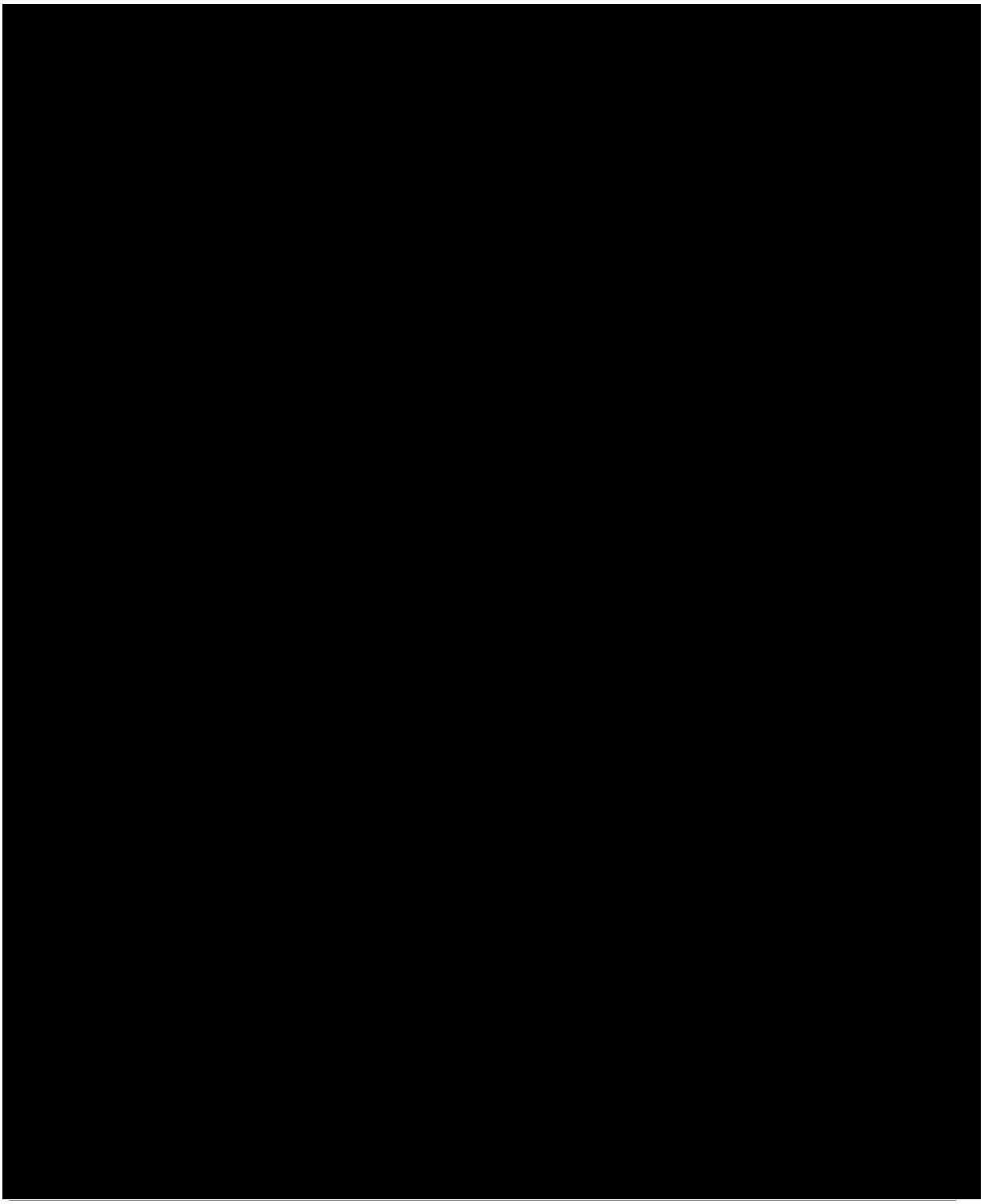








5.10 APPENDIX 10 LEICESTER COUGH QUESTIONNAIRE



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5.11 APPENDIX 11 PGIC/PGIS QUESTIONNAIRE

Patient Global Impression of Change (PGIC)

Please choose the response below that best describes the overall change in your bronchiectasis symptoms since you started taking the study injection.

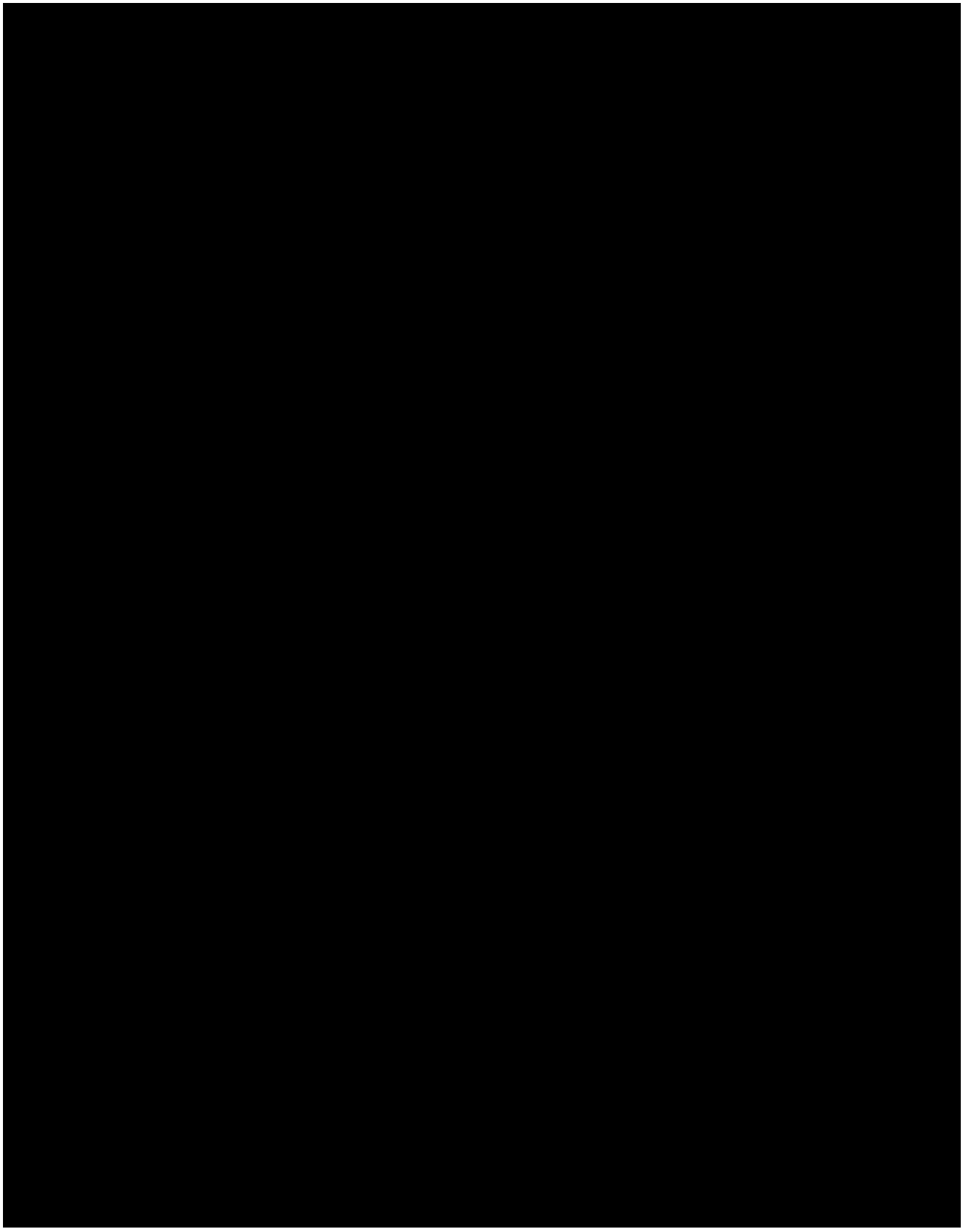
- ☐ Very much better (1)
- ☐ Much better (2)
- ☐ A little better (3)
- ☐ No change (4)
- ☐ A little worse (5)
- ☐ Much worse (6)
- ☐ Very much worse (7)

Patient Global Impression of Severity (PGIS)

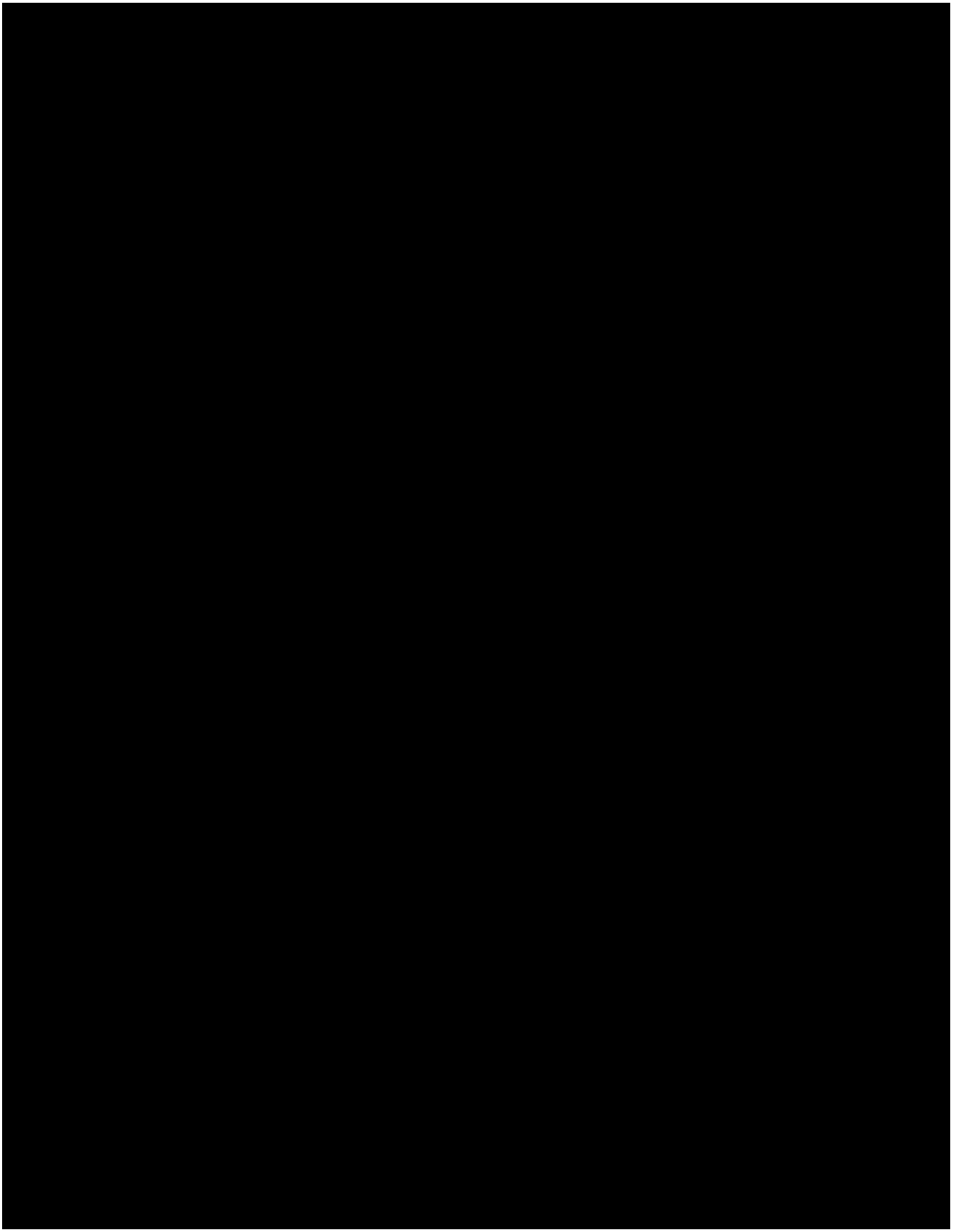
Please choose the response below that best describes the severity of your bronchiectasis symptoms over the past week.

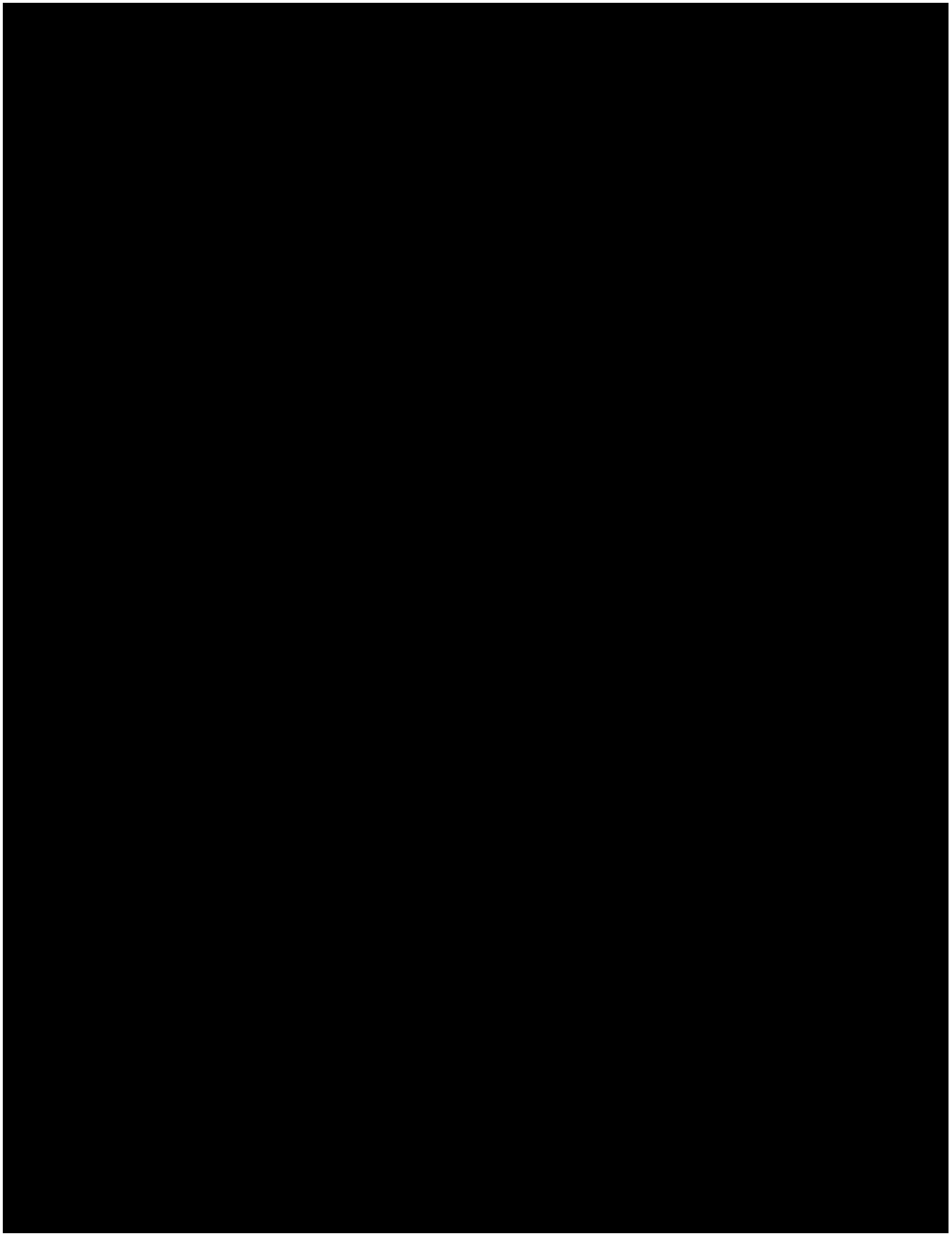
- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

5.12 APPENDIX 12 EQ-5D-5L QUESTIONNAIRE

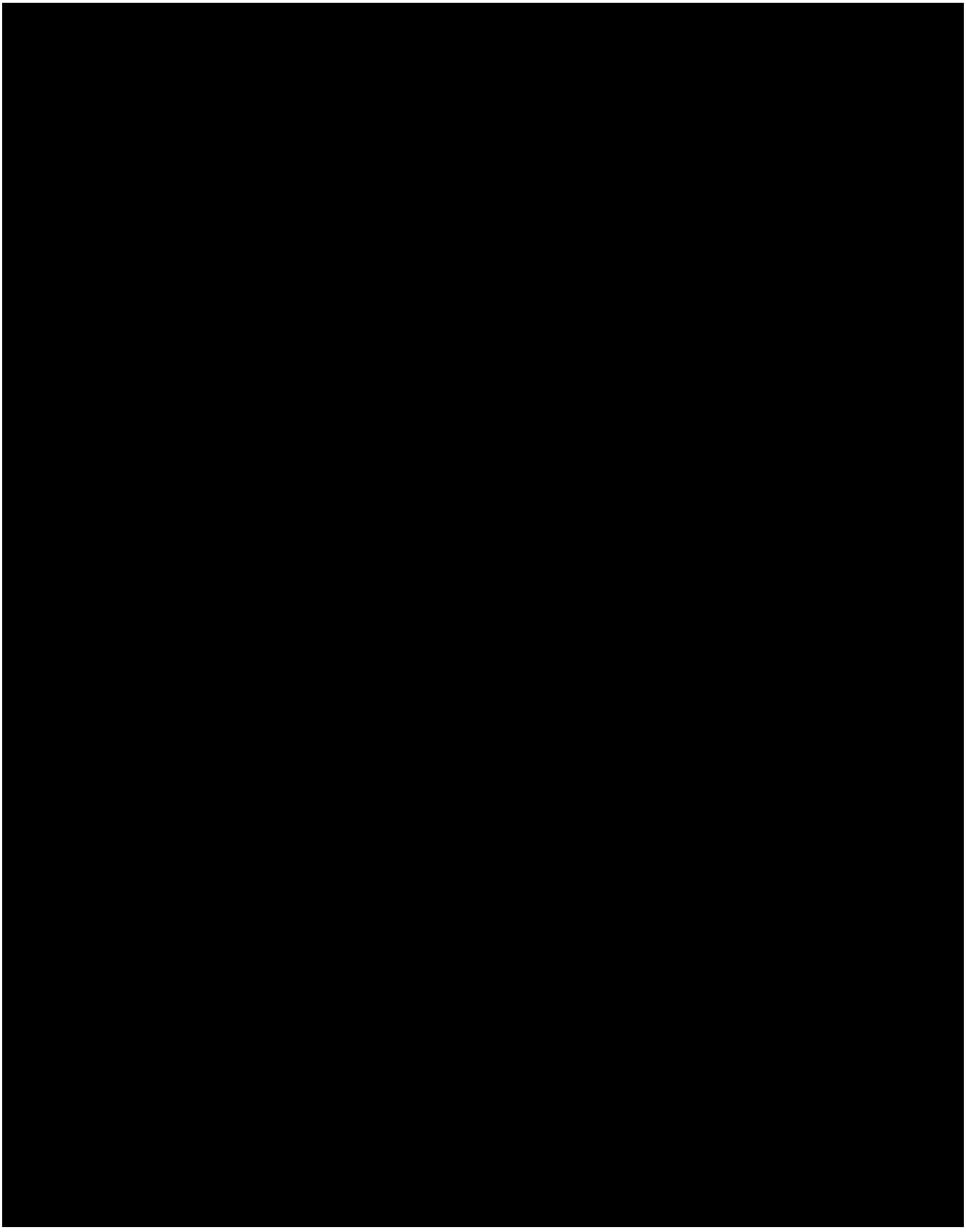


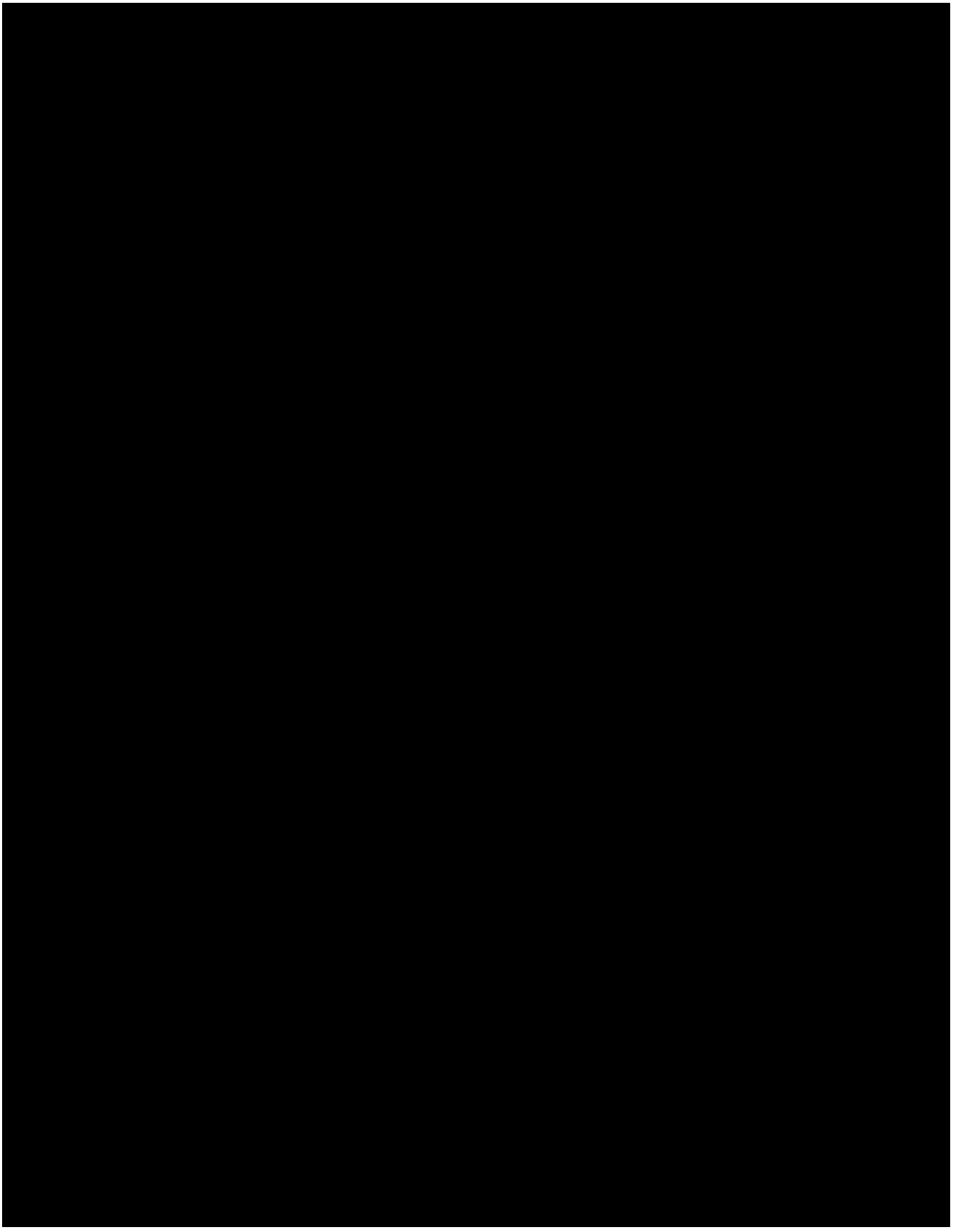
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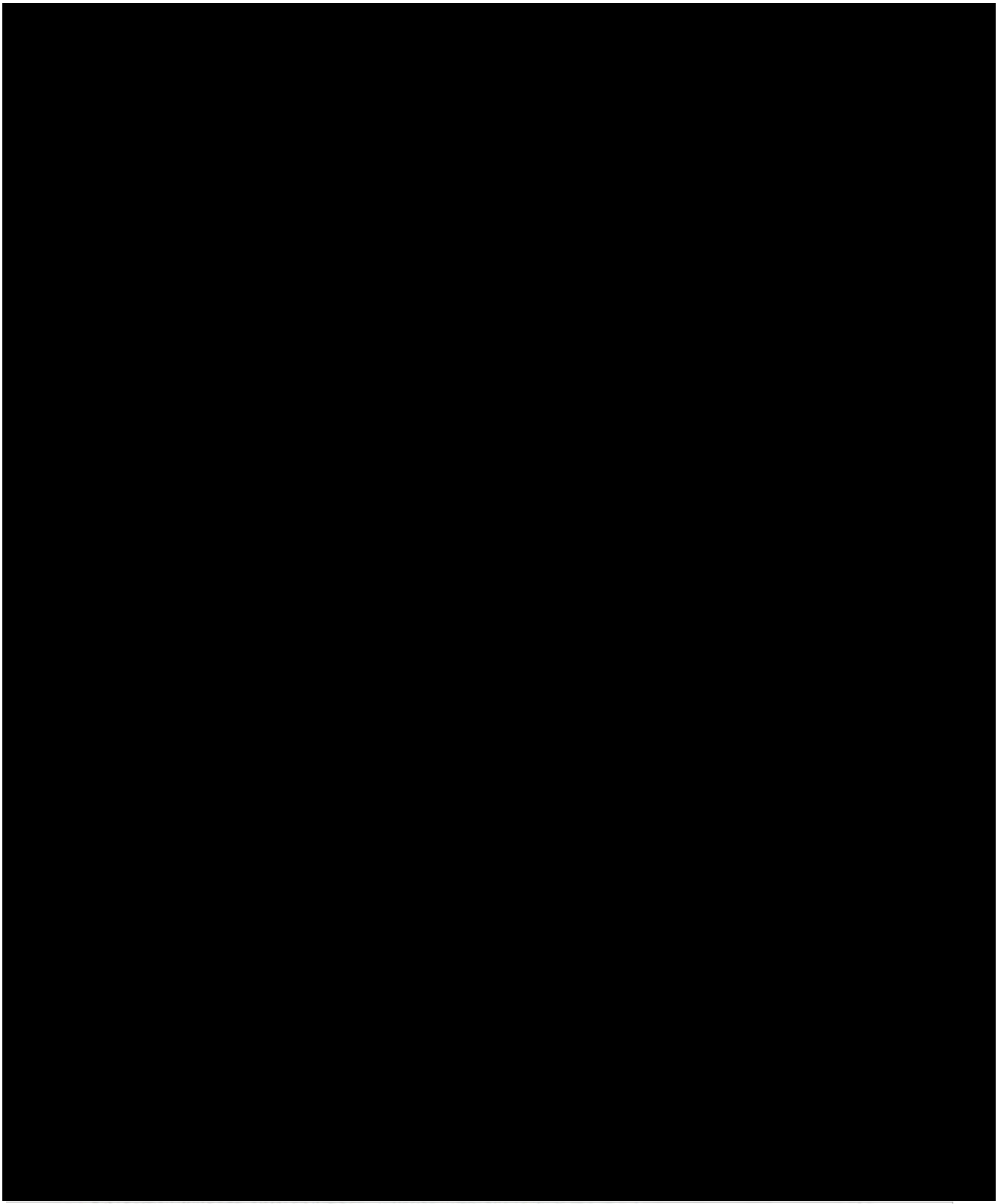
5.13 APPENDIX 13 SNOT-22 QUESTIONNAIRE

The SNOT-22 is a PRO questionnaire designed to assess the impact of CRS on patients HRQoL.The SNOT-22 has 22 items covering symptoms, social/emotional impact, productivity, and sleep consequences of CRS. The recall period is past 2 weeks. Each item is rated on a 6-point Likert scale response option, ranging from 0 (No problem) to 5 Problem as bad as it can be) A global score ranging from 0 to 110 is calculated by summing the responses to all items; higher score indicates greater rhinosinusitis-related health burden. The SNOT-22 is categorized into 5 domains, these include: Nasal (Items 1, 2, 3, 4, 5, 6, 7, and 12); Ear/Facial (Items 8, 9, 10, and 11); Sleep (Items 13, 14, 15, and 16); Function (Items 17, 18, and 19); Emotion (Items 20, 21, and 22). The domain scores are presented as the average item score per domain with higher score representing higher burden.

Missing scores:

The global score is the sum of response to each of the 22 questions. For responses with some item scores are missing, the global score will be imputed as mean of the completed scores× 22, providing at least 50% of items have been completed. If more than 50% of items are missing, the global score is set to missing.

The score for each domain is the average of response to each question in that domain. For responses with some item scores are missing, the domain score will be imputed as mean of the completed items in that domain, providing at least 50% of items in that domain have been completed. If more than 50% of items in a domain are missing, the score for that domain is set to missing.



SNOT-20 Copyright© 1996 by Jay F. Piccirillo, M.D., Washington University School of Medicine, St. Louis, Missouri
SNOT-22 Developed from modification of SNOT-20 by National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis Royal College of Surgeons of England.

5.14 APPENDIX 15 CALCULATION OF BRONCHIECTASIS SEVERITY INDEX

[redacted]

MODIFIED MEDICAL RESEARCH COUNCIL BREATHLESSNESS SCORE

[redacted]

6 REFERENCES

1. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD. 2005;2(1):75-9.

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5. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med. 2014;189(5):576-85.

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