

STATISTICAL ANALYSIS PLAN

Protocol title:	Randomized, double-blind, placebo-controlled, parallel-group Phase 3 study to evaluate the efficacy, safety, and tolerability of SAR440340/ REGN3500/ itepekimab (anti-IL-33 mAb) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)
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VERSION HISTORY

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

This SAP is based on protocol amendment 01 dated 20 Sept 2022 for Study EFC16750 and Study EFC16819. The major changes in these protocol amendments are summarized in [Section 5.2](#).

The first participant was randomized on 06 January 2021 for Study EFC16750 and on 08 March 2021 for Study EFC16819. This SAP is finalized before conduct of the interim analysis.

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 multinational, randomized, double-blind, placebo-controlled, parallel group (3 groups), 52-week, Phase 3 itepekimab/SAR440340 EFC16750 (AERIFY-1) and EFC16819 (AERIFY-2) studies. These two studies are planned to support registration of itepekimab in the proposed COPD indication and are being conducted in parallel. Both studies enroll former smokers and are identical, except that AERIFY-2 will also enroll an additional cohort of current smokers into two parallel groups.

1.1 STUDY DESIGN

EFC16750 (AERIFY-1) and EFC16819 (AERIFY-2) are both multinational, randomized, double-blind, placebo-controlled, parallel group, Phase 3 studies to assess the efficacy, safety, and tolerability of two dosing regimens of itepekimab in patients with moderate-to-severe COPD on an established triple (LAMA + LABA + ICS) or double background therapy (ICS + LABA or LAMA + LABA) who are former smokers. AERIFY-2 also includes an additional cohort of current smokers to further evaluate the efficacy and safety profile in this population.

Former smokers (AERIFY-1 and AERIFY-2)

For the **former smoker** participants in both AERIFY-1 and AERIFY-2: after a screening period of 3 to 5 weeks, participants are centrally randomized (using permuted block randomization schedule) via interactive response technology (IRT) in a 1:1:1 ratio to itepekimab 300 mg Q2W SC, itepekimab 300 mg Q4W SC, or matching placebo. The randomization is stratified by country (some countries may be pooled together), screening blood eosinophil count (<300 or ≥ 300 /mm³), and background inhaler therapy (triple or double) at baseline. To ensure enrollment according to the intended distribution of background inhaler therapy, and eosinophil count, the number of participants enrolled into each stratification group are controlled and monitored as follows:

- Double background therapy (ICS + LABA or LAMA + LABA): up to approximately 35% of participants
- Eosinophils ≥ 300 /mm³: approximately 35% of participants

52 weeks treatment duration portion

A total of approximately 930 (or up to 960 participants for AERIFY-1 to compensate for the shorter-than-expected observation duration in Ukraine participants due to the Ukraine and Russia military conflict, see [Section 2](#) for details) former smoker participants will be randomized into the three treatment groups (310 participants per treatment group) in each study (1860 former smoker participants in both studies). These participants will have a 52-week treatment period, followed by a 20-week safety follow-up period.

Variable treatment duration portion

For the AERIFY-1 and AERIFY-2 former smoker cohorts, a potential variable treatment duration is introduced to enroll additional randomized participants to compensate for the loss of power for the original study sample size because of the lower-than-expected rate of acute exacerbations of COPD observed due to COVID-19 pandemic. The variable treatment portion will begin after all the planned number of participants in the 52 weeks treatment portion have been enrolled. The additional participants enrolled for the variable treatment portion will have a maximum of up to 52 weeks treatment duration or until the last participant completes a minimum treatment of 24 weeks. The number of additional participants to be enrolled ranges from 0 (ie, no compensation) to up to 207 for each study, where the exact number will be determined based on the blinded annualized exacerbation rate observed approximately 3 months prior to all the planned number of participants in the 52 weeks treatment portion have been enrolled. Details are provided in [Section 2](#).

Hence, all former smokers enrolled in the trials will have a planned treatment period between 24 and 52 weeks, and a 20-week safety follow-up period.

Current smokers (AERIFY-2 only)

For the **current smoker** cohort in AERIFY-2 only: after a screening period of 3 to 5 weeks, participants are centrally randomized separately (using permuted block randomization schedule) via IRT in a 1:1 ratio to itepekimab 300 mg Q2W SC or matching placebo. The randomization stratification factors, and stratification group caps to ensure enrollment according to intended distribution of background therapy and eosinophil count, are the same as that for the former smoker cohort.

Initially, a total of approximately 240 current smokers (120 participants per arm) is planned to be randomized 1:1 to receive either itepekimab 300 mg Q2W SC or matching placebo to itepekimab. Due to the lower-than-expected rate of acute exacerbations of COPD observed due to COVID-19 pandemic at the time of protocol amendment 01, an additional 40 participants will be enrolled to maintain the targeted precision of the estimate.

All participants enrolled in the current smoker cohort will have a 52-week treatment period, followed by a 20-week safety follow-up period.

1.2 OBJECTIVE AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
Evaluate the efficacy of itepekimab compared with placebo on the annualized rate of acute moderate-or-severe COPD exacerbations in former smokers with moderate-to-severe COPD	Annualized rate of moderate or severe acute exacerbation of COPD (AECOPD)^a over the placebo-controlled treatment period [The primary estimand will be a treatment policy/while-on-treatment estimand]
Secondary	
Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in former smokers with moderate-to-severe COPD	[Key Secondary] Change from baseline in pre-BD FEV1 at Week 24 - Change from baseline in post-BD FEV1 at Week 24 and at Week 52 - Change from baseline in pre-BD FEV1 at Week 52
Evaluate the efficacy of itepekimab compared to placebo on occurrence of AECOPD in former smokers with moderate-to-severe COPD	Time to first moderate or severe AECOPD over the placebo-controlled treatment period
Evaluate the efficacy of itepekimab compared with placebo on severe AECOPD in former smokers with moderate-to-severe COPD	- Annualized rate of severe AECOPD over the placebo-controlled treatment period - Time to first severe AECOPD over the placebo-controlled treatment period
Evaluate the efficacy of itepekimab compared with placebo on corticosteroid-treated AECOPD in former smokers with moderate-to-severe COPD	Annualized rate of corticosteroid-treated AECOPD over the placebo-controlled treatment period
Evaluate the efficacy of itepekimab compared with placebo on respiratory symptoms in former smokers with moderate-to-severe COPD	Change from baseline in E-RS:COPD total score at Week 24 and at Week 52
Evaluate the efficacy of itepekimab compared with placebo on FEV1 slope in former smokers with moderate-to-severe COPD	Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after Week 4
Evaluate the efficacy of itepekimab compared with placebo on health-related quality of life (HRQoL) as assessed by St. George's Respiratory Questionnaire (SGRQ) in former smokers with moderate-to-severe COPD	- Change from baseline in SGRQ total score at Week 24 and at Week 52 - Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24 and at Week 52
Evaluate the safety and tolerability of itepekimab in former smokers with moderate-to-severe COPD	- Incidence of TEAEs, AESIs, SAEs, and AEs leading to permanent treatment discontinuation - Incidence of potentially clinically significant laboratory test, vital signs, and ECGs abnormalities in the treatment-emergent period
Evaluate the pharmacokinetic (PK) profile of itepekimab in former smokers with moderate-to-severe COPD	Functional itepekimab concentrations in serum from baseline to end of study

Objectives	Endpoints
- Evaluate immunogenicity to itepekimab in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on the annualized rate of acute moderate-or-severe COPD exacerbations in current smokers with moderate-to-severe COPD (AERIFY-2 only) - Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in current smokers with moderate-to-severe COPD (AERIFY-2 only) - Evaluate the safety and tolerability of itepekimab in current smokers with moderate-to-severe COPD (AERIFY-2 only) - Evaluate the PK profile of itepekimab in current smokers with moderate-to-severe COPD (AERIFY-2 only) - Evaluate immunogenicity to itepekimab in current smokers with moderate-to-severe COPD (AERIFY-2 only)	- Incidence of treatment-emergent anti-itepekimab antibodies responses throughout the study - Annualized rate of moderate or severe acute exacerbation of COPD (AECOPD) over the placebo-controlled treatment period - Change from baseline in pre-BD FEV1 at Week 24 and at Week 52 - Incidence of TEAEs, AESIs, SAEs, and AEs leading to permanent treatment discontinuation - Incidence of potentially clinically significant laboratory, vital signs, and ECGs abnormalities in the treatment-emergent period - Functional itepekimab concentrations in serum from baseline to end of study - Incidence of treatment-emergent anti-itepekimab antibodies responses throughout the study
Tertiary/Exploratory^b	
- Evaluate the efficacy of itepekimab compared with placebo on healthcare utilization in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on predictors of mortality in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on reduction in oral corticosteroid and antibiotic use in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on respiratory vital signs in former smokers with moderate-to-severe COPD - Evaluate the effect of itepekimab compared with placebo on biomarkers in former smokers with moderate-to-severe COPD	- Annualized number of days of healthcare resource utilization over the placebo-controlled treatment period - Annualized number of ER and hospital days related to AECOPD - Proportion of participants with BODE Index score >1 point decrease (=improvement) at Week 52 - Proportion of participants with pre-BD FEV1 improvement ≥100 mL at Week 24 and at Week 52 - Number of days on oral corticosteroids and antibiotics over the placebo-controlled treatment period - Change from baseline in resting oxygen saturation at Week 52 - Change from baseline in blood eosinophils and neutrophils at Weeks 4, 8, 12, 24, 36, and 52 - Change from baseline at Weeks 4, 12, 24, and 52 in the following: - Blood total IL-33 - Blood CRP

Objectives	Endpoints
To characterize the effects of itepekimab on gene expression and to study genetic factors that may predict itepekimab safety/efficacy	- Pharmacogenomics analysis (optional) - DNA sampling - RNA sampling

AECOPD = acute exacerbation of COPD; AE = adverse event; AESI = adverse event of special interest; BD = bronchodilator(y); BODE = Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ER = emergency room; E-RS:COPD = Evaluating Respiratory Symptoms in COPD; FEV1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life; IL-33 = interleukin 33; PK = pharmacokinetic(s); RNA = ribonucleic acid; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire; TEAE = treatment-emergent adverse event.

- a* Moderate exacerbations are recorded by the Investigator and defined as acute worsening of respiratory symptoms that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations are recorded by the Investigator and defined as AECOPD requiring hospitalization, or observation for >24 hours in an emergency department/urgent care facility or resulting in death. For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days between any course of systemic steroids/antibiotics or 14 days between discharge and new admission in case of hospitalization (severe events only).
- b* Other exploratory endpoints including PGIS, PGIC, and EQ-5D-5L will be described in other sections of the SAP.

1.2.1 Estimands

Estimands defined for primary and secondary endpoints are summarized in below [Table 2](#), [Table 3](#) and [Table 4](#). More details are provided in [Section 4](#).

Table 2 - Summary of primary and supportive estimands for the primary endpoint

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event (ICEs) handling strategy and missing data handling	Population-level summary
Primary objective: Evaluate the efficacy of itepekimab compared with placebo on the annualized rate of acute moderate or severe COPD exacerbations in former smokers with moderate-to-severe COPD (AERIFY-1 and AERIFY-2).				
Primary endpoint Primary estimand (Treatment policy estimand)	The annualized rate of moderate-or-severe AECOPD over the placebo-controlled treatment period	AERIFY-2 ITT former smokers	The following ICEs may occur: - Early discontinuation of study treatment. - Taking prohibited medications post randomization. - Taking study treatment not as randomized (eg, dispensing error). - Change in background therapy during the treatment period. It is noted that using systemic corticosteroids and/or antibiotics to treat exacerbation of COPD is not considered an ICE as it is a criterion for AECOPD definition, and it does not prevent continued study participation, nor exclude the possibility of additional AECOPD events. The ICEs will be handled using treatment policy strategy as follows: - 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 AECOPD events during the planned treatment period 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. - For participants taking prohibited medications, all the data observed during their planned treatment period (as defined above) will be included in the analyses. - If a participant takes study treatment not as randomized for any reason, the participant will be included in treatment group as initially randomized.	- Annualized rate of moderate or severe AECOPD during the planned placebo-controlled treatment period by treatment group. - Rate ratio (RR) for between treatment group comparisons, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and corresponding 2-sided 95% CI, as estimated with a negative binomial regression model described below. The primary analysis model will include the total number of moderate or severe AECOPD events that occur during the planned treatment period as the response variable, with treatment group, region, screening eosinophil strata (<300 cells/mm³ or ≥300 cells/mm³), controller therapy (triple, double) strata, baseline disease severity (as % predicted post-BD FEV1 used as continuous variable) and the total number of severe AECOPD events within 1 year prior to the study (0 or ≥1) as covariates. Log-transformed observation duration will be the offset variable.

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event (ICEs) handling strategy and missing data handling	Population-level summary
			4. 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. Missing data handling: Missing data assumption for the primary estimator: 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 AECOPD events that may happen after study discontinuation and up to end of the planned treatment duration. Sensitivity estimators: Sensitivity analysis focusing on the assumptions about missing data will be performed by varying assumptions about the rates of exacerbations after early study withdrawal. For example, assume that participants with missing data from the experimental arms had an expected event rate shifted to that of the placebo arm (ie, jump to reference), or had a greater exacerbation rate post withdrawal than those who withdrew from the placebo arm. A range of such assumptions will be considered to find a tipping point. Details can be found in Section 4.3.4.	
Primary endpoint Primary estimand (Treatment policy/While-on-treatment estimand)	The annualized rate of moderate-or-severe AECOPD over the placebo-controlled treatment period	AERIFY-1 ITT	The 4 ICEs specified above will be handled in the same way using treatment policy strategy. In addition, below ICE is applicable for AERIFY-1 study (no participants are planned to be enrolled in Ukraine for AERIFY-2 study). 5. Ukraine and Russia military conflict. The military conflict that began in Ukraine on 24th of February 2022 has led to disruptions in the conduct of the study in that region, including premature site closures, unexpected unavailability of site personnel for prolonged periods of time, loss to follow-up, early treatment discontinuations, inability to perform source data verification,	- Annualized rate of moderate or severe AECOPD during the planned placebo-controlled treatment period by treatment group. - Rate ratio (RR) for between treatment group comparisons, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and corresponding 2-sided 95% CI, as estimated with a negative binomial regression model described below.

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event (ICEs) handling strategy and missing data handling	Population-level summary
			and difficulty in supplying study drug to sites. Also access to the Healthcare system is expected to be impaired. These challenges have led to difficulties in performing protocol-specified procedures, including administering, or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. Since the primary endpoint (moderate or severe AECOPD) are defined by healthcare use (initiation of systemic corticosteroids and/or antibiotics, prolonged stay at an emergency department/urgent care facility and/or admission to a hospital), a direct effect of the military conflict on the outcome of the study cannot be ruled out. As a result, the ICE of Ukraine and Russia military conflict will be handled using <i>while-on-treatment strategy</i> as follows: 5. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the efficacy analyses. Missing data handling: 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. Sensitivity estimators: Sensitivity analysis focusing on the assumptions about missing data will be performed by varying assumptions about the rates of exacerbations after early study withdrawal. For example, assume that participants with missing data from the experimental arms had an expected event rate shifted to that of the placebo arm (ie, jump to reference), or had a greater exacerbation rate post withdrawal than those who withdrew from the placebo arm. A range of such assumptions will be considered to find a tipping point. Details can be found in Section 4.3.4.	The primary analysis model will include the total number of moderate or severe AECOPD events that occur during the planned treatment period as the response variable, with treatment group, region, screening eosinophil strata (<300 cells/mm³ or ≥300 cells/mm³), controller therapy (triple, double) strata, baseline disease severity (as % predicted post-BD FEV1 used as continuous variable) and the total number of severe AECOPD events within 1 year prior to the study (0 or ≥1) as covariates. Log-transformed observation duration will be the offset variable.

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event (ICEs) handling strategy and missing data handling	Population-level summary
Primary endpoint Supportive estimand (While-on-treatment estimand)	Annualized rate of moderate or severe AECOPD during placebo-controlled treatment period	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	The ICEs will be handled in the same way as specified for the primary estimand except that: 1. Only the events observed during the on-treatment period (from first administration of IMP to End of Treatment (EOT) visit for completers; otherwise to the last administration of IMP + 14 days) will be included in the analysis. Missing data handling: To account for a shorter duration of follow-up of participants who withdraw 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.	The same as for the Primary endpoint/Primary estimand above.
Primary endpoint Supportive estimand (Treatment policy estimand)	Annualized rate of moderate or severe AECOPD during placebo-controlled treatment period	• AERIFY-1 ITT	All the ICEs, including the ICE of Ukraine and Russia military conflict, will be handled in the same way using the treatment policy estimand as specified for the primary estimand. All the data observed during their planned treatment period will be included in the analyses. Missing data handling: To account for a shorter duration of follow-up of participants who withdraw 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.	The same as for the Primary endpoint/Primary estimand above.

AECOPD = acute exacerbation of COPD; BD = bronchodilator(y); CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; ICE = intercurrent event; ICS = inhaled corticosteroid; IMP = investigational medicinal product; ITT = intent-to-treat; MAR = missing at random; MMRM = mixed -effect model with repeated measures; Q2W = every 2 weeks; Q4W = every 4 weeks; RR = rate ratio; SC = subcutaneous(ly).

Table 3 - Summary of primary estimand for the key secondary endpoint

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in former smokers with moderate-to-severe COPD (AERIFY-1 and AERIFY-2).				
Key secondary endpoint Primary Estimand (Treatment policy/While-on-treatment estimand)	Change from baseline in pre-BD FEV1 at Week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	The first 4 ICEs will be handled using treatment policy strategy as follows: 1. Early discontinuation of study treatment for any reason before completing the planned treatment period: All pre-BD FEV1 data collected during the planned treatment period will be included in the analysis irrespective of treatment adherence. 2. Taking prohibited medications during the planned treatment period: All pre-BD FEV1 data will be included in the analysis irrespective of use of prohibited medications. 3. 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). 4. For participants with change in background therapy, all the data observed during the planned treatment period will be included in the analyses. The ICE of Ukraine and Russia military conflict (applicable to AERIFY-1 only) will be handled using while-on-treatment strategy as follow: 5. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022, for the efficacy analyses. Missing data handling: Missing data assumption for the primary estimator: 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.	• Mean change from baseline in pre-BD FEV1 at Week 24 by treatment group. • Difference in the mean change from baseline in pre-BD FEV1 at Week 24 between treatment groups, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and the corresponding 2-sided 95% CI, as estimated using an MMRM approach. The model will include change from baseline in pre-BD FEV1 values up through to Week 24 as response variable, and treatment, age (continuous variable), sex, baseline height (continuous variable), region, screening eosinophil strata (<300 cells/mm³ or ≥300 cells/mm³), controller therapy strata (triple, double), visit, treatment-by-visit interaction, and baseline pre-BD FEV1 value used as continuous variable and baseline-by-visit interaction as covariates.

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
			Sensitivity estimators: Sensitivity analyses to assess the robustness of the conclusion of the primary estimator will be performed using pattern mixture model by multiple imputation for missing data. Details can be found in Section 4.4.1.4.	
Key secondary endpoint: Supportive estimand (While-on-treatment estimand)	Change from baseline in pre-BD FEV1 at Week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	The ICEs will be handled using the same way as specified for the primary estimand except for: • Only the data observed during the on-treatment period (from first administration of IMP to EOT visit for completers; otherwise to the last administration of IMP + 14 days) will be included in the analysis. Missing data handling: The 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.	The same as for the Key secondary endpoint/Primary estimand above.
Key secondary endpoint: Supportive estimand (Treatment policy estimand)	Change from baseline in pre-BD FEV1 at Week 24	• AERIFY-1 ITT	All the ICEs, including the ICE of Ukraine and Russia military conflict, will be handled in the same way using the treatment policy estimand as specified for the primary estimand. All the data observed during their planned treatment period will be included in the analyses. Missing data handling: The 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.	The same as for the Key secondary endpoint/Primary estimand above.

AECOPD = acute exacerbation of COPD; BD = bronchodilator(y); CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; ICE = intercurrent event; ICS = inhaled corticosteroid; IMP = investigational medicinal product; ITT = intent-to-treat; MAR = missing at random; MMRM = mixed-effect model with repeated measures; Q2W = every 2 weeks; Q4W = every 4 weeks; RR = rate ratio; SC = subcutaneous(ly).

Table 4 - Summary of primary estimand for other secondary endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in former smokers with moderate-to-severe COPD (AERIFY-1 and AERIFY-2).				
Other secondary endpoints Treatment policy/While-on-treatment estimand	Change from baseline in post-BD FEV1 at Week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	The ICEs, ICEs handling, and the missing data handling are defined/described in the same way as those specified for the Treatment policy/While-on-treatment estimand for the key secondary endpoint of Change from baseline in pre-BD FEV1 at Week 24 (see Table 3).	• Mean change from baseline in post-BD FEV1 at Week 24 by treatment group. • Difference in the mean change from baseline in post-BD FEV1 at Week 24 between treatment groups, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and the corresponding 2-sided 95% CI, as estimated using an MMRM approach. The same model as that for pre-BD FEV1 at Week 24 (see Table 3) will be used.
Other secondary endpoints Treatment policy/While-on-treatment estimand	Change from baseline in pre-BD FEV1 at Week 52	• AERIFY-1 ITT-Week 52 population • AERIFY-2 ITT-Week 52 population former smokers	The ICEs, ICEs handling, and the missing data handling are defined/described in the same way as those specified for the Treatment policy/While-on-treatment estimand for the key secondary endpoint of Change from baseline in pre-BD FEV1 at Week 24 (see Table 3). The analysis of change from baseline in pre-BD FEV1 at Week 52 will be performed on the ITT-Week 52 population (defined in Section 3), which includes all the patients who have the opportunity to complete 52 weeks of treatment period based on their randomization dates, regardless of whether the patient is enrolled in the 52 weeks treatment duration portion, or in the additional variable treatment duration portion. All patients in the ITT-Week 52 population have a planned treatment duration of 52 weeks.	• Mean change from baseline in pre-BD FEV1 at Week 52 by treatment group. • Difference in the mean change from baseline in pre-BD FEV1 at Week 52 between treatment groups, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and the corresponding 2-sided 95% CI, as estimated using an MMRM approach. The same model as that for pre-BD FEV1 at Week 24 (see Table 3) will be used; the

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
				response variable will include change from baseline in pre-BD FEV1 values up through to Week 52.
Other secondary endpoints Treatment policy/While-on-treatment estimand	Change from baseline in post-BD FEV1 at Week 52	- AERIFY-1 ITT-Week 52 population - AERIFY-2 ITT-Week 52 population former smokers	The ICEs, ICEs handling, and the missing data handling are defined/described in the same way as those specified for the Treatment policy/While-on-treatment estimand for the key secondary endpoint of Change from baseline in pre-BD FEV1 at Week 24 (see Table 3). The analysis of change from baseline in post-BD FEV1 at Week 52 will be performed on the ITT-Week 52 population (defined in Section 3).	- Mean change from baseline in post-BD FEV1 at Week 24 and at Week 52 by treatment group. - Difference in the mean change from baseline in post-BD FEV1 at Week 24 and at Week 52 between treatment groups, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and the corresponding 2-sided 95% CI, as estimated using an MMRM approach. The same model as that for pre-BD FEV1 at Week 24 (see Table 3) will be used; the response variable will include change from baseline in post-BD FEV1 values up through to Week 52 as response variable.
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on occurrence of AECOPD, severe AECOPD, and corticosteroid-treated AECOPD in former smokers with moderate-to-severe COPD (AERIFY-1 and AERIFY-2).				
Other secondary endpoints: Treatment policy/While-on-treatment estimand	Time to first moderate or severe AECOPD over the placebo-controlled treatment period	- AERIFY-1 ITT - AERIFY-2 ITT former smokers	The following ICEs may occur: - Early discontinuation of study treatment. - Taking prohibited medications post randomization. - Taking study treatment not as randomized (eg, dispensing error). - Change in background therapy during the treatment period. - Ukraine and Russia military conflict (only applicable to AERIFY-1 study). The first 4 ICEs will be handled using treatment policy strategy as follows:	Hazard ratio (HR) for between treatment group comparisons, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and corresponding 2-sided 95% CI, as estimated with a Cox regression model described below. The time to first moderate or severe AECOPD will be analyzed using a Cox regression model. The model will include the time to the first event as the

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
			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, AECOPD events and related data would be collected and reported over the entire planned placebo-controlled treatment period for all study participants even if some participants may have discontinued the study treatment. Analytically, the time to first moderate or severe AECOPD over the planned placebo-controlled treatment period analysis is performed regardless of the occurrence of the ICEs or when do the ICEs occur. For participants without any AECOPD events, the time from randomization to the date of treatment completion or treatment discontinuation up to their planned treatment period (event time will be considered as censored at date of EOT or the last contact date within the planned treatment duration) will be used in the analysis. The ICE of Ukraine and Russia military conflict will be handled using while-on-treatment strategy as follow: for participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022, for the analyses.	dependent variable, and treatment group, screening eosinophil strata, region, controller therapy strata, baseline disease severity (as % predicted post-BD FEV1, used as continuous variable), and number of severe AECOPD events within 1 year prior to the study (0 or ≥ 1) 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 AECOPD events over time will be calculated.
	Annualized rate of severe AECOPD over the placebo-controlled treatment period	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	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 AECOPD over the placebo-controlled treatment period.	Same as those for the primary endpoint of annualized rate of moderate-or-severe AECOPD over the planned placebo-controlled treatment period.
	Time to first severe AECOPD over the placebo-controlled treatment period	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	The ICEs, their handling, and the missing data handling procedures are defined/described in the same way as those for the secondary endpoint of time to first moderate or severe AECOPD over the placebo-controlled treatment period.	Same as those for the secondary endpoint of time to first moderate or severe AECOPD over the planned placebo-controlled treatment period.

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
	Annualized rate of corticosteroid-treated AECOPD over the placebo-controlled treatment period	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	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 AECOPD over the placebo-controlled treatment period.	Same as those for the primary endpoint of annualized rate of moderate-or-severe AECOPD over the planned placebo-controlled treatment period.
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on respiratory symptoms in former smokers with moderate-to-severe COPD (AERIFY-1 and AERIFY-2).				
Other secondary endpoints: Treatment policy/While-on-treatment estimand	Change from baseline in E-RS:COPD total score at week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	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 change from baseline in pre-BD FEV1 at Week 24 and at Week 52.	• Mean change from baseline in E-RS:COPD total score at Week 24 and at Week 52 by treatment group; • Difference in the mean change from baseline in E-RS:COPD total score and three domain scores at Week 24 and at Week 52 between treatment groups, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and the corresponding 2-sided 95% CI, as estimated using an MMRM approach.
	Change from baseline in E-RS:COPD total score at week 52	• AERIFY-1 ITT-Week 52 population • AERIFY-2 ITT-Week 52 population former smokers		
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on FEV1 slope in former smokers with moderate-to-severe COPD (AERIFY-1 and AERIFY-2).				
Other secondary endpoints: Treatment policy/While-on-treatment estimand	Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after Week 4	• AERIFY-1 ITT • AERIFY-2 ITT former smokers	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 post-BD FEV1 at Week 52. All participants regardless of their planned treatment duration will be included in the analyses.	Individual post-BD FEV1 slope will be derived as the slope of a linear regression model with the post-BD FEV1 (L) at each visit after the initial bronchodilator effect period (up to the end of the planned treatment period) as the response variable and the time (continuous variable) as the independent variable for each participant. Estimated post-BD FEV1 slopes for each treatment group, 95% CIs, and p-values

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
				on the slope differences between active treatment groups and placebo will be derived from a mixed-effects model with repeated post-BD FEV1 measured after the initial bronchodilator effect period (up to the end of the planned treatment period) as the outcome, age, sex, baseline height (continuous variable), region, screening eosinophil strata, controller therapy strata, treatment group, time (continuous variable) and treatment-by-time interaction and baseline post-BD FEV1 (continuous variable) as covariates. Intercept and time are random effects in the model. • Due to the insufficient power to detect the between-group difference in rate of change in each single study, the slope analysis will also be performed by pooling data from the two COPD Phase 3 studies, ie, the AERIFY-1 study, and the AERIFY-2 study. • A sensitivity analysis on the rate of change in post-BD FEV1 will be performed by including the 20-week post-treatment follow-up period.

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on HRQoL as assessed by SGRQ in former smokers with moderate-to-severe COPD (AERIFY-1 and AERIFY-2).				
Other secondary endpoints: Treatment policy/While-on-treatment estimand	Change from baseline in SGRQ total score at Week 24	AERIFY-1 ITT AERIFY-2 ITT former smokers	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 change from baseline in pre-BD FEV1 at Week 24 and at Week 52.	Mean change from baseline in SGRQ total score at Week 24 and at Week 52 by treatment group. Difference in the mean change from baseline in SGRQ total score and three domain scores (symptoms, activity, and impacts) at Week 24 and at Week 52 between treatment groups, eg, itepekimab 300 mg SC Q2W vs placebo, itepekimab 300 mg SC Q4W vs placebo, and the corresponding 2-sided 95% CI, as estimated using an MMRM approach.
	Change from baseline in SGRQ total score at Week 52	- AERIFY-1 ITT-Week 52 population - AERIFY-2 ITT-Week 52 population former smokers		
Other secondary endpoints: Treatment policy/While-on-treatment/composite estimand	Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24	- AERIFY-1 ITT - AERIFY-2 ITT former smokers	The ICEs and their handlings are defined/described in the same way as those for the key secondary endpoint of change from baseline in pre-BD FEV1 at Week 24 and at Week 52. Missing data handling: Participants with missing SGRQ total score at Week 24 (or at Week 52) will be considered as non-responders (composite strategy).	- Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24 and at Week 52 by treatment group will be analyzed using a logistic regression model. The model will include treatment, screening eosinophil strata, region, controller therapy strata, and baseline SGRQ total score as covariates. - Odds Ratio, 95% CI and p-value for the treatment comparison vs placebo.
	Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 52	- AERIFY-1 ITT-Week 52 population - AERIFY-2 ITT-Week 52 population former smokers		

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on the annualized rate of acute moderate or severe COPD exacerbations in current smokers with moderate-to-severe COPD (AERIFY-2 only).				
Other secondary endpoints Treatment policy estimand	The annualized rate of moderate-or-severe AECOPD over the placebo-controlled treatment period	AERIFY-2 ITT current smokers	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 AECOPD over the placebo-controlled treatment period for former smokers.	Same as those for the primary endpoint of annualized rate of moderate-or-severe AECOPD over the placebo-controlled treatment period for former smokers.
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in current smokers with moderate-to-severe COPD (AERIFY-2 only).				
Other secondary endpoints Treatment policy estimand	Change from baseline in pre-BD FEV1 at Week 24 and at Week 52	AERIFY-2 ITT current smokers	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 change from baseline in pre-BD FEV1 at Week 24 and at Week 52 for former smokers.	Same as those for the key secondary endpoint of change from baseline in pre-BD FEV1 at Week 24 and at Week 52 for former smokers.

2 SAMPLE SIZE DETERMINATION

Number of former smokers for the 52 weeks treatment duration portion (original sample size)

The sample size calculation for AERIFY-1 and for the former smokers' group enrolled in AERIFY-2 is based on a comparison between itepekimab 300 mg SC Q2W or Q4W versus placebo with regard to annualized rate of moderate-to-severe AECOPD over the 52-week treatment period. Taking into account the prior data from the proof-of-concept (POC) study ACT15104 and the objectives of the current studies, the following assumptions were made:

- Two-sided significance level of 0.049 (an administrative penalty of 0.001 will be taken from the significance level used at final analysis due to a planned interim analysis (IA).
- 1:1:1 randomization.
- 52-week treatment period with an average treatment duration per participant of [REDACTED] years to account for minimal loss of follow-up due to early study discontinuation.
- An annualized placebo moderate-or-severe AECOPD rate of [REDACTED].
- The number of exacerbations follows a negative binomial distribution with a dispersion parameter of [REDACTED].

With a total of 930 participants per study (310 participants per arm), each of the current studies have a 90% power to detect a 30% relative reduction in the annualized rate of moderate-to-severe AECOPD for itepekimab 300 mg Q2W or Q4W versus placebo in the ITT population for AERIFY-1 and former smokers for AERIFY-2. The minimum detectable risk reduction is around [REDACTED] %.

As indicated in [Section 4.6](#), the key secondary endpoint of change from baseline in pre-BD FEV1 at Week 24 will be tested at 0.029 alpha level for the multiplicity control. Based on the 0.029 significant level, each study also has a 90% power to detect an 85.8 mL difference (or 85% power to detect an 80 mL difference) in the change from baseline in pre-BD FEV1 at Week 24 for itepekimab 300 mg Q2W or Q4W versus placebo in the ITT population for AERIFY-1 and former smokers for AERIFY-2, assuming a common standard deviation of [REDACTED] mL. The minimum detectable difference between groups is approximately [REDACTED] mL.

As stated in [Section 1.2.1](#), due to the Ukraine and Russia military conflict, for participants who enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, the outbreak of the military conflict) for the primary efficacy analyses. For AERIFY-1 study, a total of 36 participants had been enrolled in Ukraine sites prior to the military conflict; For AERIFY-2, no participants are planned to be enrolled in Ukraine. The sample size for AERIFY-1 study will be increased by approximately 30 participants (ie, from 930 to 960) to compensate for the shorter-than-expected observation duration in participants impacted by humanitarian crises (eg, Ukraine).

Number of former smokers for the potential variable treatment duration portion

Because environmental exposure, viral infections, and bacterial infections are all known underlying causes of COPD exacerbations, clinical and behavioral practices (eg, masking and social distancing) during COVID-19 pandemic may have impacted our assumptions for placebo

exacerbation rates used to power this study. Lower-than-expected rate of acute exacerbations of COPD has been observed in health economics data, publications, and other COPD studies which is likely due to fewer respiratory infections resulting from the practice of social distancing and/or mask wearing (1, 2, 3). As a result, the power based on the original sample size might not be sufficient. For AERIFY-1 and AERIFY-2 former smoker cohorts, a potential variable treatment duration portion (maximal 52 weeks, minimal 24 weeks) will be added after all the initially planned participants have been enrolled in the 52 weeks treatment portion to compensate for the loss of power because of the lower-than-expected rate of COPD exacerbations due to COVID-19 pandemic. The increase in sample size with the participants enrolled in the variable treatment portion will enable the study to have at least 85% power to detect a 30% risk reduction and a minimum detectable risk reduction of ■■■ (which is considered as the minimum clinically relevant treatment effect (4)).

To achieve this goal, the sample sizes of AERIFY-1 and the AERIFY-2 former smoker cohorts may be adjusted based upon the blinded exacerbation rate observed approximately 3 months prior to the last of the planned 930 participants (or up to 960 participants for AERIFY-1 to compensate for the unexpected loss of participants' treatment exposure due to the Ukraine and Russia military conflict) being enrolled. If the observed unadjusted blinded annualized rate of investigator reported moderate-to-severe exacerbations is ≥ 1 , then no additional participants will be enrolled; otherwise, additional participants will be enrolled into the variable treatment duration portion based on the blinded exacerbation rate scenarios shown in Table 5. A maximum of 207 additional patients will be recruited in case the observed blinded exacerbation rate is below 0.75. All additional patients enrolled to preserve the power of the study will have a variable treatment duration (minimum of 24 weeks, maximum of 52 weeks).

Table 5 - Summary of sample size adjustment based upon observed blinded AECOPD rate

Observed blinded AECOPD rate	Estimated Placebo rate	Power to detect 30% risk reduction with the original sample size	Addition of variable treatment portion to preserve a minimum detectable risk reduction (MDD) of ■■■ (AERIFY-1 or AERIFY-2 Former smoker cohort)		
			Minimum detectable risk reduction (MDD)	Total Additional participants to be randomized for each study	Power to detect a 30% risk reduction
1 or above	≥ 1.25	$\geq 87.3\%$	■■■	0 (no compensation)	$\geq 87.3\%$
≥ 0.95 - <1	1.19	86.6%		9	86.9%
≥ 0.9 - <0.95	1.13	85.6%		36	86.9%
≥ 0.85 - <0.9	1.06	84.4%		75	86.9%
≥ 0.80 - <0.85	1	83.3%		108	86.7%
≥ 0.75 - <0.8	0.94	81.9%		150	86.6%
<0.75	0.88	80.5%		207 (maximum compensation)	86.7%

Note: The original sample size calculation was based on placebo AECOPD rate of ■■■ had 90% power to detect a 30% relative reduction.

Number of current smokers (AERIFY-2 only)

For AERIFY-2, in addition to the main population of former smoker participants, the study will also enroll a secondary population of participants who are current smokers. The original targeted enrollment for the current smoker cohort is approximately a total of 240 current smokers (N=120 per arm). Assuming the rate of moderate-to-severe AECOPD is similar between itepekimab and placebo within current smokers as was seen in the POC study (ie, an annualized moderate-or-severe AECOPD rate of ■■■), with 240 participants there is an approximately 80% probability to observe a risk reduction of less than 15% at the end of the study, and approximately 10% probability to observe a risk reduction of more than 20%. The precision of the estimate of risk reduction is around 29.3% (95% CI half-width).

As mentioned previously, lower-than-expected rate of acute exacerbations of COPD has been observed due to the COVID-19 pandemic (1, 2, 3). As a result, approximately 40 additional current smokers will be needed to be enrolled in the AERIFY-2 study to maintain the operating characteristics as specified in Table 6, especially to maintain the targeted precision of the estimate $\leq 30\%$ if the annualized rate of moderate to severe exacerbations in the placebo group drops as low as ■■■. All participants enrolled in the current smoker cohort of AERIFY-2 will have a planned 52-week treatment period.

Table 6 - Sample size calculation for Current Smoker cohort (AERIFY-2)

Placebo rate		Sample size / arm	Prob of observing a risk reduction <15%	Prob of observing a risk reduction >20%	Precision of the estimate (95% CI half width)
Initial assumption	■■■	120	81.50%	10.35%	29.3%
Estimated based on RWE and blinded data	1.0	120	79.90%	12.80%	32.1%
		140	82.05%	10.55%	30.0%

For AERIFY-2, the former smokers and current smokers will be randomized separately. In AERIFY-1 and both cohorts in AERIFY-2 study, the randomization will be stratified by country, screening blood eosinophil count (<300 cells/mm³ or ≥ 300 cells/mm³), and controller therapy (triple or double).

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 7 - Populations for analyses

Population	Description
Enrolled	All participants who sign the informed consent form (ICF)
Randomized	The randomized population includes all participants with a treatment kit number allocated and recorded in the interactive response technology (IRT) database, and regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered randomized and will not be included in any efficacy populations but will be included in the safety population.
Intent-to-treat (ITT)/efficacy	All randomized participants analyzed according to the treatment group as randomized. The ITT population includes randomized participants from both the 52 weeks treatment duration portion and the variable treatment duration portion.
ITT-Week 52 population	The ITT-Week 52 population includes all the patients who have the opportunity to complete 52 weeks of treatment period based on their randomization dates, regardless of whether the patient is enrolled in the 52 weeks treatment duration portion, or in the additional variable treatment duration portion. All patients in the ITT-Week 52 population have a planned treatment duration of 52 weeks. Note, if the sample size is not increased as per Section 2 (ie, no variable treatment duration portion will be added), then ITT-Week 52 population is identical to the ITT population.
Safety	The safety population includes all participants exposed to IMP, regardless of the amount of exposure, analyzed according to the treatment actually received. Randomized participants for whom it is unclear whether they took the study treatment will be included in the safety population as randomized. Participants randomized to placebo who inadvertently receive itepekimab, will be included in the itepekimab group for safety analyses. The pharmacodynamic analyses will be performed on the safety population.
Covid-19 Impacted population	The Covid-19 Impacted population includes participants with any critical or major deviation related to COVID-19 or permanently discontinue study treatment related to COVID-19.
Pharmacokinetic (PK)	The PK population includes all participants in the safety population with at least one non-missing result for functional itepekimab concentration in serum after first dose of the study treatment. Participants will be analyzed according to the treatment actually received.
Antidrug antibody (ADA)	ADA population includes all participants in the safety population who have at least one non-missing ADA result in the itepekimab ADA assay after first dose of the study treatment. Participants will be analyzed according to the treatment actually received.
Former smoker cohort (AERIFY-2 only)	All participants randomized to the former smoker cohort in IRT. Former smokers defined as participants with a history of ≥ 10 pack-years who are not currently reported smoking at Screening and smoking cessation must have occurred ≥ 6 months prior to the Screening.
Current smoker cohort (AERIFY-2 only)	All participants randomized to the current smoker cohort in IRT. Current smokers defined as participants with a history of ≥ 10 pack-years who are currently reported smoking (participants who smoked at least 1 cigarette per day on average during the past 7 days) at screening.

Efficacy analysis population

Former smokers:

- For the AECOPD related endpoints (eg, moderate-or-severe AECOPD, severe AECOPD, time to first moderate-or-severe AECOPD, etc) and the endpoints assessed at Week 24 (eg, change from baseline in pre-BD FEV1 [or post-BD FEV1, E-RS score, SGRQ, etc] at Week 24), efficacy analysis population for AERIFY-1 will be the ITT population; for AERIFY-2 will be ITT former smoker cohort.
- For the endpoints assessed at Week 52 (eg, change from baseline in pre-BD FEV1 [or post-BD FEV1, E-RS score, SGRQ, etc] at Week 52), efficacy analysis population for AERIFY-1 will be the ITT-Week 52 population; for AERIFY-2 will be ITT-Week 52 former smoker cohort.

Current smokers:

- The efficacy analysis population for all the endpoints is the ITT current smoker cohort.

Safety analysis population

Safety analyses will be performed in the safety population for AERIFY-1; in the safety population former smoker cohort, and safety population current smoker cohort for AERIFY-2.

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 safety population as randomized.

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

If >10% participants are impacted by the COVID-19 pandemic, additional summaries by COVID-19 subgroups will be provided. Participants impacted by the COVID-19 pandemic are defined as randomized participants with any critical or major deviation related to COVID-19 or who permanently discontinued study intervention related to COVID-19.

4 STATISTICAL ANALYSES

Analyses will be performed separately on the former smoker and current smoker cohorts in AERIFY-2.

All sections below are applicable for the former smoker cohorts in both the AERIFY-1 and AERIFY-2 studies. Analyses for the current smoker cohort for AERIFY-2 are specified in [Section 4.4.3](#).

4.1 GENERAL CONSIDERATIONS

Continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, 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 investigational medicinal product (IMP). For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

All efficacy analyses will be performed by treatment group and in the ITT/efficacy population for AERIFY-1, and in the ITT/efficacy population of former smokers for AERIFY-2 defined above unless otherwise specified (see [Table 7](#) for definitions of analysis populations). In addition, for the summary of baseline values and demographics characteristics, the randomized population will be used as appropriate.

For estimation purposes, similar efficacy analyses will also be performed on the ITT current smoker cohort for the AERIFY-2 study. Details are provided in [Section 4.4.3](#).

The calculation of the baseline for E-RS:COPD scores is specified in [Section 4.4.2.7](#).

Observation period for safety analyses

The observation period will be divided into 3 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 from the first IMP administration to the last IMP administration + 154 days (ie, to the end of 20-week 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 onwards.

- The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or lost to follow-up or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).
- The core database lock will be planned based on the date at 52 weeks after the last of the planned number of participants in the 52 weeks treatment portion is randomized, or alternatively on the date at 24 weeks after the last additional randomized participants, if the sample size is increased as per [Section 2](#), whichever is later. Analyses will be based on all data collected up to this database lock and will be considered as the final analysis in the CSR.

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in [Table 7](#) 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 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 including due to COVID-19 or Ukraine/Russia military conflict
- 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 including due to COVID-19 or Ukraine/Russia military conflict
- 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 and according to COVID-19 impact (ie, deviations related to the COVID-19 pandemic and deviations not related to the COVID-19 pandemic) or Ukraine/Russia military conflict.

Note that data from patients with deviations will not be excluded from the ITT population for efficacy or safety analyses. The data handling to account for the intercurrent event (ICE) of Ukraine/Russia military conflict are specified in [Section 1.2.1](#).

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint(s)

The primary efficacy endpoint is the annualized rate of moderate-or-severe acute exacerbations of COPD (AECOPD) over the placebo-controlled treatment period. Moderate exacerbations are recorded by the Investigator and defined as acute worsening of respiratory symptoms that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations are recorded by the Investigator and defined as AECOPD requiring hospitalization, stay for >24 hours in an emergency department/urgent care facility, or resulting in death. For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days between any course of systemic steroids/antibiotics or 14 days between discharge and new admission in case of hospitalization (severe events only).

AECOPD recorded in eCRF will go through a confirmatory adjudication by experts independent of sponsor for the evaluation. Details of the adjudication process are described in the AC Charter/Manual of Operation. Only the adjudicated confirmed AECOPD will be used for analysis.

4.3.2 Main analytical approach

The primary estimand for the primary endpoint is the treatment policy estimand except for participants enrolled in Ukraine, for whom the primary estimand will be a “while-on-treatment” policy estimand (as defined by ICH-E9-R1) considering the start of the military conflict as an intercurrent event (details are provided in [Table 2](#)).

The primary analysis population for the efficacy endpoints will be the ITT population (former smoker cohort for AERIFY-2 study).

The statistical hypotheses for comparing itepekimab against placebo on the primary endpoint of annualized rate of moderate to severe COPD exacerbations 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.

The annualized rate of moderate or severe AECOPD will be analyzed using a negative binomial regression model. The model will include the total number of moderate or severe AECOPD events that occur during the planned treatment period as the response variable, with treatment group, region (see [Section 5.3](#) for region definition), screening eosinophil strata (<300 /mm³ or

≥ 300 /mm³), controller therapy (triple, double) strata, baseline disease severity (as % predicted post-BD FEV1 used as continuous variable), and the total number of severe AECOPD events within 1 year prior to the study (0 or ≥ 1) as covariates. Log-transformed observation duration will be the offset variable. Parameters will be estimated using the maximum likelihood method with the Newton-Raphson algorithm. The estimated annualized event rate for each treatment group and its 2-sided 95% CIs will be derived from the negative binomial model. The event rate ratio of each itepekimab regimen against placebo, and the corresponding 2-sided 95% CI and p-value will also be provided.

As defined in [Table 2](#), all moderate or severe AECOPD 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 AECOPD during the planned treatment period will be included in the primary analysis. Similarly, if a participant withdraws from the study prior to the end of the planned treatment period, all observed moderate or severe AECOPD 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. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis. No imputation will be performed for the unobserved AECOPD events that may happen after study discontinuation and prior to the end of the planned treatment period.

4.3.3 Supplementary/Supportive analyses

On-treatment analysis

The supportive estimand for the primary endpoint will be a while-on-treatment estimand. As defined in [Table 2](#), only the AECOPD events observed during the on-treatment period (from first administration of IMP to the EOT visit for completers; otherwise to the last administration of IMP + 14 days) will be included in the analysis. Off -treatment events of participants who prematurely discontinue treatment will be excluded from the analysis.

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 AECOPD events occurring during the on-treatment period as the response variable and the log transformed duration of the on-treatment period will be the offset variable.

Treatment-policy for all patient data including Ukraine participants (applicable to AERIFY-1 only)

The supportive estimand for the primary endpoint will be a treatment-policy estimand. The same analysis will be performed as described for the primary endpoint based on the treatment policy approach defined in [Table 2](#), but for all patient data including Ukraine participants (ie, data cutoff date of Feb 24, 2022 will not be applied for participants enrolled in Ukraine).

4.3.4 Sensitivity analysis

Sensitivity analysis excluding participants who resumed smoking during the study

To mitigate the impact of nonadherence to smoking abstinence on the results on the primary analysis, sensitivity analysis of the primary endpoint will be performed to remove participants who resumed smoking during the study. Patients who resumed smoking during the study are identified by 'Substance use since last visit = yes' for tobacco in Smoking Status eCRF.

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, the number of events that could occur in the period from study discontinuation to the end of planned treatment duration will be estimated based on a negative binomial regression model using observed data with adjustment of the treatment group, region, controller therapy strata, screening eosinophil strata, number of severe exacerbation events within 1 year prior to the study (0 or ≥ 1), and post-BD FEV1 percent predicted at baseline. The period from study discontinuation to the end of planned treatment duration will be the exposure time. Once the number of events in the period is imputed, the total number of events in the planned treatment duration will enter the negative binomial regression model as described in the primary analysis with the offset equal to the log-transformed planned treatment duration.

- Control-based (jump to reference) PMM-MI

For each participant with missing data of exacerbation events, the number of events that could occur in the period from study discontinuation to the end of planned treatment duration will be estimated based on the same negative binomial regression model mentioned in the previous bullet point, except the imputation will be based on the estimate of the control group only. Once the number of events in the period from study discontinuation to the end of planned treatment duration is imputed, similar model as in the PMM-MI will be used.

- Tipping point analysis

For each participant with missing data of exacerbation events, the number of events that could occur in the period from study discontinuation to the end of planned treatment duration will be estimated in a similar fashion as PMM-MI, based on various event rates. If the participant is on itepekimab, the event rate will be increased and if the participant is on placebo, the event rate will be decreased. The adjusted rate will then be used to impute the number of events that would occur in the period with missing data. A sequence of increasing/decreasing event rates will be explored until p-value becomes >0.049 .

Technical details on the imputation and analyses methods are provided in a separate programming document.

4.3.5 Subgroup analyses

To assess the homogeneity of treatment effects across various subgroups, analyses will be performed for the primary efficacy endpoint of the annualized rate of moderate or severe AECOPD with respect to the following subgroups (categories might be combined if $<10\%$ of participants):

- Age group (<65 , 65 to <75 , ≥ 75)
- 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 (AERIFY-1: Asia: India, China and Taiwan, province of China; Latin America: Argentina, Chile, and Mexico; East Europe: Russia, Ukraine, Hungary, Poland, Czech Republic, Romania, Bulgaria, and Slovakia; Western Countries: Greece, Israel, Italy, and USA. AERIFY-2: Asia: India, Japan and South Korea; Latin America: Argentina, Brazil, Chile and Mexico; East Europe: Russia, Turkey, Hungary, Poland, Czech Republic, and Bulgaria; Western Countries: Denmark, Spain, Israel, France, Netherlands, Norway, Portugal, Germany, United Kingdom, South Africa, Canada, and USA)
- Background therapy (triple, double; triple, ICS+LABA, LABA+LAMA)
 - In addition, the subgroup of participants who are either on triple therapy or are on double therapy because triple therapy is not advisable* will also be analyzed.
 - * Includes participants on double therapy at baseline due to safety concerns, lack of efficacy or contra-indication to one component of triple therapy, or on LABA+LAMA with a low eosinophil count (defined as either with low eosinophils as the reason of being on LABA+LAMA entered in the eCRF or with a blood eosinophil count <100 cells/mm³ at screening or baseline).

- Background ICS dose at randomization (high for >500 mcg fluticasone equivalent, medium for >250 and ≤500 mcg, and none/low for ≤250 mcg, see [Section 5.15](#))
- Screening blood eosinophil stratum (<300 cells/mm³, ≥300 cells/mm³)
- Baseline blood eosinophil level (<150 cells/mm³, ≥150 to <300 cells/mm³, ≥300 cells/mm³; <150 cells/mm³, ≥150 cells/mm³; <300 cells/mm³, ≥300 cells/mm³)
- Baseline CAT score (< median, ≥ median; note, the median value will be determined based on AERIFY-1 and AERIFY-2 former smokers pooled)
- Baseline % predicted post-BD FEV1 (<50%, ≥50%)
- Smoking cessation duration for former smokers prior to screening visit (< median, ≥ median)
- Permanently stop smoking for current smokers at any time during the treatment period (AERIFY-2 only; yes, no)
- Number of moderate or severe COPD exacerbation events within one year prior to screening visit (1, 2, ≥3)
- Baseline SGRQ score (< median, ≥ median)
- Baseline E-RS:COPD total score (< median, ≥ median)
- Baseline BODE Index (< median, ≥ median)
- Baseline CRP (< median, ≥ median)
- Participants using Azithromycin or Roflumilast (no)
- COVID-19 impacted population (yes, no)
- COVID-19 impacted sites (yes, no)
- Participants with COVID-19 infection during the treatment period (yes, no)

The treatment effects for the primary endpoint for these subgroups will be provided using the same model as for the primary analysis. Rate ratio between treatment and control and the corresponding 95% CI will be provided within each subgroup. Treatment-by-subgroup interaction and its p-value will be derived by a negative binomial regression model. The model will include treatment, screening eosinophil strata, region, number of severe COPD exacerbations experienced in previous year (0 versus ≥1) at baseline, post-BD FEV1 percent predicted at baseline, subgroup (if different from the aforementioned covariates) and subgroup-by-treatment interaction. Forest plots will also be provided.

In addition to the analysis in each of the studies, statistical analysis for subgroups with a) triple controller therapy only and b) who are either on triple therapy or are on double therapy because triple therapy is not advisable (on double therapy due safety concerns, lack of efficacy or contraindications to one component of triple therapy, or on LABA+LAMA with low eosinophils <100 cells/mm³) will be further conducted using the **pooled** data of AERIFY-1 and AERIFY-2 (former smokers only). Details will be specified in a separate ISE SAP.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Key/Confirmatory secondary endpoint(s)

4.4.1.1 Definition of endpoint(s)

The key secondary efficacy endpoint is the change from baseline in pre-BD FEV1 at Week 24.

4.4.1.2 Main analytical approach

The change from baseline in pre-BD FEV1 at Week 24 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline in pre-BD FEV1 values up through to Week 24 as the response variable, and treatment, age (continuous variable), sex, baseline height (continuous variable), region, screening eosinophil strata, controller therapy strata (triple, double), visit, treatment by-visit interaction, and baseline pre-BD FEV1 value (continuous variable) and baseline-by-visit interaction 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 in pre-BD FEV1 at Week 24 will be derived from the mixed-effect model. Difference in LS mean change from baseline, the corresponding 95% CI and p-value will be provided for comparison of each itepekimab regimen against placebo.

The primary estimand for the secondary endpoint is the treatment policy estimand except for participants enrolled in Ukraine, for whom the primary estimand is a “while-on-treatment” policy estimand (as defined by ICH-E9-R1) considering the start of the military conflict as an intercurrent event (details are provided in [Table 3](#)). Participants who discontinue IMP before the end of the planned treatment period will be asked and encouraged to return to the clinic for all remaining study visits and the additional off treatment pre-BD FEV1 values measured during the planned treatment period will be included in the analysis. All pre-BD FEV1 data measured up through to Week 24 will also be included in the analysis irrespective of use of prohibited medications. For participants who withdraw from the study before the end of the planned treatment period, pre-BD FEV1 values will be missing after study discontinuation or last contact. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis. No imputation will be performed for missing values in this analysis; the missing data will be handled using the MMRM model which assumes that missing data are missing at random (MAR).

4.4.1.3 Supplementary analysis

On-treatment analysis (excluding data measured when participants do not adhere to the treatment regimen)

The supportive estimand for the primary endpoint will be a while-on-treatment estimand. As defined in [Table 3](#), only the data observed during the on-treatment period (from first administration of IMP to the EOT visit for completers; otherwise to the last administration of IMP

+ 14 days) will be included in the analysis. Off-treatment events of participants who prematurely discontinue treatment will be excluded from the analysis. To assess the treatment effect when the participants adhere to the study treatment as directed, on-treatment pre-BD FEV1 measurements will be analyzed using a similar MMRM model as for the primary pre-BD FEV1 analysis, including the same set of covariates and estimation algorithm. The model will include on-treatment change from baseline in pre-BD FEV1 values up to the planned treatment period as response variables. A pre-BD FEV1 value is considered as on-treatment if it is measured on or before the EOT visit for completers; otherwise on or before the last dose date + 14 days.

Treatment-policy for all patient data including Ukraine participants (applicable to AERIFY-1 only)

The supportive estimand for the primary endpoint will be a treatment-policy estimand. The same analysis will be performed as described for the key secondary endpoint based on the treatment policy approach defined in [Table 3](#), but for all patient data including Ukraine patients (ie, data cutoff date of Feb 24, 2022 will not be applied for participants enrolled in Ukraine).

4.4.1.4 Sensitivity analysis

Sensitivity analyses for missing data in the key secondary endpoint

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

Pattern-mixture multiple imputations: Missing pre-BD FEV1 values will be imputed multiple times using a regression model. The covariates to be included are sex, baseline height, baseline FEV1 value, treatment group, visit and treatment-by-visit interaction, baseline FEV1-by-visit interaction, screening eosinophil strata, controller therapy strata, and region. Forty imputations will be performed. For each imputation, the change from baseline in pre-BD FEV1 at Week 24 will be analyzed. Statistical inference obtained from all imputed data will be combined using Rubin's rule.

Control-based multiple imputations: Missing values will be imputed sequentially for each assessment time point using a regression model. Only estimates of the placebo group will be used to fit the MI models.

Technical details on the imputation and analyses methods are provided in a separate document.

4.4.1.5 Subgroup analyses

To assess the consistency treatment effects across the subgroup levels, subgroup analyses will be conducted for the change from baseline in pre-BD FEV1 at Week 24 with the same set of subgroups as defined for the annualized rate of moderate or severe AECOPD events in [Section 4.3.5](#).

4.4.2 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 4](#). The estimand for all other endpoints is the treatment policy estimand except for patients enrolled in Ukraine, for whom the estimand will be a “while-on-treatment” policy estimand (as defined by ICH-E9-R1) considering the start of the military conflict as an intercurrent event.

4.4.2.1 Change from baseline in pre-BD FEV1 at Week 52

The analysis model for this endpoint is identical to the analysis of the key secondary efficacy endpoint, the average change from baseline to Week 24 in pre-BD FEV1, except that here we focus on the value at Week 52, not at Week 24. The model will include change from baseline in pre-BD FEV1 values up through Week 52 as the response variable. Only the participants with 52-week as their planned treatment duration will be included in the analysis of change from baseline in pre-BD FEV1 at Week 52 (ITT-Week 52 population).

4.4.2.2 Change from baseline in post-BD FEV1 at Week 24 and at Week 52

The analysis model for post-BD FEV1 at Week 24 is identical to the analysis of the pre-BD FEV1 at Week 24, and the analysis model for post-BD FEV1 at Week 52 is identical to the analysis of the pre-BD FEV1 at Week 52, except that the baseline post-BD FEV1 will be included as a covariate instead of baseline pre-BD FEV1. Only the participants with 52-week as their planned treatment duration will be included in the analysis of change from baseline in post-BD FEV1 at Week 52 (ITT-Week 52 population).

4.4.2.3 Time to first moderate or severe AECOPD over the placebo-controlled treatment period

The time to first moderate or severe AECOPD will be analyzed using a Cox regression model. The model will include the time to the first event as the dependent variable, and treatment group, screening eosinophil strata, region, controller therapy strata, baseline disease severity (as % predicted post-BD FEV1, used as continuous variable), and number of severe AECOPD events within 1 year prior to the study (0 or ≥ 1) 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.

Time to first moderate or severe AECOPD is defined as the onset date of the first moderate or severe AECOPD - randomization date + 1. If the participants did not experience any moderate to severe AECOPD events, the event time will be considered as censored at date of EOT or the last contact date within the planned treatment duration. All off-treatment moderate or severe AECOPD during the planned treatment period will be included in the analysis.

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

4.4.2.4 Annualized rate of severe AECOPD over the placebo-controlled treatment period

This will be analyzed with the same model as the primary endpoint of “Annualized rate of moderate or severe AECOPD over the planned treatment period”, but only severe AECOPD events will be taken into consideration. No sensitivity or supplementary analysis will be performed for this endpoint.

In addition, this endpoint will be analyzed for the pooled AERIFY-1 and AERIFY-2 former smoker population. The analysis method for the pooled population will be the same as the individual study. A study covariate will be added into the model to account for between-study differences.

4.4.2.5 Time to first severe AECOPD over the placebo-controlled treatment period

This will be analyzed similar to the secondary endpoint of “Time to first moderate or severe AECOPD during the planned treatment period and other time to event endpoints”, but only severe AECOPD events will be taken into consideration.

4.4.2.6 Annualized rate of corticosteroid-treated AECOPD over the placebo-controlled treatment period

This will be analyzed with the same model as the primary endpoint of “Annualized rate of moderate or severe AECOPD over the planned treatment period”, but only moderate or severe AECOPD events which are treated with a regimen containing systemic corticosteroids for their AECOPD, and at the time of the AECOPD, will be taken into consideration. No sensitivity or supplementary analysis will be performed for this endpoint.

4.4.2.7 Change from baseline in E-RS: COPD total score at Week 24 and at Week 52

The Evaluating Respiratory Symptoms (E-RS) in COPD (E-RS: COPD) scale is a part of the EXacerbations of Chronic Pulmonary Disease Tool (EXACT) instrument tool (5). It is a derivative instrument used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD. The E-RS utilizes the 11 respiratory symptom items contained in the 14-item EXACT (see [Section 5.6](#)).

The daily RS-Total score is computed by taking the sum of the 11 items comprising the instrument. It has a range of 0 to 40, with higher values indicating more severe respiratory symptoms.

The same summation procedure is used to derive the three daily domain scores:

- RS-Breathlessness (sum of items 7, 8, 9, 10, and 11; score range 0–17)
- RS-Cough and Sputum (sum of items 2, 3, 4; score range 0–11)
- RS-Chest Symptoms (sum of items 1, 5, 6; score range 0–12)

The E-RS:COPD total score and each of the RS domain scores is defined as the mean within-participant score over 7 days, with data present for a minimum of 4 of the 7 days prior to the visit. If fewer than 4 days of data are available in the 7-day window, the RS scores cannot be calculated and will be considered as missing. Change from baseline in E-RS:COPD total score and three domain scores at Week 24 and at Week 52 will be analyzed using the MMRM approach described for the analysis of pre-BD FEV1. For E-RS:COPD total score at Week 24, the model will include E-RS:COPD total scores at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, and 24, whereas for E-RS:COPD at Week 52, the model will include E-RS:COPD total scores at Weeks 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 24, 32, 40, 48, and 52, regardless of whether the participant is on treatment or not when the endpoint is measured. The model covariates will be treatment, screening eosinophil strata, region, controller therapy strata, visit, treatment-by-visit interaction, baseline E-RS:COPD score, and baseline score-by-visit interaction. Difference in LS means, the corresponding 95% CI, and p-value will be provided for the comparison of each itepekimab regimen versus placebo. Only the participants with 52 weeks as their planned treatment duration will be included in the analysis of change from baseline in E-RS:COPD total score at Week 52.

Cumulative distribution function (CDF) of change from baseline in E-RS:COPD total score at Week 24 and at Week 52 will be presented by treatment group.

Each of the three domain scores will be analyzed in the similar way as E-RS:COPD total score. Figures showing plots of change from baseline over time will be generated for the E-RS:COPD and each RS domain score by treatment group.

4.4.2.8 Rate of change in post-BD FEV1 (L/yr) from baseline (post-BD FEV1 slope) after Week 4

Rate of change in post-BD FEV1 (L/yr) (or post-BD FEV1 slope) after a period of initial improvement in post-BD FEV1 in the active treatment arms will be analyzed. Repeated post-BD FEV1 after Week 4 up to the end of the planned treatment period will be analyzed correspondingly using a linear mixed-effects model with age, sex, baseline height (continuous variable), region, screening eosinophil strata, controller therapy strata, 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. Formal statistical inferences including estimated post-BD FEV1 slopes for each treatment group, 95% CIs and p-values on the slope differences between active treatment groups and placebo derived from a mixed-effects model will be provided.

Individual post-BD FEV1 slope will be calculated as the slope of a linear regression model with the post-BD FEV1 (L) at each visit after Week 4 (up to the end of the planned treatment period) as the response variable and the time (continuous variable) since randomization as the independent variable for each participant. Descriptive statistics including number of participants, mean, standard error of the individual post BD FEV1 slopes will be provided. Estimated from the linear mixed-effects model, least squares (LS) means, difference in LS means and the corresponding 95% confidence intervals (CI) will also be provided.

Due to potential low power to detect the between-group difference in rate of change in each single study, the slope analysis will also be performed by pooling data from the two current studies, ie, AERIFY-1 and AERIFY-2 studies. The analysis population will be the ITT population for AERIFY-1 combined with the ITT population in AERIFY-2 former smoker cohort. The analysis method for the pooled population will be the same as each of the individual study. A study covariate will be added into the model to account for between-study differences. In addition, a sensitivity analysis on the rate of change in post-BD FEV1 will be performed by including the 20 weeks follow-up period. Details will be specified in a separate ISE SAP.

4.4.2.9 Change from baseline in SGRQ total score at Week 24 and at Week 52

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 5.11](#)). 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 [6]). Likewise, the domain scores range from 0–100, with greater scores indicative of greater impairment. See [Section 5.12](#) for the scoring algorithm and handling of missed items.

This questionnaire is assessed at baseline and at Weeks 12, 24, 36, 52, and 72.

Change from baseline in SGRQ total score and the three domain scores at Week 24 and at Week 52 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 measured up through to Week 24; whereas for change from baseline in SGRQ total score and the three domain scores at Week 52, the model will include all SGRQ scores measured up through to Week 52, 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, screening eosinophil strata, region, controller therapy strata, visit, treatment-by-visit interaction, baseline score, and baseline score-by-visit interaction. The missing questionnaire items are handled as specified in [Section 5.12](#); no further imputation will be performed on missing scores. Difference in LS means, the corresponding 95% CI, and p-value will be provided for the comparison of each itepekimab regimen versus placebo. Only the participants with 52-week as their planned treatment duration will be included in the analysis of change from baseline in SGRQ total score at Week 52 (ITT-Week 52 population).

Figures of change from baseline over time for SGRQ total score and the three SGRQ domain scores by treatment group will be generated. Cumulative distribution function (CDF) of change from baseline in SGRQ at Week 24 and at Week 52 will be presented by treatment group.

4.4.2.10 Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24 and at Week 52

The proportion of participants with SGRQ improvement (reduction) ≥ 4 points at Week 24 and at Week 52, whether the participant is still on treatment or not, will be analyzed using a logistic regression model. The model will include treatment, screening eosinophil strata, region, controller therapy strata, and baseline SGRQ total score as covariates. Participants with SGRQ improvement < 4 points or missing SGRQ total score at Week 24 (or at Week 52) will be considered as non-responders. The Week 52 analysis will be restricted to patients with a planned 52-week treatment period.

The odds ratio of being a responder comparing each itepekimab regimen to placebo will be provided along with the corresponding 95% CI and p-value. Descriptive statistics including number and percentage of responders will also be provided.

To assess the treatment effect when participants adhere to the study treatment as directed, the same analysis will be conducted in those participants in the ITT population who completed Week 24 or Week 52.

4.4.3 Other secondary endpoint(s) for AERIFY-2 current smoker cohort

4.4.3.1 Annualized rate of moderate-or-severe acute exacerbations of COPD (AECOPD) over the planned placebo-controlled treatment period.

The analysis model for this endpoint is identical to the analysis of the primary efficacy endpoint described in [Section 4.3](#) except that the analysis will be performed on AERIFY-2 current smoker cohort. No sensitivity or supplementary analysis will be performed for this endpoint.

4.4.3.2 Change from baseline in pre-BD FEV1 at Week 24 and at Week 52

The analysis model for this endpoint is identical to the analysis of the key secondary efficacy endpoint described in [Section 4.4.1](#) except that the analysis will be performed on AERIFY-2 current smoker cohort. No sensitivity or supplementary analysis will be performed for this endpoint.

All other secondary endpoints described in [Section 4.4.2](#) will also be performed on the AERIFY-2 current smoker cohort for estimation purposes.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

The tertiary/exploratory endpoints are as follows:

- Annualized number of days of healthcare resource utilization over the placebo-controlled treatment period
- Annualized number of ER and hospital days related to AECOPD
- Proportion of participants with BODE Index score >1 point decrease (=improvement) at Week 52
- Proportion of participants with pre-BD FEV1 improvement ≥ 100 mL at Week 24 and at Week 52
- Number of days on oral corticosteroids and antibiotics over the planned treatment period
- Change from baseline in resting oxygen saturation (just before the 6MWD) at Week 52

Healthcare resource utilization

Analyses of healthcare resource utilization will be performed outside of the CSR under the responsibility of the Health Economics and Value Assessment (HEVA) department of Sanofi.

BODE Index (Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index)

The BODE Index is a composite measure composed of a Performance Outcome Measure, a Patient-Reported Outcome Measure and a Biomarker. The BODE Index is a multidimensional grading system to assess the respiratory and systemic expressions of COPD. It comprises 4 domains: 1) Degree of pulmonary impairment (FEV1 percent predicted); 2) Patient's perception of symptoms (mMRC); and 2 independent domains: the 6 Minute Walking Distance (6MWD) and the Body-Mass Index (BMI). Each domain can be scored independently; the global score ranges from 0 to 10, with a higher score indicating a higher risk of death (see [Section 5.9](#) for scoring algorithm details). The BODE index is assessed at Visit 2 (Week 0) and EOT visit (Week 52).

4.5.2 Main analytical approach

Annualized number of ER and hospital days related to AECOPD and the total number of days on oral corticosteroids and antibiotics over the planned treatment period will be summarized by intervention group.

Descriptive summaries for the 4 components of BODE index (FEV1 percent predicted, mMRC, 6MWD and BMI) at baseline, Week 52 and change from baseline at Week 52 will be provided. Proportion of participants with BODE Index score >1 point decrease (=improvement) at Week 52 will be analyzed with a logistic regression model. The model will include treatment, screening eosinophil strata, controller therapy strata (triple, double), region, and baseline BODE Index score as covariates. Participants with BODE Index score >1 point decrease (=improvement) will be

considered as a responder. Patients with missing BODE index will be considered as non-responders. Only patients with a planned 52 weeks treatment period will be included in this analysis. Odds ratio of being a responder comparing itepekimab to placebo will be provided along with the corresponding 95% CI and p-value.

For proportion of participants with pre-BD FEV1 improvement ≥ 100 mL at Week 24 and at Week 52, a logistic regression model will be used to compare percentage participants with pre-BD FEV1 improvement ≥ 100 mL in itepekimab and placebo at Week 24 and at Week 52. The model will include treatment, screening eosinophil strata, controller therapy strata (triple, double), region, baseline pre-BD FEV1 as covariates. Participants with pre-BD FEV1 improvement ≥ 100 mL at Week 24 or at Week 52 will be considered as a responder. Patients with missing pre-BD FEV1 values will be considered as non-responders. Odds ratio of being a responder comparing itepekimab to placebo will be provided along with the corresponding 95% CI and p-value.

Changes from baseline in resting oxygen saturation (just before 6MWD) will be summarized descriptively (number, arithmetic and geometric means, SD, SEM, CV, median, minimum and maximum) by treatment group and time point.

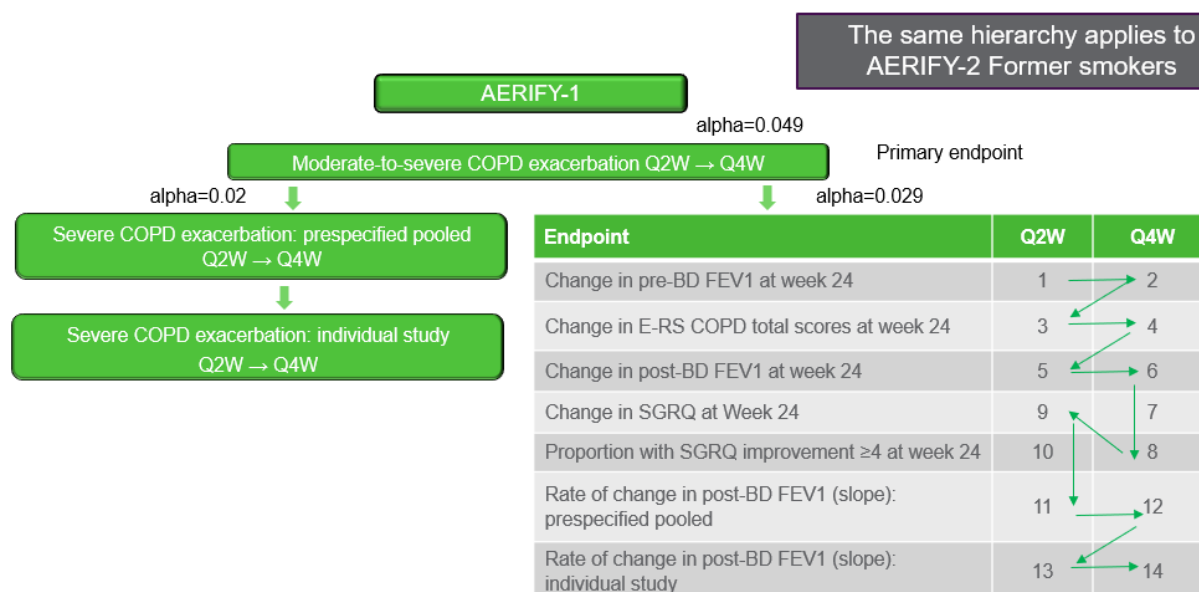
4.6 MULTIPLICITY ISSUES

Multiplicity is considered for the significance testing of multiple efficacy endpoints, and it is considered for the AERIFY-1 study and the former smoker cohort of the AERIFY-2 study.

Due to the planned futility interim analysis, an administrative penalty of 0.001 will be taken from the significance level used at the final analysis; that is, a 2-sided $\alpha=0.049$ will be used for the final primary efficacy analysis. No further multiplicity adjustment will be taken for the interim analysis.

At the final analysis, the annualized rate of moderate-or-severe AECOPD during the planned treatment period will be first tested between 300 mg Q2W and placebo at the 2-sided 0.049 significance level. If it is significant, then the primary endpoint for 300 mg Q4W will be tested.

Figure 1 - Hierarchical order of efficacy endpoints



As shown in Figure 1, after the primary endpoint, the alpha will be split – the endpoints of change in pre-BD FEV1, change in E-RS total score, change in post-BD FEV1, change in SGRQ, proportion with SGRQ improvement ≥ 4 , rate of change in post-BD FEV1 (slope; prespecified pooled), and rate of change in post-BD FEV1 (slope; individual study) will be tested in the order as specified in Figure 1 based on an alpha of 0.029; and the endpoints of severe AECOPD (prespecified pooled) and severe AECOPD (individual study) will be tested in the order as specified in Figure 1 based on an alpha of 0.02. The endpoints of severe AECOPD and rate of change in post-BD FEV1 (slope) from AERIFY-1 and AERIFY-2 former smokers will be pooled together to be tested in the hierarchy before the endpoints to be tested in each individual study, as the two studies are not sufficiently powered to detect the treatment effects by each individual study.

Due to the COVID-19 pandemic, the clinical and behavioral practices have been modified which impacts the course of disease including the frequency of acute COPD exacerbations. Based on the Real-World Evidence data, a decrease of an average of approximately 50% of severe AECOPD has been seen compared to the previous 3 years (2017-2019) (1, 2, 3). As a result, the power of the severe AECOPD is greatly impacted and decreased from 90% to approximately 50% to detect a rate reduction of 45%. Therefore, the individual study is not sufficiently powered to detect the treatment effect for severe AECOPD and it is necessary to pool the data from the 2 studies in order to make a meaningful inference.

Regarding the rate of change endpoint (slope), each individual study is underpowered to detect the treatment effect since the between-group difference in the rate of change in post-BD FEV1 after a period of initial bronchodilator effect is primarily driven by the natural decline in lung function from the placebo patients, which is only expected to be between 30 to 40 mL per year. Therefore, it is also necessary to pool the data from the 2 studies in order to make a meaningful inference for this endpoint.

4.7 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in [Section 3](#), unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially 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.

4.7.1 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.

4.7.2 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 (TEAE)s: 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 8](#).

Table 8 - 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
- TEAE leading to death
- Any TEAE leading to permanent intervention discontinuation

The AE summaries of [Table 9](#) will be generated with number (%) of participants experiencing at least one event.

Table 9 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT Primary SOC and PT PT Primary and secondary SOC, HGLT, HLT and PT
Common TEAE (≥5% in any group)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC, HGLT, HLT and PT Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE	Primary SOC HGLT, HLT and PT Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC, HGLT, HLT and PT
TEAE leading to permanent intervention discontinuation	Primary SOC, HGLT, HLT and PT Primary SOC and PT

Type of AE	MedDRA levels
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC, HGLT, HLT and PT
Pre-treatment AE	Primary SOC and PT Overview ^a
Post-treatment AE	Primary SOC and PT Overview ^a
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 9](#) the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods
- Deaths in non-randomized or randomized but not treated participants

Cardiovascular assessment

All deaths and potential CV events reported by the investigator, identified by pre-specified search criteria described in the Cardiovascular Adjudication Committee (CAC) charter will be prospectively adjudicated in a blinded manner by an external CAC. The committee will adjudicate qualifying events according to the CAC charter.

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 ([Section 5.17](#) provides further categorization of CV event, non-CV event).

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.

Furthermore, events classified as cardiovascular will be evaluated according to the following composite endpoints:

- **Major Cardiovascular Adverse Events (MACE):** cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke
- MACE + hospitalization for unstable angina
- Cardiovascular death: death resulting from myocardial infarction, stroke, pulmonary embolism, heart failure, procedure-related death or other cardiovascular cause.
- Hospitalization: for unstable angina, for atrial fibrillation/flutter, for other symptomatic arrhythmias, for transient ischemic attack.
- Other cardio/cerebrovascular events: non-fatal heart failure, peripheral arterial event, pulmonary embolism, non-acute coronary syndrome/myocardial ischemia, others.

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 10. Number (%) of participants experiencing at least one event will be provided for each event of interest. The risk difference (asymptotic 95% CI with continuity correction) will be computed for the itepekimab dose versus placebo. Tables will be sorted as indicated in Table 10.

Table 10 - Selections for AESIs and other AEs of interest

AE Grouping	Selection
AESI	
Significant ALT elevation	eCRF AECAT = 'ALT increase' is checked and AESIIN = 'Y.'
Anaphylactic or systemic allergic reaction requiring treatment (medically reviewed)	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 to IMP administration for final determination of an anaphylactic or systemic allergic reaction or not.
Severe injection site reactions (ISRs) that last longer than 24 hours	AE category = "Injection Site Reaction" and AESIIN = "Y"
Serious infection	Primary SOC = 'Infections and infestations' and with serious status.
Infection requires parenteral (IV, IM, SC) antimicrobial therapy	AE category = "Infection Event" and AESIIN = 'Y'.
Infection requires oral antimicrobial therapy for longer than 2 weeks	eCRF Infection Event Form FAMEDYN= 'Y' and AESIIN = 'Y'.
Parasitic infection	eCRF Infection Event Form Infection Type = 'Parasitic' and AESIIN = 'Y'.
Opportunistic infection	eCRF Infection Event Form FAOPYN= 'Y' and AESIIN = 'Y'.
Malignancy	Sub-SMQ (20000091)– Malignant or unspecified tumors
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	Symptomatic Overdose is answered Yes, with Overdose of IMP answered Yes on AE eCRF.
Symptomatic overdose with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP answered Yes on AE eCRF.
Other selected AE Grouping	
Injection site reaction	HLT = 'Injection site reactions'
COVID-19 related AEs	SMQ [20000237] COVID-19 narrow search

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 each 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 TEAE leading to permanent study drug 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
- Number of participants with any specific TEAE adjusted by the exposure duration at risk. For each specific TEAE, Kaplan-Meier estimates of cumulative incidence at Week 12, 24, 36 and 52 and K-M plot may be provided to depict the course of onset over time if the number of events is large enough.
- Number (%) of participants with injection site reactions by the related injection.
- Number (%) of participants with different number of injection site reactions.

In addition, the following summaries during the TEAE period will be provided for participants who received COVID-19 vaccine:

- Number (%) of participants who received at least one dose of COVID-19 vaccine by manufacturer (eg, Pfizer-BioNTech, Moderna, Sinovac)
- Number (%) of participants with any TEAE that occurred within 2 weeks after COVID-19 vaccine (applicable to TEAEs within 2 weeks from both 1st and 2nd dose of COVID-19 vaccine for vaccines with 2 shots)
- Number (%) of participants with any treatment emergent SAE, by primary SOC and PT
- Number (%) of participants with any TEAE leading to treatment discontinuation, by primary SOC and PT
- Number (%) of participants with any TEAE leading to death, by primary SOC and PT

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) 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), uric acid
 - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin)
- Urinalysis:
 - Urinalysis for quantitative analysis: pH, specific gravity
- Vital signs: pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg) in a semi-supine or sitting position after 5 minutes, weight (kg), respiratory rate (breaths per minute), temperature (degrees Celsius) and height (cm; screening only).
- ECG variables: heart rate, PR, QRS, QT, and QTcF intervals after 10 minutes of rest in the supine position.

Quantitative analyses

For all laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each analysis window, the last value during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables and ECG variables.

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

Analyses according to PCSA

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, vital signs and ECG variables above, 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 ($>3 \times \text{ULN}$) and total bilirubin elevation ($>2 \times \text{ULN}$) 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 $>5 \text{ ULN}$) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value $\leq \text{ULN}$ 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 , $>20 \text{ ULN}$).

4.8 OTHER ANALYSES

4.8.1 PK analyses

Predose itepekimab concentrations in serum at Visit 2 (Day 1), itepekimab trough levels at Week 2, Week 4, Week 8, Week 12, Week 24, Week 36, Week 52/EOT Visit and posttreatment itepekimab concentrations in serum at Week 58 and Week 72/EOS Visit will be provided.

These PK parameters will be summarized in the itepekimab 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 then the concentration will not be taken into account.

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

4.8.2 Immunogenicity analyses

Anti- itepekimab antibody (ADA) blood samples will be collected before injection at Visit 2 (Day 1), Week 12, Week 24, Week 52 and follow up at Week 72/EOS Visit. For patients who discontinue early from 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.

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 follows:

- 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** ($1000 \leq \text{Titer} \leq 10000$)
- **High** (Titer >10000)

Samples that tested positive in the ADA assay will be further tested for the presence of neutralizing antibodies (NAb). Samples that tested negative for ADA will not be assayed for NAb and NAb results will be imputed as negative. The NAb status will be categorized as follows:

Negative: Samples that test negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay.

Positive: Samples positive in NAb assays.

The following summaries will be provided based on ADA population:

Baseline summary:

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

Association with exposure, safety and efficacy

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

Association between ADA and impact on drug concentration profile

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

Association between ADA and safety

- Association of safety versus key ADA variables may be explored. The safety assessment may focus on the following events:
 - Injection site reaction (serious or severe and lasting 24 hours or longer)
 - Hypersensitivity reactions
 - Anaphylactic reactions
 - TEAEs leading to permanent treatment discontinuations
- Number (%) of patients with these events may be summarized by ADA patient classifications.

Association between ADA and efficacy

- Association between the key ADA variables and key efficacy endpoints may be explored. The following efficacy endpoints may be analyzed by ADA patient classifications:
 - Annualized rate of moderate or severe AECOPD
 - Mean change from baseline in pre-BD FEV1 at Week 24
 - Lack of efficacy (defined as permanent treatment discontinuation due to lack of efficacy).

4.8.3 Other quality of life analyses

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

The PGIC ([Section 5.10](#)) is a 1-item questionnaire that asks the participant to provide the overall self-assessment of change in their COPD symptoms on a 7-point scale, compared to just before the participant started taking the study treatment. Response choices are 0 = “Very much better”, 1 = “Moderately better”, 2 = “A little better”, 3 = “No change”, 4 = “A little worse”, 5 = “Moderately worse”, 6 = “Very much worse”. PGIC will be assessed at Visit 14 (Week 24) and EOT visit (Week 52).

The PGIS ([Section 5.10](#)) is a 2-items questionnaire that asks participants to provide the overall self-assessment of their COPD symptom severity and overall COPD 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 14 (Week 24) and EOT visit (Week 52).

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

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

The European quality of life-5D scale (EQ-5D) ([Section 5.8](#)) 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 ([7](#)). 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 ([8](#)) 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) and EOT visit (Week 52).

Change from baseline in EQ-5D-5L single index score and EQ VAS at Week 52 will be analyzed using the MMRM approach described for the analysis of pre-BD FEV1. The model will include records up through Week 52, 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, screening eosinophil strata, region, controller therapy strata, 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 95% 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 and Week 52) for the quantitative variables of EQ-5D-5L single index score and EQ VAS. No missing data will be imputed.

4.8.4 Pharmacodynamic/genomics endpoints

Pharmacodynamic endpoints include:

- **Whole blood biomarkers:** blood eosinophil and neutrophil count measured at Visits 1A, 2, 3, 4, 6, 8, 14, 20, EOT, follow-up visit 1 (F1 at Week 58) and EOS.
- **Serum C-reactive protein (CRP) level:** measured at Visits 1A, 2, 3, 4, 6, 8, 14, 20, EOT, F1 (Week 58) and EOS.
- **Serum biomarkers:** total interleukin-33 (IL33) measured at Visits 2, 4, 8, 14, EOT, F1 (Week 58) and EOS

Optional endpoints (for participants who signed the optional pharmacogenetic/pharmacogenomic informed consent): Whole blood messenger RNA for sequencing (RNAseq) or whole transcriptome are measured at Visits 2, 8, 14, 20 and EOT and will be stored for future analysis.

All biomarkers listed above will be summarized in the Safety population. Baseline values will be the last value collected prior to the first IMP. Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) of biomarkers at baseline will be summarized. Summary plots (mean +/- standard error of the mean) on values at each visit, absolute changes from baseline and percent changes from baseline will be provided for each biomarker by treatment group and visit.

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

4.8.5 Follow-up period (20 weeks) analyses

- AECOPD analyses will be performed for the “moderate or severe AECOPD events”, “severe AECOPD events”, and “corticosteroids-treated AECOPD events” in the 20-week follow-up period, and in the combined duration of the treatment and follow-up periods.

Descriptive statistics including mean, median, standard deviation, minimum, maximum, and interquartile range at baseline, EOT (Week 52/pEOT), F1 (6 weeks after EOT/pEOT) and EOS (20 weeks after EOT/pEOT) (see analysis window [Table 15](#)) and changes from baseline will be summarized for each treatment group for the following parameters:

- Pre and post-BD FEV1
- SGRQ symptoms score, activity score, impacts score, and total score
- E-RS:COPD breathlessness score, cough and sputum score, chest symptoms score, and total score

- EQ-5D-5L index score and VAS score
- All clinical laboratory variables, eg, blood eosinophil count, blood neutrophil count, CRP
- PK and ADA: Serum concentrations of itepekimab, anti-itepekimab antibody
- Biomarker: Total interleukin-33
- Vital signs: systolic BP, diastolic BP, pulse rate, respiratory rate, body temperature, and body weight

Plots for mean change from baseline over the follow-up period will also be provided. For AERIFY 2, all analyses will be done separately for former and current smokers' cohorts.

Adverse events in the 20-week follow up period are included in the analyses of all adverse events in the TEAE period described in [Section 4.7.2](#).

4.9 INTERIM ANALYSES

A non-binding futility IA is planned to be performed after a minimum of approximately [REDACTED] of total original planned randomized former smoker participants (approximately [REDACTED] participants) have completed at least a minimum of [REDACTED] in each of both planned Phase 3 studies combined: Study AERIFY-1 and Study AERIFY-2 (former smokers only). The proportion of the total planned number of former smokers that completed 24 weeks for each study must be at least 30%. There is no plan to change the conduct of this trial except to possibly stop the trial due to lack of efficacy. The outcome of the IA will inform whether both studies continue or are stopped.

Any unblinded interim analysis will be performed by an external independent group that supports the Data Monitoring Committee (DMC), which is separated from personnel involved in the trial conduct. The independent DMC will review the unblinded IA results and recommend action based upon criterion that is specified in the IA plan and communication document. The IA plan and communication document will include the details on prespecified non-binding futility criterion, the analyses to be included, methods to be used, and the processes and procedure intended to control access to comparative interim results to preserve trial integrity, and will be finalized prior to the interim administrative look.

Anyone involved in the conduct of the study (participants, Investigators, and study team) will remain blinded and will not have access to the IA results.

An administrative penalty of 0.001 will be taken from the significance level used at final analysis.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

6MWD:	6 minute walking distance
ADA:	antidrug antibody
AE:	adverse event
AECOPD:	acute exacerbation of COPD
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
BD:	bronchodilator
BMI:	body mass index
BODE Index:	body-mass index, airflow obstruction, dyspnea, and exercise capacity index
CDF:	cumulative distribution function
CI:	confidence interval
COPD:	chronic obstructive pulmonary disease
CRP:	C-reactive protein
CV:	coefficient of variation
DMC:	data monitoring committee
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
EQ-5D:	European quality of life-5D scale
ER:	emergency room
E-RS: COPD:	Evaluating Respiratory Symptoms in COPD
EXACT:	EXAcerbations of Chronic Pulmonary Disease Tool
FEV1:	forced expiratory volume in 1 second
HGLT:	high level group term
HLT:	high level term
HRQoL:	health-related quality of life
IA:	interim analysis
ICE:	intercurrent event
ICF:	informed consent form
ICS:	inhaled corticosteroid
IMP:	investigational medicinal product
IRT:	interactive response technology
ITT:	intent-to-treat
LABA:	long-acting beta agonist
LAMA:	long-acting muscarinic antagonist
LLT:	lower-level term
MACE:	major cardiovascular adverse events
MAR:	missing at random
MCF:	mean cumulation function
MedDRA:	medical dictionary for regulatory activities
mMRC:	modified medical research council dyspnea scale

MMRM:	mixed-effect model with repeated measures
PCSA:	potentially clinically significant abnormality
PGIC:	Patient Global Impression of Change
PGIS:	Patient Global Impression of Severity
PMM-MI:	pattern mixture model - multiple imputation
PRO:	patient reported outcome
PT:	preferred term
Q2W:	every two weeks
Q4W:	every 4 weeks
RNA:	ribonucleic acid
RR:	rate ratio
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SEM:	standard error of the mean
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 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s). In general, the statistical methods remain unchanged by the protocol amendment 1 except for the increase in sample size and the change in assessment timepoints for key secondary and some secondary endpoints.

The major statistical changes in the protocol amendment 1 are summarized in [Table 11](#).

Table 11 - Major statistical changes in protocol amendment(s)

Document	Approval Date	Changes	Rationale
Original Protocol	25-Sept-2020 (EFC16750) 15-Oct-2020 (EFC16819)	Not Applicable	Original protocol

Document	Approval Date	Changes	Rationale
Amended Clinical Trial Protocol 1	20-Sept-2022	To increase the sample size and add a potential variable treatment duration portion (maximal 52 weeks, minimal 24 weeks) for former smokers to the original study design	To ensure the study is adequately powered, despite a lower-than-expected blinded exacerbation rate due to the pandemic era.
		Sample size increase: up to 30 participants (AERIFY-1 only)	To ensure the study is adequately powered, due to the unexpected loss of treatment exposure in participants impacted by the Ukraine and Russian military conflict.
		Sample size increase: 40 participants in current smoker cohort (AERIFY-2 only)	The rate of acute exacerbations of COPD for current smokers at the time of protocol amendment 01 is lower than expected. As a consequence, the precision of the estimate changed from 29.3 to 32.1%. It is estimated that approximately 40 additional current smokers will be needed to be enrolled in the AERIFY-2 study to bring the precision of the estimate back to 30.0%.
		Key secondary endpoint: Change from baseline in pre-BD FEV1 to be evaluated at Week 24 instead of Week 52	The PK concentration steady state is expected to be reached by week 24 and to minimize the missing data due to early dropouts.
		Secondary endpoint: Change from baseline in pre-BD FEV1 at Week 24 changed to Week 52	Due to change of timepoint assessment in key secondary endpoint.
		Secondary endpoints: added Week 24 evaluation timepoint on top of Week 52 for the change from baseline in post-BD FEV1, E-RS:COPD total score, SGRQ total score, and proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score,	The PK concentration steady state is expected to be reached by Week 24.

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 (≥ 40 to < 50 , ≥ 50 to < 65 , ≥ 65 to < 75 , ≥ 75)
- 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, non-Hispanic or Latino, Not Reported, Unknown)
- region (AERIFY-1: Asia: India, China and Taiwan, province of China; Latin America: Argentina, Chile and Mexico; East Europe: Russia, Ukraine, Hungary, Poland, Czech Republic, Romania, Bulgaria, and Slovakia; Western Countries: Greece, Israel, Italy, and USA. AERIFY-2: Asia: India, Japan, and South Korea; Latin America: Argentina, Brazil, Chile and Mexico; East Europe: Russia, Turkey, Hungary, Poland, Czech Republic, and Bulgaria; Western Countries: Denmark, Spain, Israel, France, Netherlands, Norway, Portugal, Germany, United Kingdom, South Africa, Canada, and USA)
- body weight group (<70, ≥70-<90, ≥90 kg)
- body mass index as quantitative variable and in categories (BMI, <25, ≥25-<30, ≥30 kg/m²)

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

- Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.
- ***Medical or surgical history***

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.

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

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

Disease characteristics at baseline

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

- Age at diagnosis of COPD (years)
- Time since diagnosis of COPD at randomization (years)
- Time since last COPD exacerbation at randomization (months)
- Number of COPD exacerbations experienced in the past one year before screening visit (quantitative variable and qualitative variable: 1, 2, 3, ≥ 4)
- Number of moderate COPD exacerbations experienced within 1 year before screening visit (Among the moderate COPD exacerbations, how many required use of (1) systemic corticosteroids and antibiotics, (2) only systemic corticosteroids, (3) only antibiotics. And if systemic corticosteroids were used to treat the moderate COPD exacerbations, the total number of treatment days in the past one year, which will be further broken down to the treatment days using oral, intravenous and intramuscular systemic corticosteroids)
- Number of severe COPD exacerbations experienced within 1 year before screening visit (Among the severe COPD exacerbations, how many required use of (1) systemic corticosteroids and antibiotics, (2) only systemic corticosteroids, (3) only antibiotics. And if systemic corticosteroids were used to treat the severe COPD exacerbations, the total number of treatment days in the past one year, which will be further broken down to the treatment days using oral, intravenous and intramuscular systemic corticosteroids)
- Time since cessation of smoking (years) for former smokers and smoking quantity in pack-years
- Baseline spirometry data including pre-bronchodilator (pre-BD) FEV1 (L), post-bronchodilator (post-BD) FEV1 (L), pre-BD and post-BD percent predicted FEV1 (%), pre-BD and post-BD FEV1/FVC (%), pre-BD and post-BD FVC (L) and pre-BD and post-BD percent predicted FVC (%)
- Baseline COPD Assessment Test (CAT) score
- Baseline EQ-5D-5L index score and EQ VAS
- Baseline St. George's Respiratory Questionnaire for COPD patients (SGRQ) score
- Baseline 6 Minute Walking Distance (6MWD) and patient's perception of symptoms (mMRC) from BODE Index
- Baseline blood eosinophil count
- Baseline blood eosinophil count group (<150 cells/mm³, ≥ 150 to <300 cells/mm³, ≥ 300 cells/mm³)
- Baseline blood eosinophil count for the eosinophil <300 /mm³ group and for the eosinophil ≥ 300 /mm³ group
- Screening blood eosinophil stratum (<300 cells/mm³, ≥ 300 cells/mm³)
- Background therapy containing ICS (Yes/No); if ICS were used, dose of ICS (quantitative variable and qualitative variable: low, medium, high [high for >500 mcg, medium for >250 and ≤ 500 mcg, and low for ≤ 250 mcg, see [Section 5.15](#)])

- Type of background therapy (Triple therapy: ICS+LABA+LAMA; Double therapy: LABA+LAMA, ICS+LABA)

Any technical details related to computation, dates, and imputations for missing dates are described in [Section 5.4](#).

Prior or concomitant medications

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

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) 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 and exposed 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. For COVID-19 vaccines, the type of vaccine (manufacturer name eg, Pfizer-BioNTech, Moderna, Sinovac etc) will be provided.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

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 12 - Analyses window definition for efficacy endpoints - Treatment period

Scheduled visit	Targeted study day	Time windows						
		Pre-BD spirometry	Post-BD spirometry	SGRQ	PGIC	PGIS	BODE Index score	EQ-5D-5L
Visit 1 (W-5 to W-3)	-35							
Week 0 (Visit 2)	1	-21-1	-21-1	≤1		≤1	≤1	≤1
Week 2 (Visit 3)	15	2-21	2-21					
Week 4 (Visit 4)	29	22-42	22-42					
Week 8 (Visit 6)	57	43-70	43-70					
Week 12 (Visit 8)	85	71-98	71-126	2-126				
Week 16 (Visit 10)	113	99-140						
Week 24 (Visit 14)	169	141-196	127-210	127-210	≤266	2-266		
Week 32 (Visit 18)	225	197-238						
Week 36 (Visit 20)	253	239-266	211-308	211-308				
Week 40 (Visit 22)	281	267-308						
Week 48 (Visit 26)	337	309-350						
Week 52	365	351-379	309-379	309-379	267-379	267-379	2-379	2-379

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.

Table 13 - Analyses window definition for safety endpoints - Treatment period

Scheduled visit	Targeted study day	Time windows				
		Vital signs and Routine urine cotinine dipstick test	Hematology, clinical chemistry, urinalysis	ECG	High-sensitivity urine cotinine/anabasine test	Physical examination
Visit 1 (W-5 to W-3)	-35					
Week 0 (Visit 2)	1	-21-1	-21-1	-21-1		≤1
Week 2 (Visit 3)	15	2-21	2-21			
Week 4 (Visit 4)	29	22-42	22-42			
Week 8 (Visit 6)	57	43-70	43-70			
Week 12 (Visit 8)	85	71-98	71-126			2-126
Week 16 (Visit 10)	113	99-140				
Week 24 (Visit 14)	169	141-196	127-210	2-266	-21 - 266	127-210
Week 32 (Visit 18)	225	197-238				
Week 36 (Visit 20)	253	239-266	211-308			211-308
Week 40 (Visit 22)	281	267-308				
Week 48 (Visit 26)	337	309-350				
Week 52	365	351-379	309-379	267-379	267-379	309-379

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed). Only measurements at pEOT/EOT and earlier are mapped to the analysis windows.

Table 14 - Analyses window definition for PK/PD endpoints - Treatment period

Scheduled visit	Targeted study day	Time windows					
		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	-21-1	≤1	≤1	≤1
Week 2 (Visit 3)	15	2-21		2-21			
Week 4 (Visit 4)	29	22-42		22-42	2-56		
Week 8 (Visit 6)	57	43-70		43-70			
Week 12 (Visit 8)	85	71-126	2-126	71-126	57-126	2-126	2-126
Week 16 (Visit 10)	113						
Week 24 (Visit 14)	169	127-210	127-266	127-210	127-266	127-210	127-266
Week 32 (Visit 18)	225						
Week 36 (Visit 20)	253	211-308		211-308		211-266	
Week 40 (Visit 22)	281						
Week 48 (Visit 26)	337						
Week 52	365	309-379	267-379	309-379	267-379	267-379	267-379

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Table 15 - Analyses window definition for endpoints for follow-up period (20 weeks) analyses

<Scheduled visit	Targeted study day	Time windows						
		Pre-BD spirometry	Post-BD spirometry	SGRQ, EQ-5D-5L	Vital signs	Hematology, clinical chemistry	ADA	PK, Total IL-33
EOT	1	-6-7	-6-7	-6-7	-6-7	-6-7	-6-7	-6-7
F1 (6 weeks after EOT)	43	8-91			8-91	8-91		8-91
EOS (20 weeks after EOT)	141	≥92	≥71	≥71	≥92	≥92	≥71	≥92

EOT are measurements taken at pEOT/EOT visits. Study days are calculated considering Day 1 as the day of pEOT/EOT visit.

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.

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 : Enzymes activities must be expressed in ULN, not in IU/L. >3 ULN >5 ULN >10 ULN >20 ULN	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 : Enzymes activities must be expressed in ULN, not in IU/L. >3 ULN >5 ULN >10 ULN >20 ULN	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 $\mu\text{mol/L}$ 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 Conjugated bilirubin dosed on a case-by-case basis. TBILI >1.5 ULN	
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 Cockcroft-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		Harrison- Principles of internal Medicine 17 th Ed., 2008.
Hyperuricemia	>408 µmol/L	
Hypouricemia	<120 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
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	
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 17 th Ed., 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
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.
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 ≥ 20 mmHg ≥ 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.

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

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CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

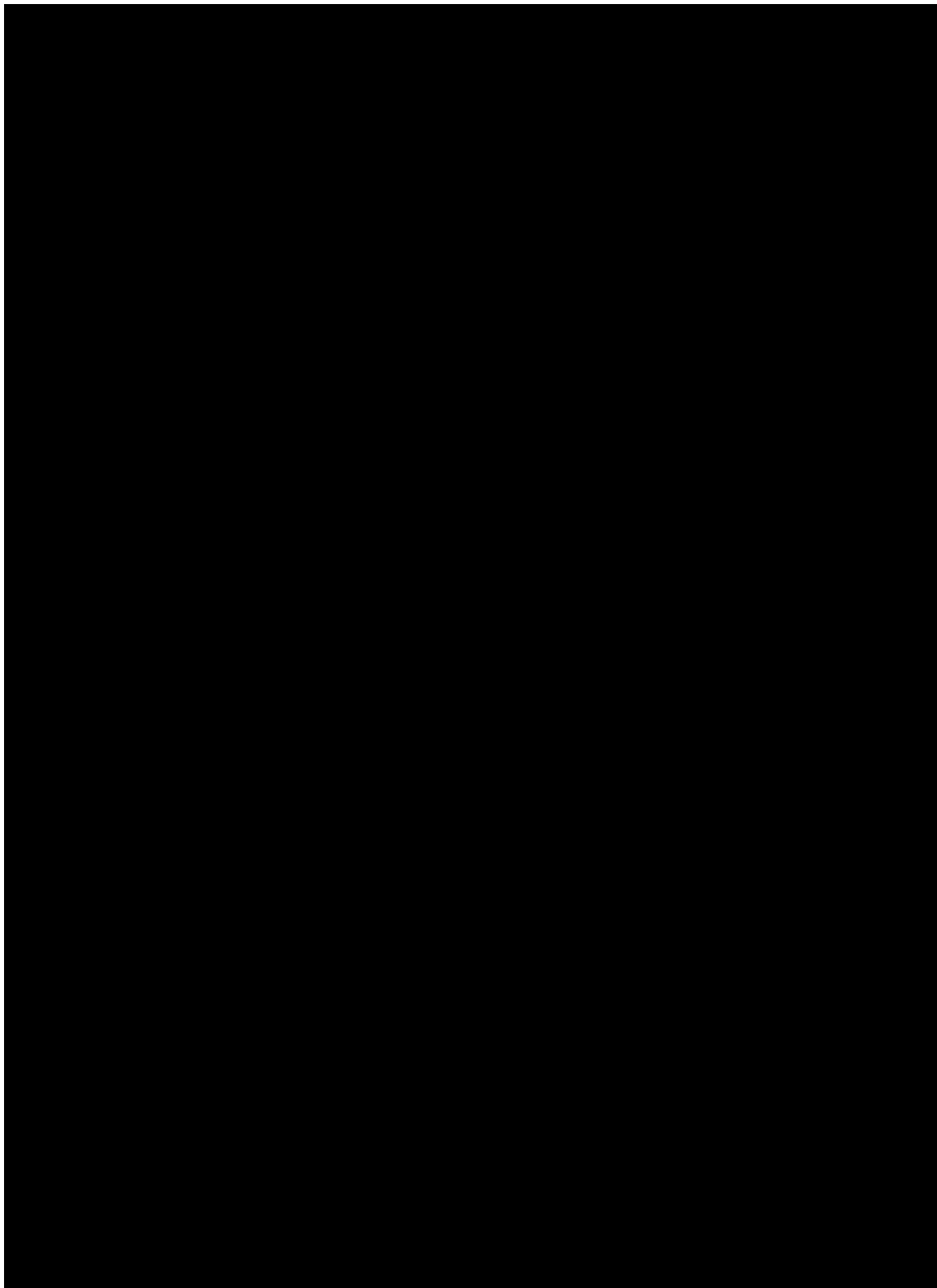
for Phase 2/3 studies

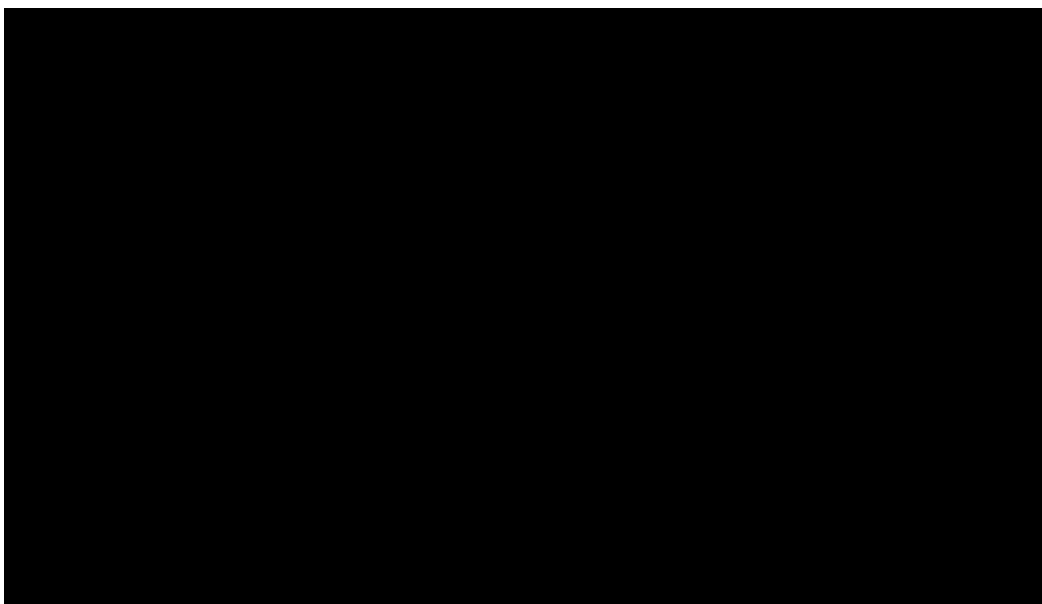
(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
QRS	>110 ms >110 msec and increase from baseline $\geq 25\%$ >120 ms >120 ms and increase from baseline $\geq 25\%$	Categories are cumulative
QT	<u>>500 ms</u>	
QTc	<u>Absolute values (ms)</u> >450 ms >480 ms >500 ms <u>Increase from baseline</u> Increase from baseline [30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and $\Delta QTc > 60$ ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

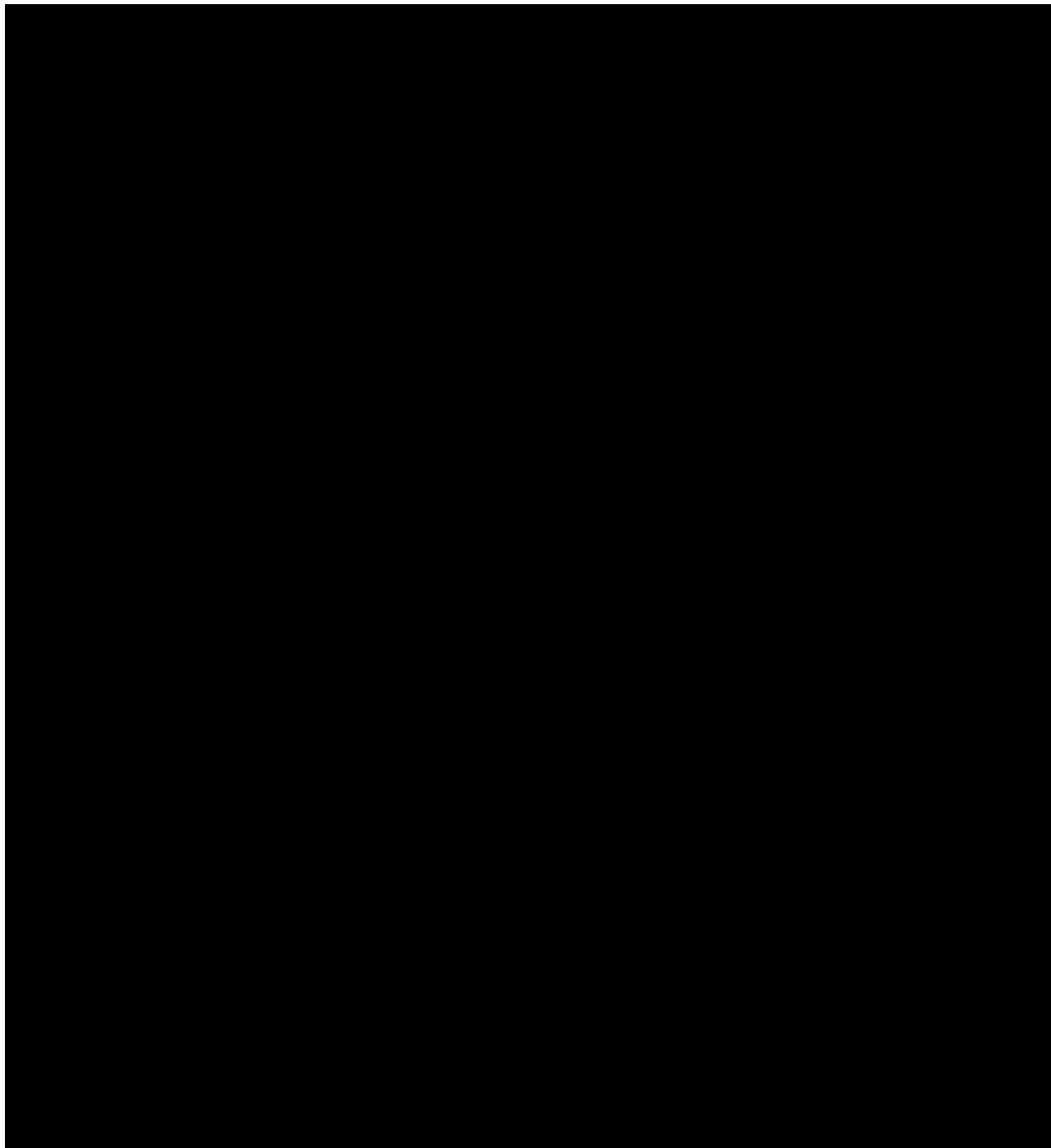
5.6 APPENDIX 6 THE EXACT AS FORMATTED FOR PERSONAL DIGITAL ASSISTANT (PDA)



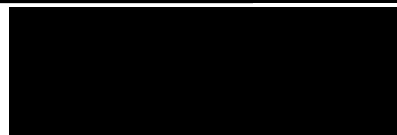




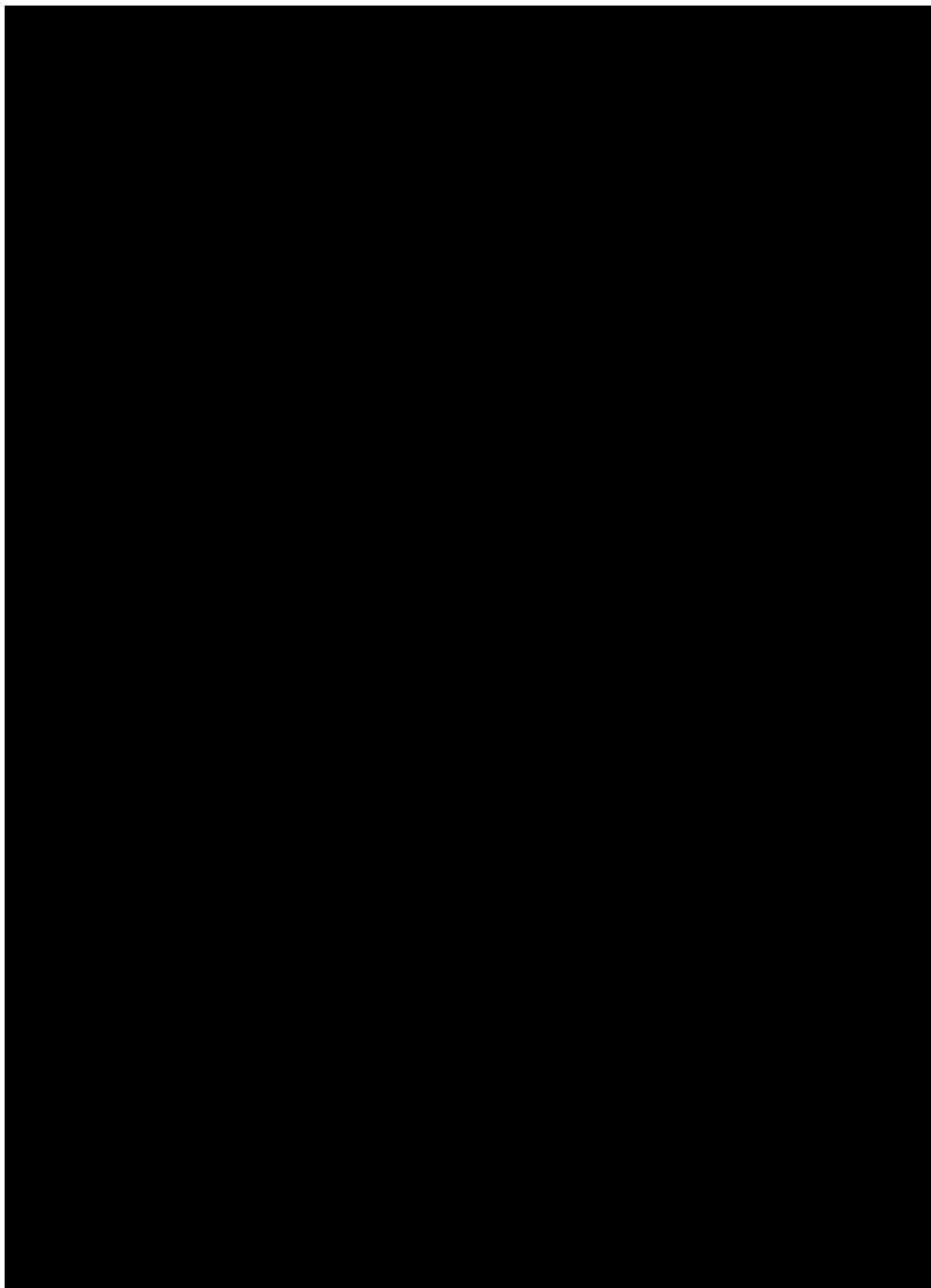
5.7 APPENDIX 7 COPD ASSESSMENT TEST (CAT)



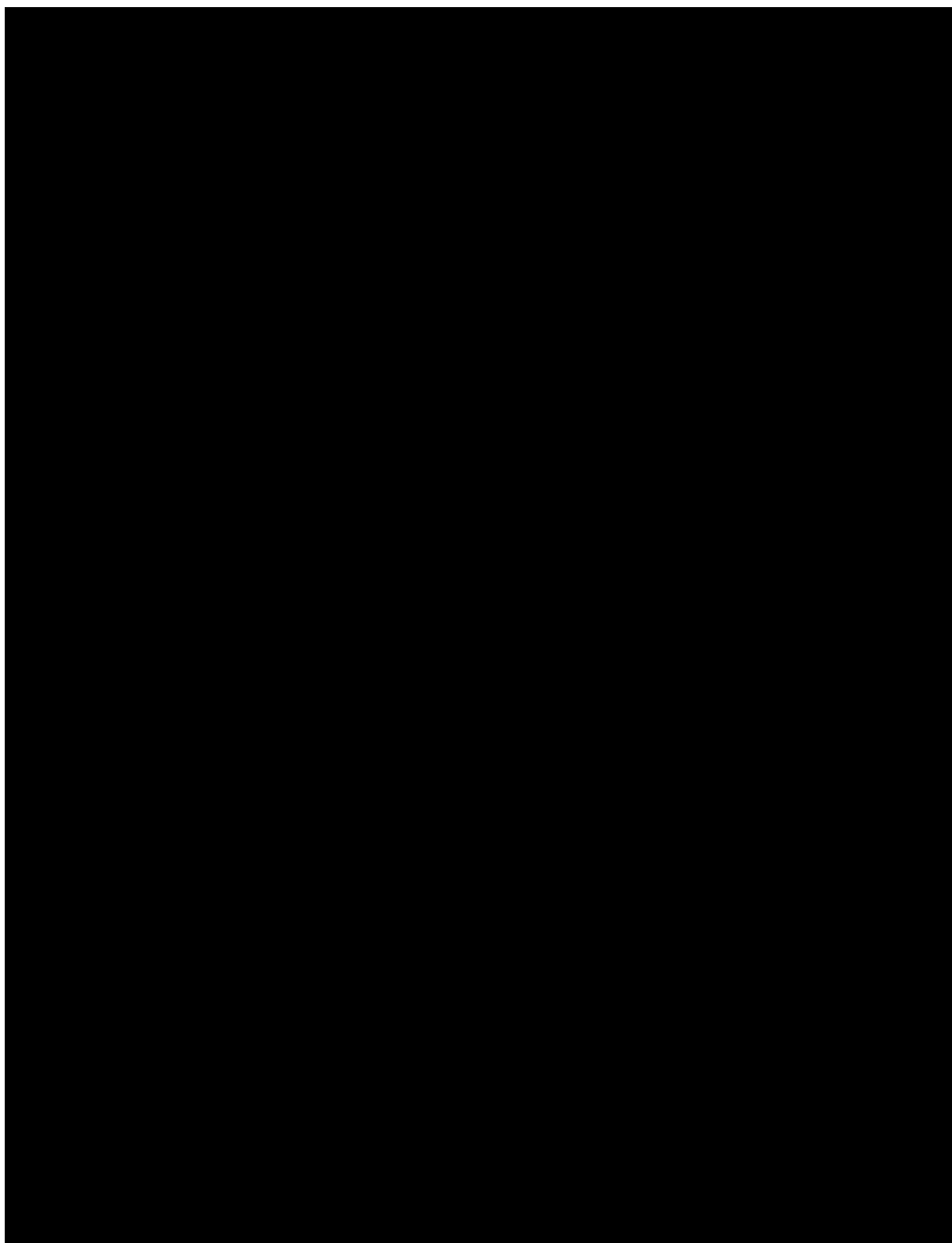
COPD Assessment Test and the CAT logo is a trade mark of the GlaxoSmithKline group of companies.
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Last Updated: February 24, 2012

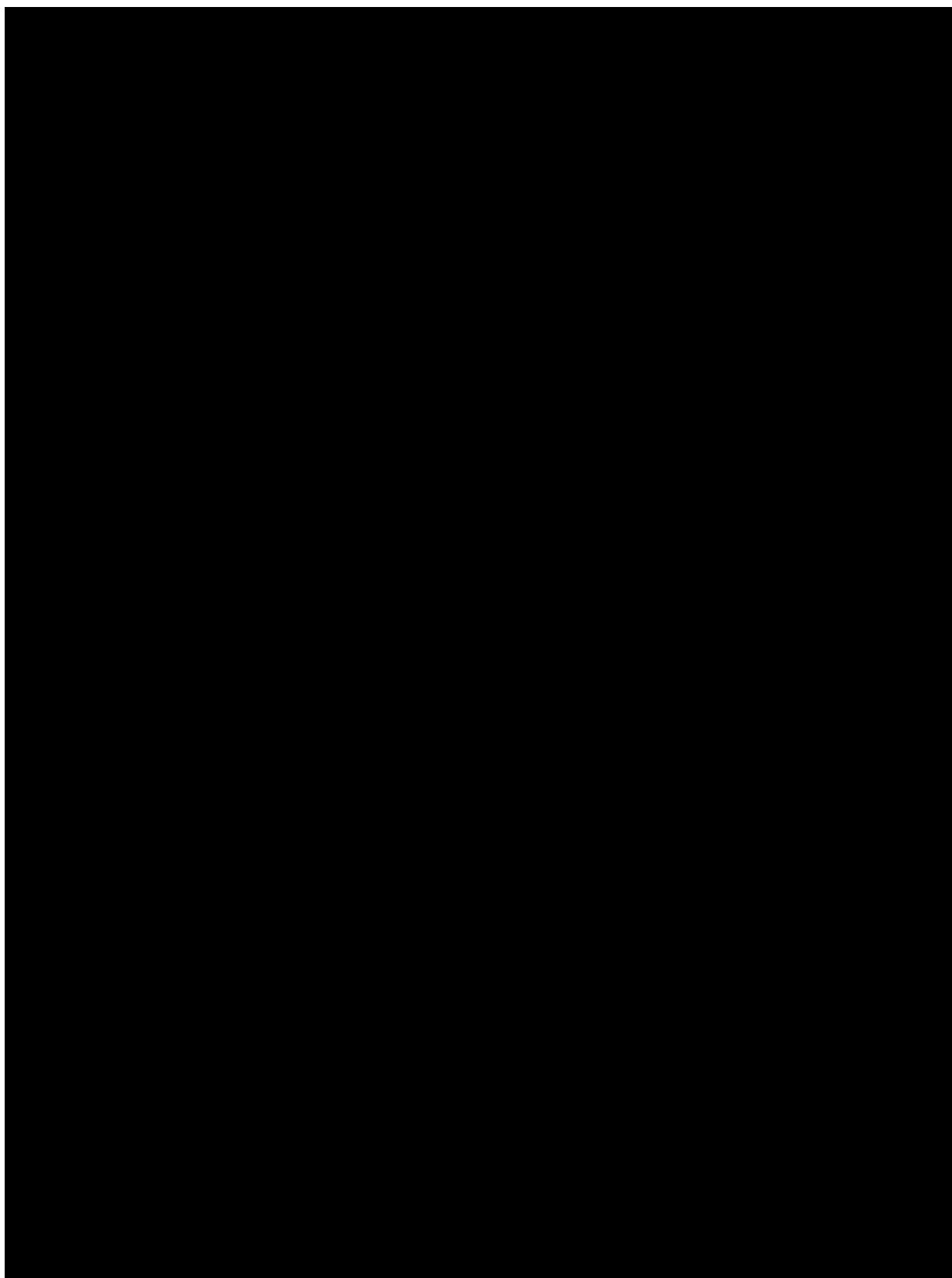


5.8 APPENDIX 8 EUROQOL QUESTIONNAIRE (EQ-5D-5L)

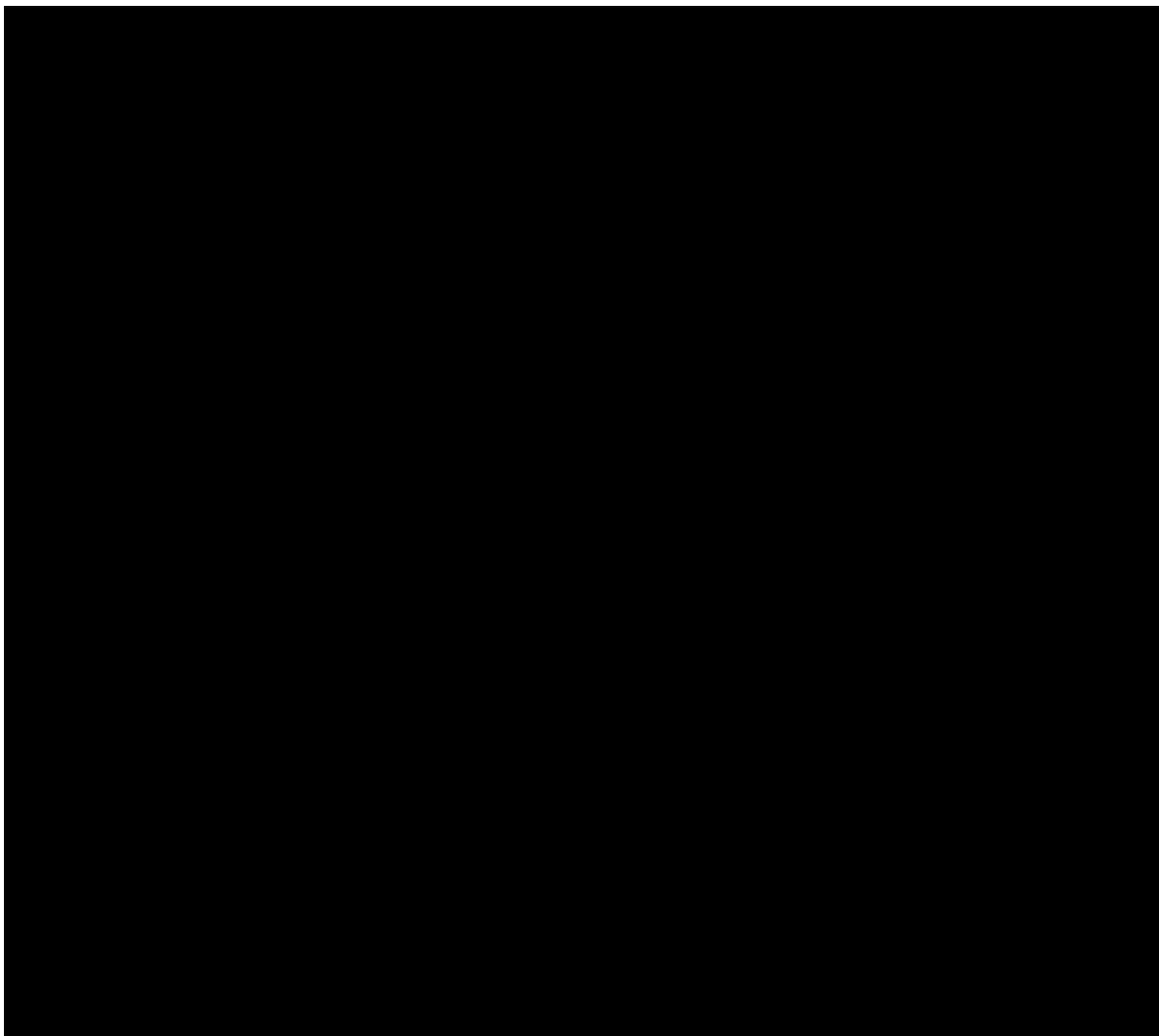


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5.9 APPENDIX 9 BODE INDEX



5.10 APPENDIX 10 PGIC/PGIS

Patient Global Impression of Severity (PGIS) of COPD symptoms

Common symptoms of chronic obstructive pulmonary disease (COPD) are shortness of breath, discomfort in chest, coughing, and bringing up mucus (phlegm).

Please choose the response below that best describes the severity of your COPD symptoms during the past week.

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

Patient Global Impression of Severity (PGIS) of COPD overall

Please choose the response below that best describes the severity of your COPD overall during the past week.

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

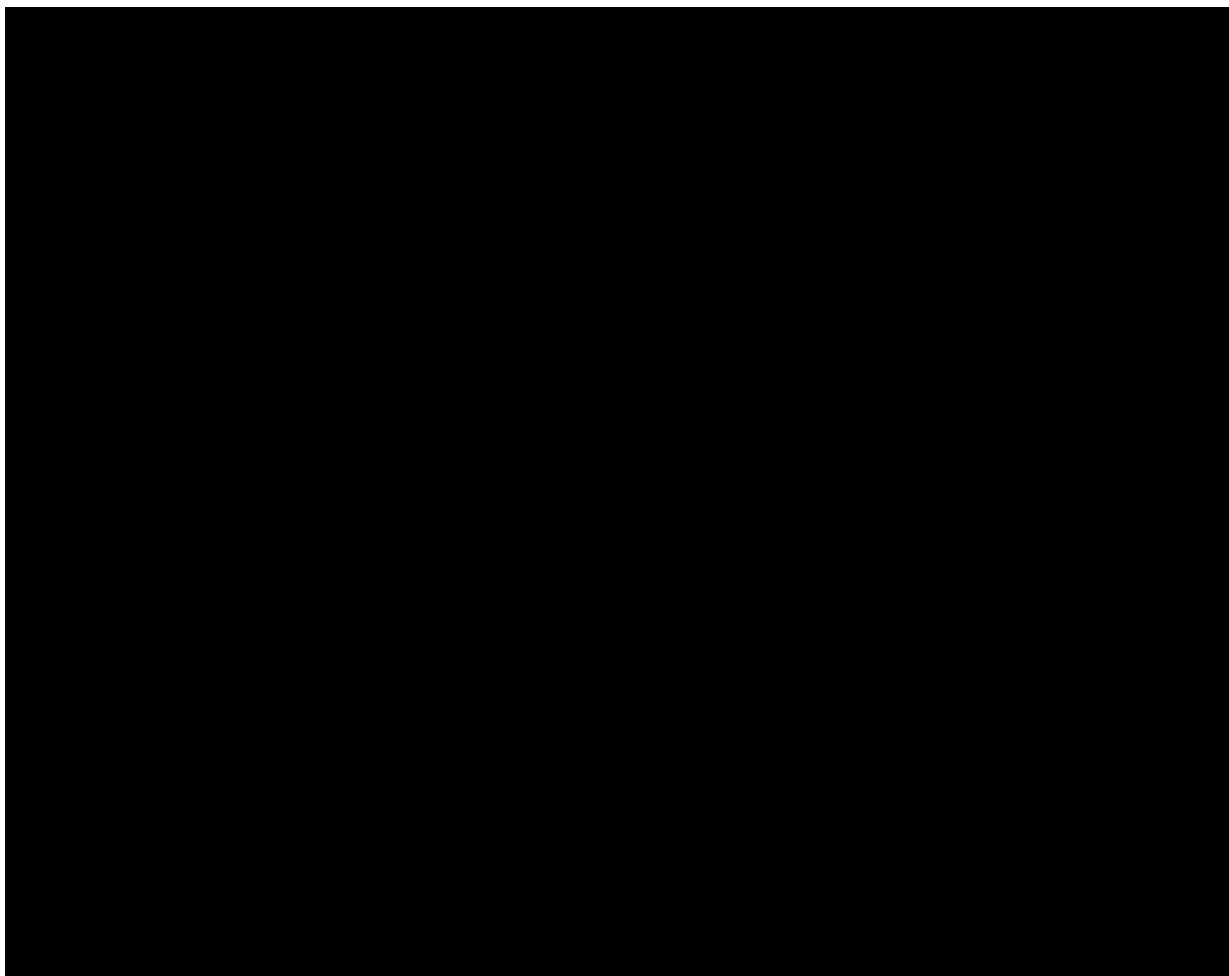
Patient Global Impression of Change (PGIC) of COPD symptoms

Common symptoms of chronic obstructive pulmonary disease (COPD) are shortness of breath, discomfort in chest, coughing, and bringing up mucus (phlegm).

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

- ☐ Very much better
- ☐ Moderately better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Very much worse

5.11 APPENDIX 11 ST GEORGE'S RESPIRATORY QUESTIONNAIRE FOR COPD PATIENTS (SGRQ)

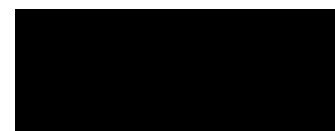


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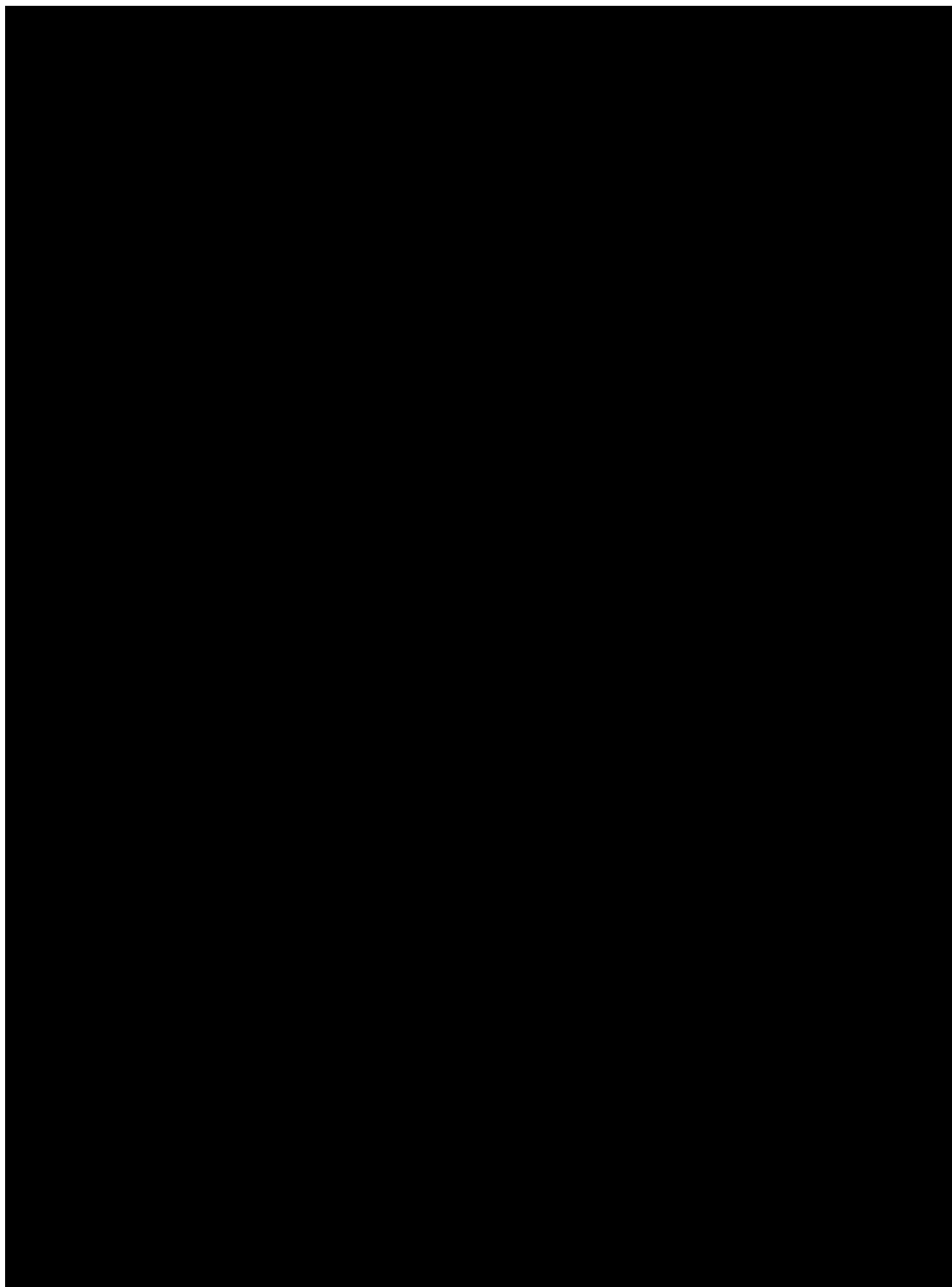
UK/ English (original) version

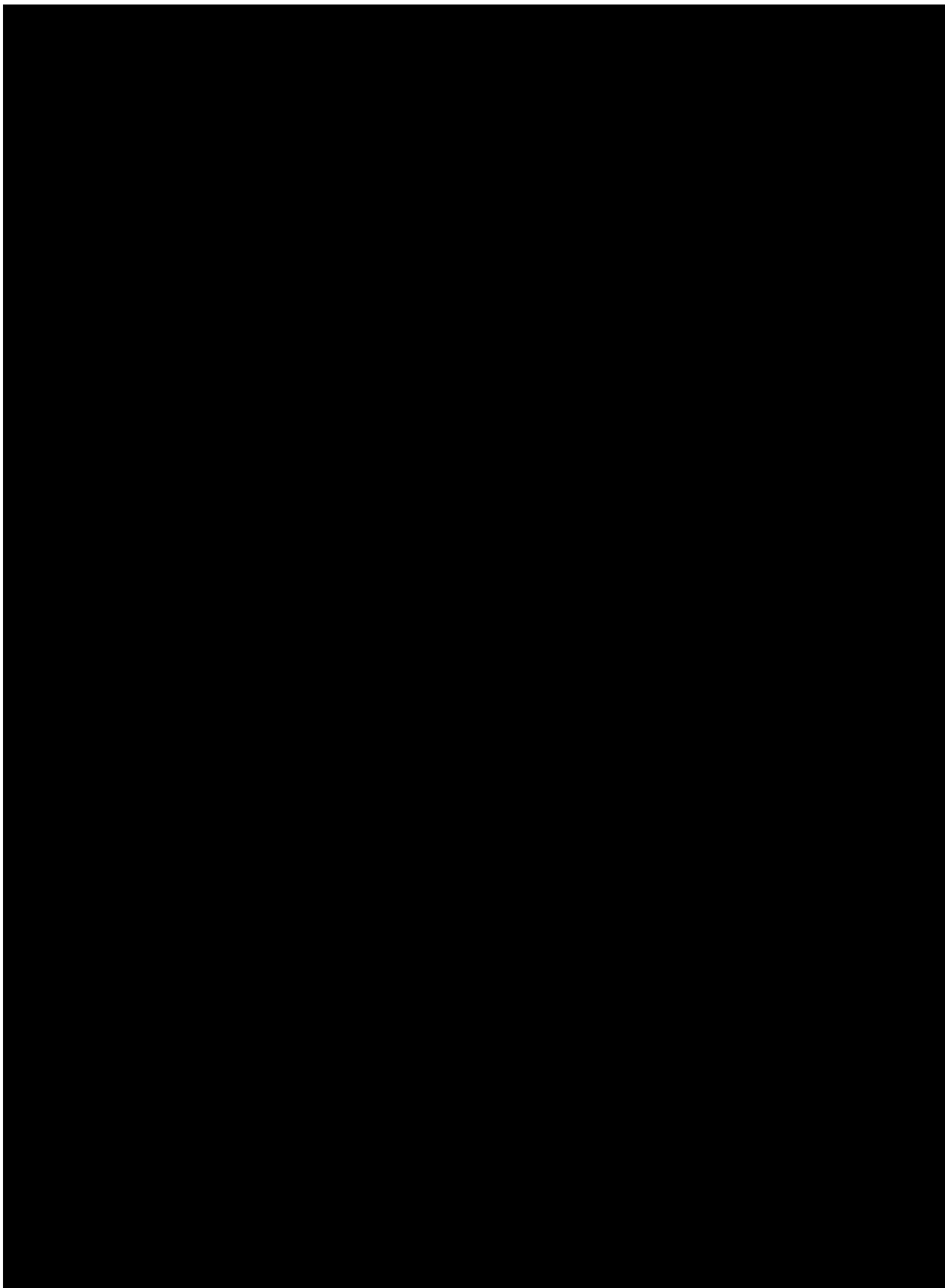
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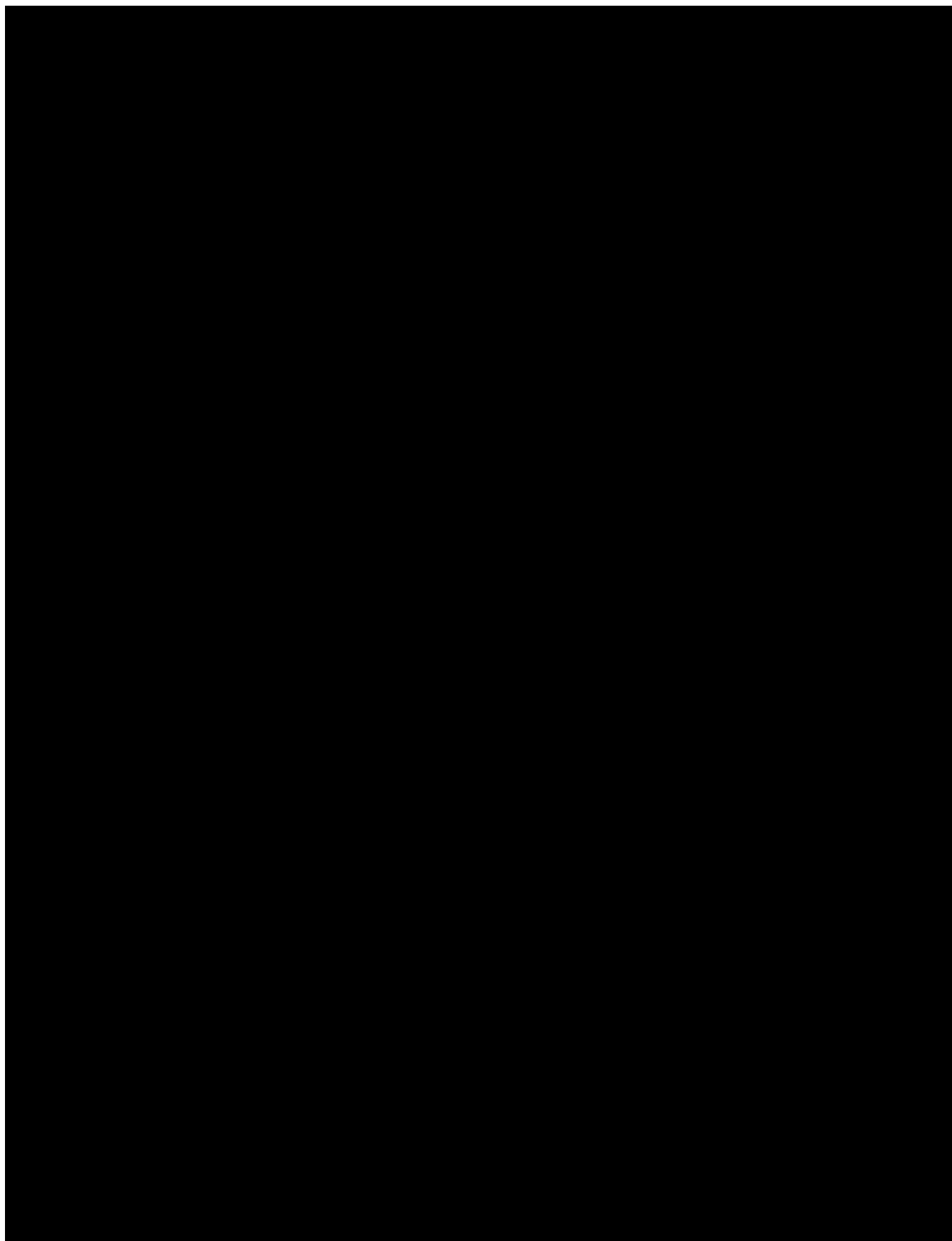
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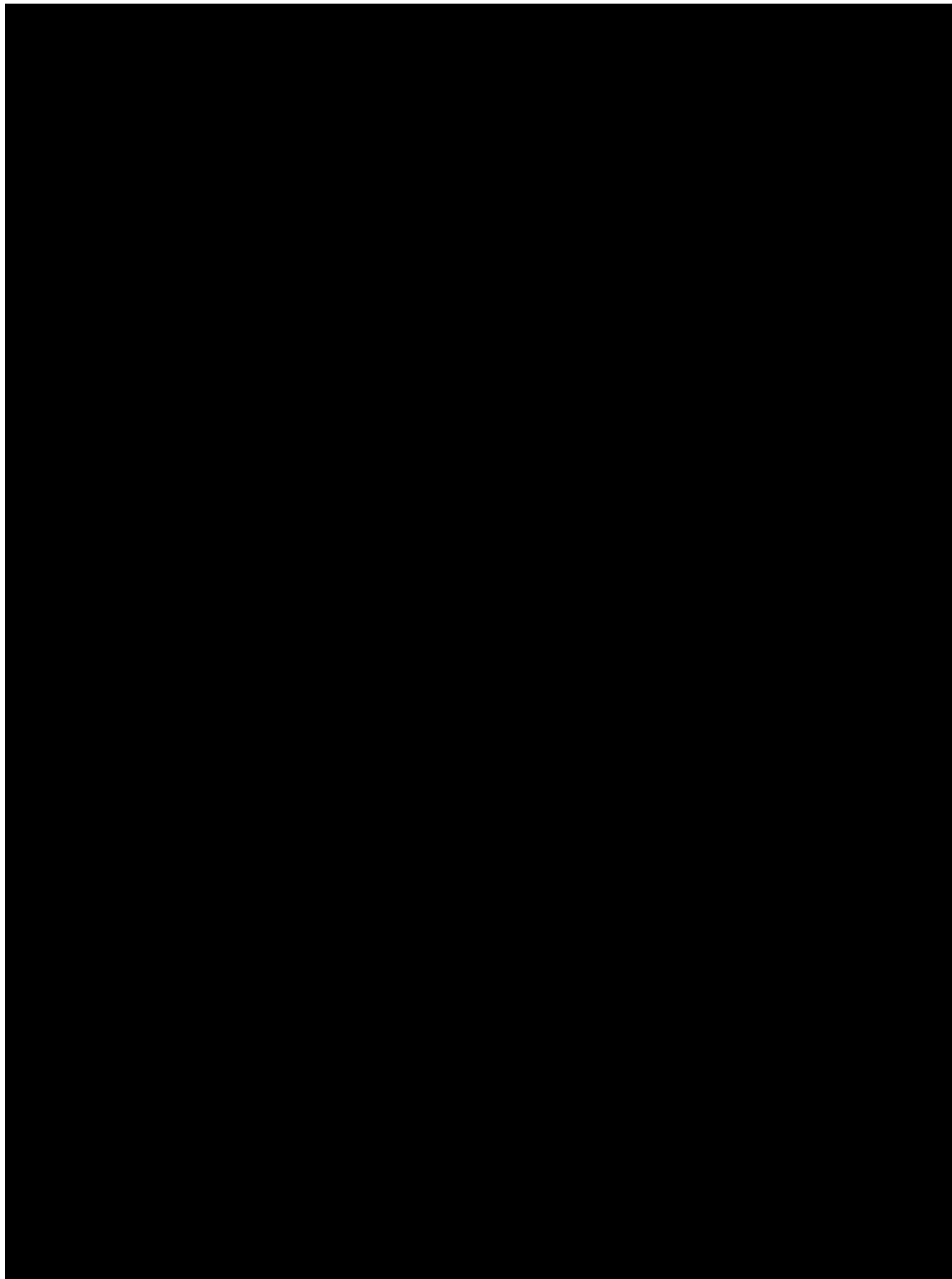


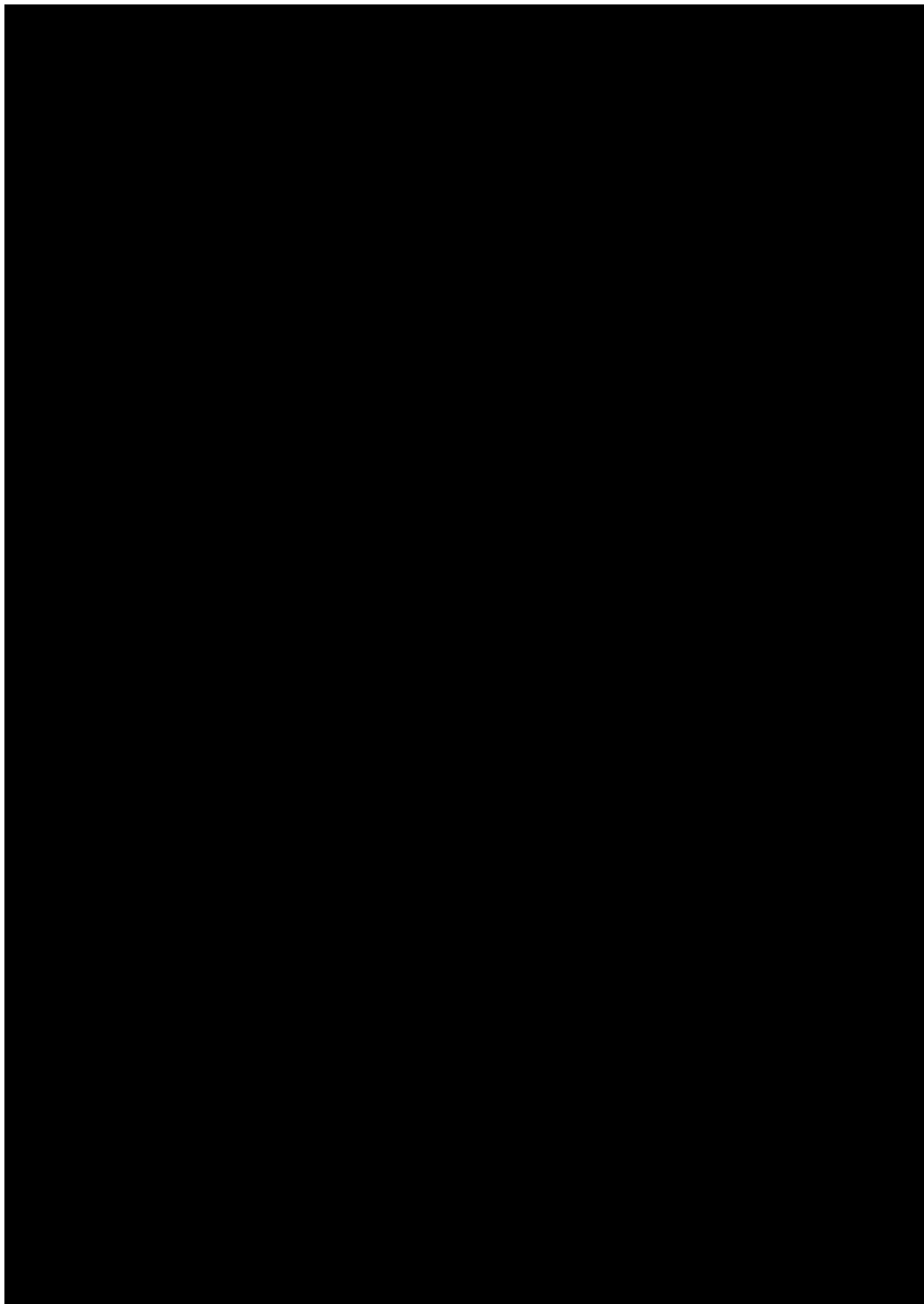
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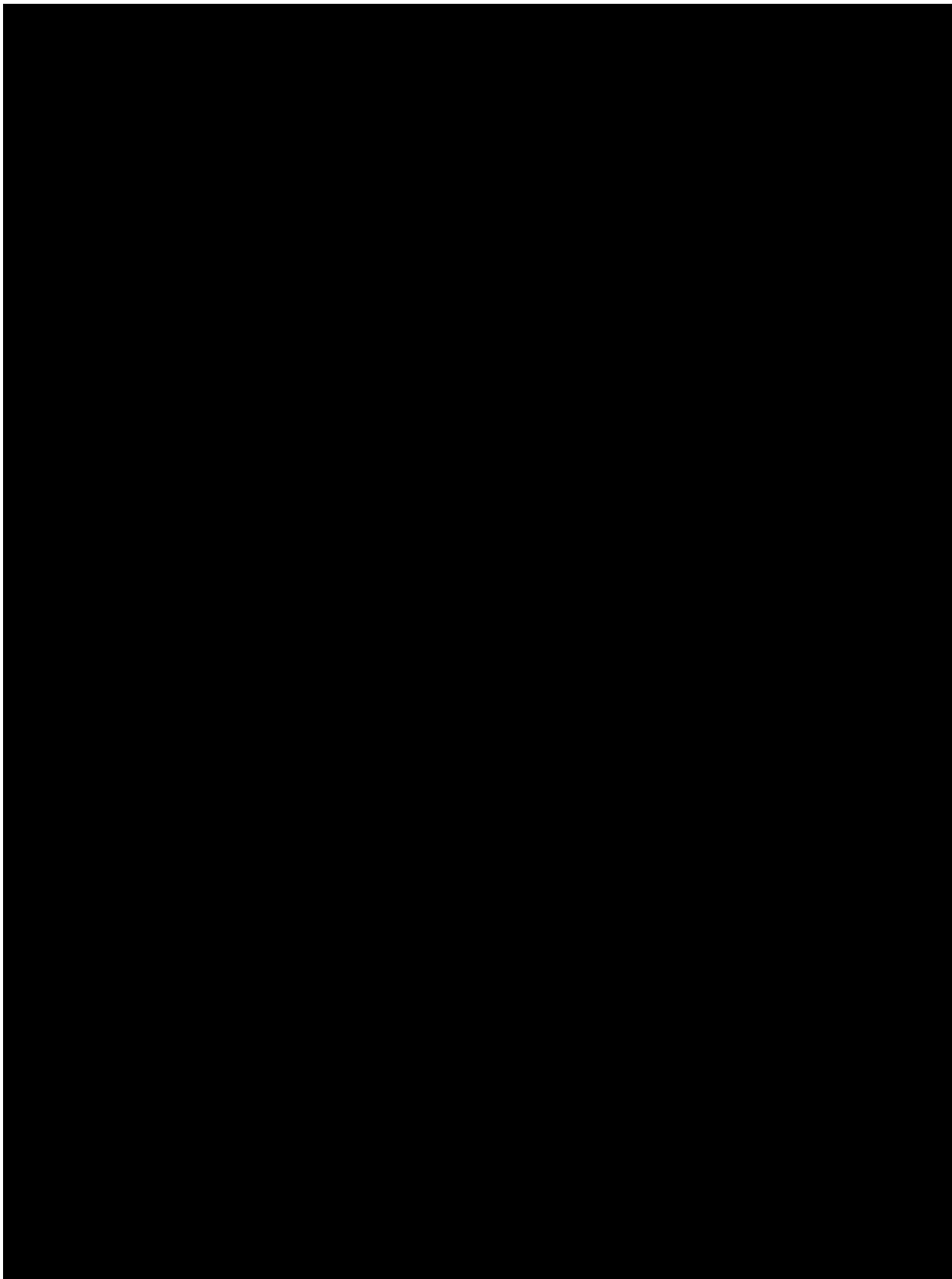


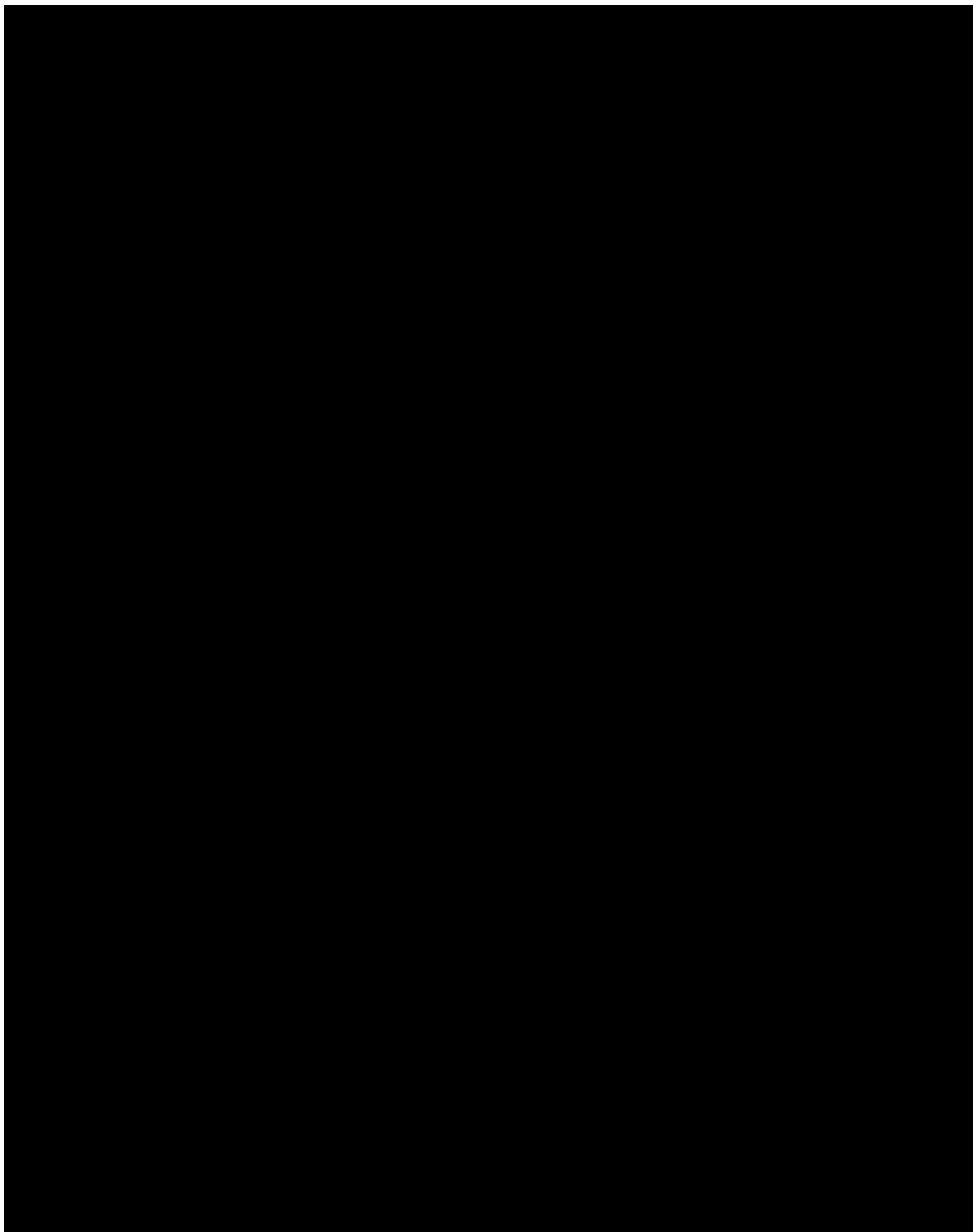


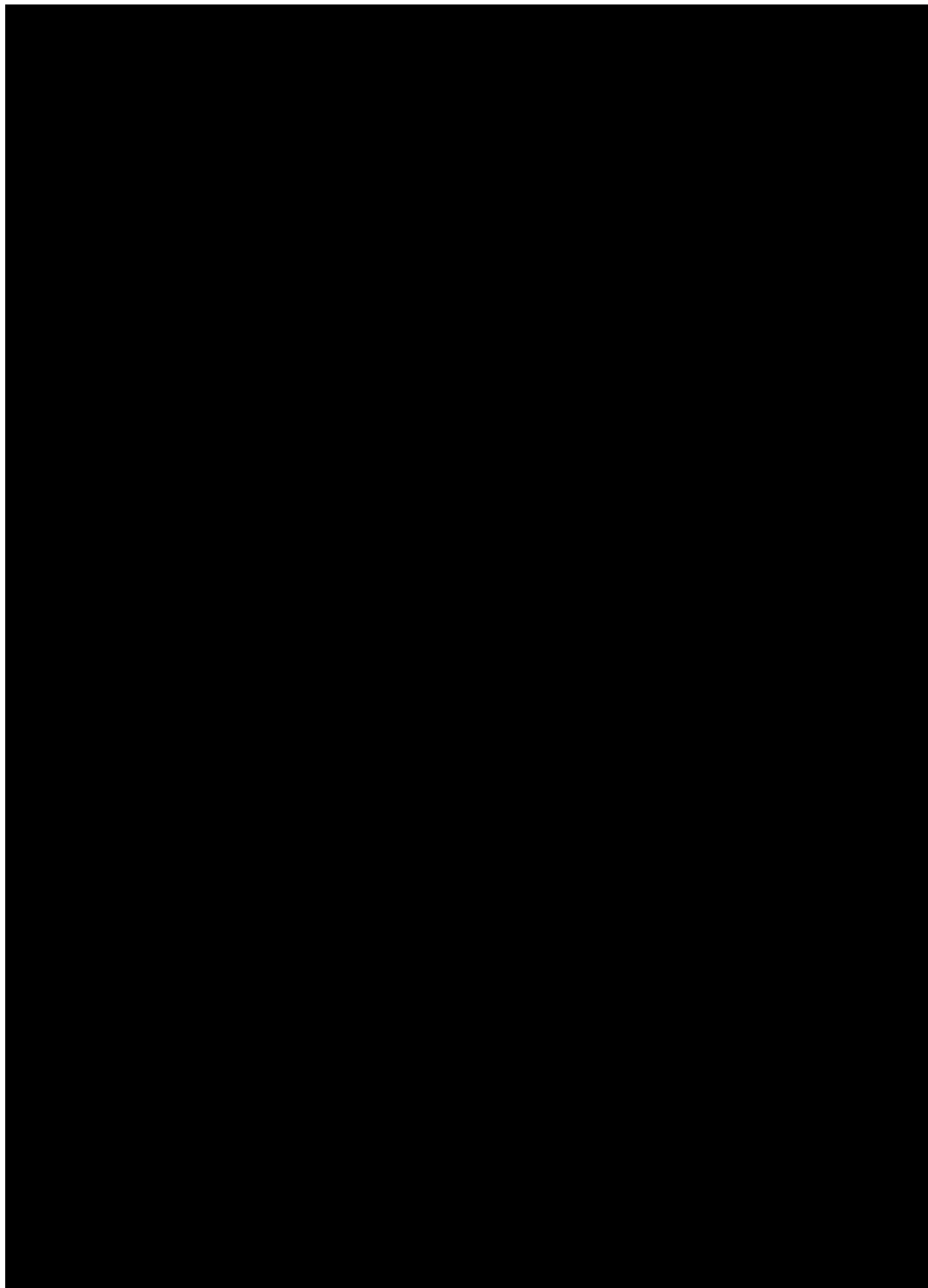


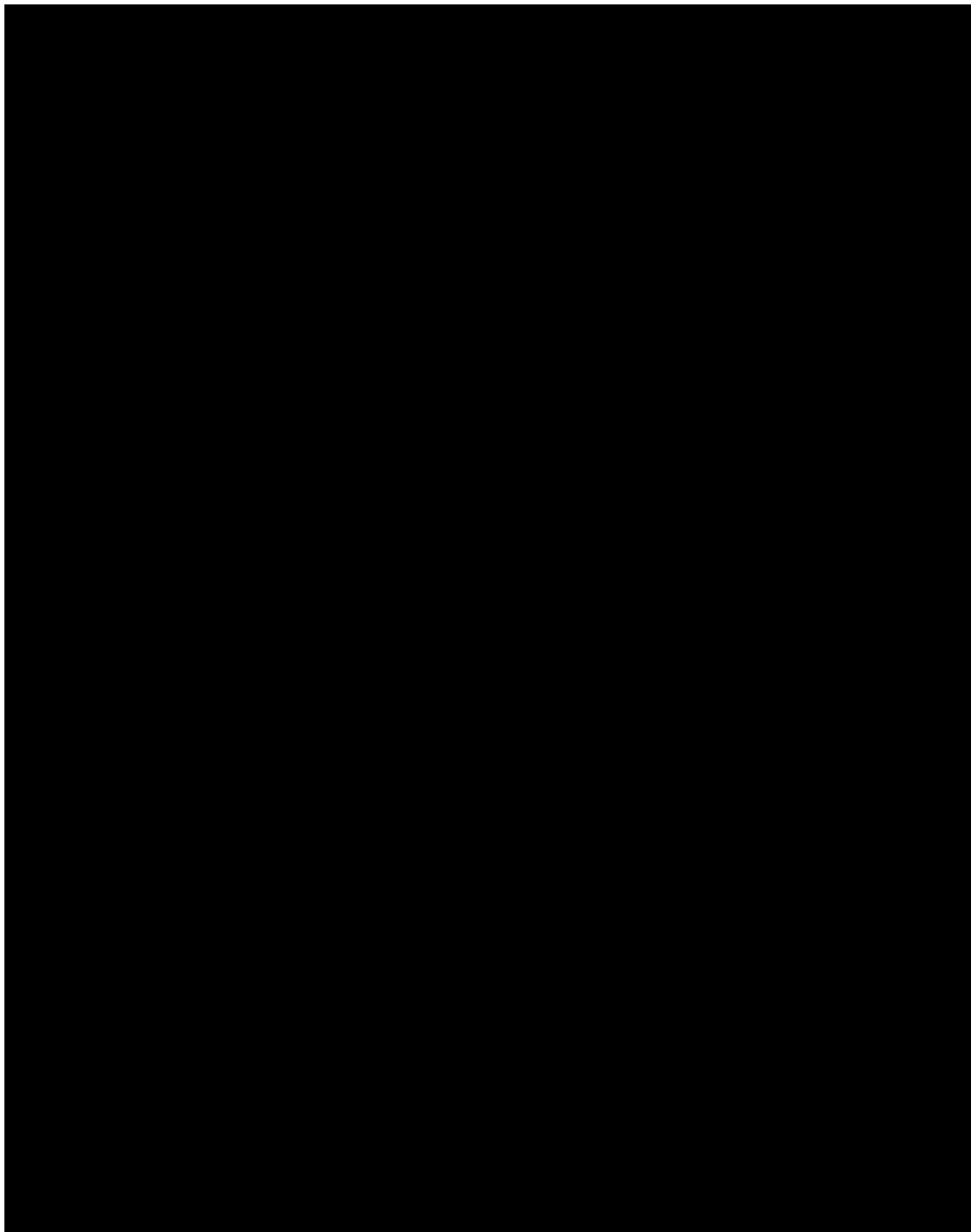


5.12 APPENDIX 12 SGRQ SCORING ALGORITHM









5.13 APPENDIX 13 LIST OF OPPORTUNISTIC INFECTIONS

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis – only systemic or extensive mucosal or cutaneous candidiasis.
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (severe/disseminated)
- Herpes Zoster
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)
- Tuberculosis (TB)

This list is indicative and not exhaustive.

5.14 APPENDIX 14 DEFINITION OF ANAPHYLAXIS

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

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

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
 - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
-

PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

5.15 APPENDIX 15 LOW, MEDIUM AND HIGH DOSE OF INHALED CORTICOSTEROIDS

Low, medium, and high dose inhaled corticosteroids

Inhaled Corticosteroid	Total Daily Dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; n.a. = not applicable; nebulas = nebulized solution

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

5.16 APPENDIX 16 SUMMARY OF STATISTICAL ANALYSES

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Annualized rate of moderate or severe AECOPD over the planned placebo-controlled treatment period	- AERIFY-1 ITT - AERIFY-2 ITT former smokers	Annualized rate of moderate or severe AECOPD (Treatment policy/while-on-treatment estimand. All off-treatment AECOPD events during the planned treatment period will be included in the analysis. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis.)	Negative binomial regression model	1. On-treatment analysis, where only the events observed during the on-treatment period (from first IMP to the EOT visit for completers; otherwise to the last administration of IMP + 14 days) will be included in the analysis. 2. Treatment-policy analysis, where all off-treatment AECOPD events during the planned treatment period will be included in the analysis for all patient data including Ukraine patients (ie, data cutoff date of Feb 24, 2022 will not be applied for patients enrolled in Ukraine). 3. Sensitivity analyses for missing data in the primary endpoint includes tipping point analysis, pattern mixture model and control-based multiple imputation methods. 4. Sensitivity analysis for primary endpoint excluding participants who resumed smoking during the study.	Yes, see Section 4.3.5 for subgroups.	The same primary analyses will also be performed in the 20-week follow-up period, and in the combined duration of the treatment and follow-up periods.

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Key Secondary Endpoint						
Change from baseline in pre-BD FEV1 at Week 24	- AERIFY-1 ITT - AERIFY-2 ITT former smokers	Change from baseline in pre-BD FEV1 at Week 24 (Treatment policy/while-on-treatment estimand. All off-treatment pre-BD FEV1 values measured during the planned treatment period up to Week 24 will be included in the analysis. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis.)	MMRM model	1. On-treatment analysis, where only the events observed during the on-treatment period (from first IMP to the EOT visit for completers; otherwise to the last administration of IMP + 14 days) will be included in the analysis. 2. Treatment-policy analysis, where all off-treatment pre-BD FEV1 values measured during the planned treatment period up to Week 24 will be included in the analysis for all patients including Ukraine patients (ie, data cutoff date of Feb 24, 2022 will not be applied for patients enrolled in Ukraine). 3. Sensitivity analyses for missing data in the key secondary endpoint includes pattern mixture model and control-based multiple imputation methods.	Yes, same set of subgroups defined for the primary endpoint.	No
Other Secondary Endpoints						
Change from baseline in pre-BD FEV1 at Week 52	- AERIFY-1 ITT- Week 52 - AERIFY-2 ITT- Week 52 former smokers - AERIFY-2 ITT current smokers	Change from baseline in pre-BD FEV1 at Week 52 (All off-treatment pre-BD FEV1 values measured up to Week 52 will be included in the analysis). For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis)	MMRM model	No	No	No

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Change from baseline in post-BD FEV1 at Week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Change from baseline in post-BD FEV1 at Week 24 and at Week 52 (All off-treatment post-BD FEV1 values measured during the planned treatment period up to Week 24 will be included in the analysis. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis)	MMRM model	No	No	No
Change from baseline in post-BD FEV1 at Week 52	• AERIFY-1 ITT- Week 52 • AERIFY-2 ITT- Week 52 former smokers • AERIFY-2 ITT current smokers	Change from baseline in post-BD FEV1 at Week 24 and at Week 52 (All off-treatment post-BD FEV1 values measured during the planned treatment period up to Week 52 will be included in the analysis. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis)	MMRM model	No	No	No
Time to first moderate or severe AECOPD over the planned placebo-controlled treatment period	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Time to first moderate or severe AECOPD (All off-treatment AECOPD events during the planned treatment period will be included in the analysis. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis)	Cox regression model	No	No	No

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Annualized rate of severe AECOPD over the planned placebo-controlled treatment period	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • Pooled population of AERIFY-1 ITT and AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Annualized rate of severe AECOPD (All off-treatment AECOPD events during the planned treatment period will be included in the analysis. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis)	Negative binomial regression model	Due to potential insufficient power to detect the between-group difference in rate of change in each single study, the analysis will also be performed by pooling data from the AERIFY-1 and AERIFY-2 studies.	No	The same primary analyses will also be performed in the 20-week follow-up period, and in the combined duration of the treatment and follow-up periods.
Time to first severe AECOPD over the planned placebo-controlled treatment period	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Time to first severe AECOPD (All off-treatment AECOPD events during the planned treatment period will be included in the analysis. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis)	Cox regression model	No	No	No
Annualized rate of corticosteroid-treated AECOPD over planned placebo-controlled treatment period	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Annualized rate of corticosteroid-treated AECOPD (All off-treatment AECOPD events during the planned treatment period will be included in the analysis. For participants enrolled in Ukraine, the data cutoff date will be set to Feb 24, 2022 (ie, outbreak of the military conflict) for the analysis)	Negative binomial regression model	No	No	The same primary analyses will also be performed in the 20-week follow-up period, and in the combined duration of the treatment and follow-up periods.

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Change from baseline in E-RS:COPD total score at Week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Change from baseline in E-RS:COPD total score at Week 24	MMRM model	No	No	No
Change from baseline in E-RS:COPD total score at Week 52	• AERIFY-1 ITT- Week 52 • AERIFY-2 ITT- Week 52 former smokers • AERIFY-2 ITT current smokers	Change from baseline in E-RS:COPD total score at Week 52	MMRM model	No	No	No
Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4 weeks	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • Pooled population of AERIFY-1 ITT and AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4 weeks	MMRM model	Due to potential insufficient power to detect the between-group difference in rate of change in each single study, the slope analysis will also be performed by pooling data from the AERIFY-1 and AERIFY-2 studies.	No	A sensitivity analysis on the rate of change in post-BD FEV1 will be performed by including the 20 weeks post-treatment follow-up period.
Change from baseline in SGRQ total score at Week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Change from baseline in SGRQ total score at Week 24	MMRM model	No	No	No

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Change from baseline in SGRQ total score at Week 52	• AERIFY-1 ITT- Week 52 • AERIFY-2 ITT- Week 52 former smokers • AERIFY-2 ITT current smokers	Change from baseline in SGRQ total score at Week 52	MMRM model	No	No	No
Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24	Logistic regression model	No	No	No
Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 52	• AERIFY-1 ITT- Week 52 • AERIFY-2 ITT- Week 52 former smokers • AERIFY-2 ITT current smokers	Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 52	Logistic regression model	No	No	No
Annualized rate of moderate or severe AECOPD over the planned placebo-controlled treatment period	• AERIFY-2 ITT current smokers	Annualized rate of moderate or severe AECOPD (All off-treatment AECOPD events during the planned treatment period will be included in the analysis.	Negative binomial regression model	No	No	The same primary analyses will also be performed in the 20-week follow-up period, and in the combined duration of the treatment and follow-up periods.

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Change from baseline in pre-BD FEV1 at Week 24	AERIFY-2 ITT current smokers	Change from baseline in pre-BD FEV1 at Week 24 (All off-treatment pre-BD FEV1 values measured up to Week 24 will be included in the analysis.	MMRM model	No	No	No
Tertiary/Exploratory Endpoints						
BODE index	- AERIFY-1 ITT- Week 52 - AERIFY-2 ITT- Week 52 former smokers - AERIFY-2 ITT current smokers	Proportion of participants with BODE Index score >1 point decrease (=improvement) at Week 52	Logistic regression model	No	No	No
Components of BODE index (FEV1 percent predicted, mMRC, 6MWD, BMI) and resting oxygen saturation (just before 6MWD)	- AERIFY-1 ITT- Week 52 - AERIFY-2 ITT- Week 52 former smokers - AERIFY-2 ITT current smokers	Change from baseline at Week 52	Descriptive	No	No	No
Annualized number of ER and hospital days related to AECOPD, Total number of days on oral corticosteroids and antibiotics over the planned treatment period	- AERIFY-1 ITT - AERIFY-2 ITT former smokers - AERIFY-2 ITT current smokers	Annualized number of ER and hospital days related to AECOPD, Total number of days on oral corticosteroids and antibiotics over the planned treatment period	Descriptive	No	No	No

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Proportion of participants with pre-BD FEV1 improvement ≥ 100 mL at Week 24	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Proportion of participants with pre-BD FEV1 improvement ≥ 100 mL at Week 24	Logistic regression model	No	No	No
Proportion of participants with pre-BD FEV1 improvement ≥ 100 mL at Week 52	• AERIFY-1 ITT-Week 52 • AERIFY-2 ITT-Week 52 former smokers • AERIFY-2 ITT current smokers	Proportion of participants with pre-BD FEV1 improvement ≥ 100 mL at Week 52	Logistic regression model	No	No	No
Other PRO Endpoints						
EQ-5D-5L	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	Change from baseline at Week 24	MMRM model	No	No	No
EQ-5D-5L	• AERIFY-1 ITT-Week 52 • AERIFY-2 ITT-Week 52 former smokers • AERIFY-2 ITT current smokers	Change from baseline at Week 52	MMRM model	No	No	No

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
PGIC, PGIS	• AERIFY-1 ITT • AERIFY-2 ITT former smokers • AERIFY-2 ITT current smokers	PGIC and PGIS of AECOPD at Week 24	Descriptive	No	No	No
PGIC, PGIS	• AERIFY-1 ITT- Week 52 • AERIFY-2 ITT- Week 52 former smokers • AERIFY-2 ITT current smokers	PGIC and PGIS of AECOPD at Week 52	Descriptive	No	No	No
Safety						
Adverse Events	Safety population: • AERIFY-1 • AERIFY-2 former smokers • AERIFY-2 current smokers	Follow safety guidelines	Descriptive	Exposure adjusted	No	AES: Risk difference vs. placebo and it's 95% CI
Laboratory, Vital signs, and ECGs	Safety population: • AERIFY-1 • AERIFY-2 former smokers • AERIFY-2 current smokers	Follow safety guidelines	Descriptive	No	No	No

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
PK						
Itepekimab serum concentration	PK population: • AERIFY-1 • AERIFY-2 former smokers • AERIFY-2 current smokers	By visit	Descriptive	No	No	No
Immunogenicity						
ADA positive, ADA negative, persistent ADA, Transient ADA	ADA population: • AERIFY-1 • AERIFY-2 former smokers • AERIFY-2 current smokers	NA	Descriptive	No	No	No

5.17 APPENDIX 17 CLASSIFICATION OF EVENTS REVIEWED BY THE COMMITTEE

The table below summarizes the categories of adjudication as agreed by the CAC. According to the source documentation provided by the site, CAC members shall rank the event in one of the following categories and subcategories.

1. DEATH ☐

In Hospital ☐ Out of Hospital ☐ Unknown ☐
 Sudden ☐ Non-Sudden ☐ Unknown ☐
 Witnessed ☐ Unwitnessed ☐ Unknown ☐
 Level of Evidence for death classification: High ☐ Moderate ☐ Low ☐

1.1. Cardiovascular death ☐

1.1.1. Myocardial infarction ☐

1.1.2. Heart failure ☐

1.1.3. Stroke ☐

1.1.1.1. Ischemic ☐

1.1.1.2. Hemorrhagic ☐

1.1.1.3. Undetermined ☐

1.1.2. Procedure-related death ☐
(Death during or after a procedure for which the CAC consider that it is not a consequence of the underlying CV condition)

1.1.3. Pulmonary Embolism ☐

1.1.4. Other CV death(Justify using a free comment below) ☐

1.2. Non-cardiovascular death (Justify using a free comment below) ☐

1.3. Undetermined cause of death ☐

2. MYOCARDIAL INFARCTION ☐

2.1. ST-elevation ☐

2.2. Non-ST elevation ☐

2.3. Type 2 MI ☐

3. HOSPITALIZATION FOR UNSTABLE ANGINA ☐

3.1. Requiring PCL ☐

3.2. Requiring CABG ☐

3.3. Requiring medical treatment only ☐

4. HOSPITALIZATION FOR ATRIAL FIBRILLATION/FLUTTER ☐

4.1. New ☐

4.2. Relapsing ☐

5. HOSPITALIZATION FOR OTHER SYMPTOMATIC ARRHYTHMIAS ☐

5.1. Supra-ventricular (other than AF/AFI) ☐

5.2. Ventricular ☐

5.2.1. Sustained ☐

5.2.2. Non-sustained ☐

6. HEART FAILURE ☐

6.1. New Heart failure ☐

6.2. Worsening of previously known heart failure ☐

7. STROKE ☐

7.1. Ischemic ☐

7.2. Hemorrhagic ☐

- 7.3. Undetermined _____ ☐
8. **HOSPITALIZATION FOR TRANSIENT ISCHEMIC ATTACK** _____ ☐
- 8.1. Endarterectomy _____ ☐
- 8.2. Carotid stenting _____ ☐
- 8.3. Medical treatment _____ ☐
9. **PERIPHERAL ARTERIAL EVENT** _____ ☐
10. **PULMONARY EMBOLISM** _____ ☐
11. **NON ACUTE CORONARY SYNDROME / MYOCARDIAL ISCHEMIA REQUIRING** _____ ☐
- 11.1. PCL _____ ☐
- 11.2. CABG _____ ☐
- Elective ☐ Urgent ☐
12. **OTHER CARDIO/CEREBROVASCULAR EVENTS**(justify using a free comment below) _____ ☐
13. **NON-CARDIO/CEREBROVASCULAR EVENTS** _____ ☐
14. Not an event to be considered for adjudication (Justify using a free comment below) _____ ☐
15. Not possible to adjudicate (Justify using a free comment below) _____ ☐

Comment:
.....

6 REFERENCES

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8. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *Pharmacoeconomics*. 2022.

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CLARIFICATIONS OF EFFICACY AND SAFETY ANALYSES AND PRE-SPECIFIED ADDITIONAL DATA ANALYSES BEFORE THE CORE DATABASE LOCK OF EFC16750 AND EFC16819 STUDIES

**Randomized, double-blind, placebo-controlled, parallel-group Phase 3 study to
evaluate the efficacy, safety, and tolerability of SAR440340/
REGN3500/itepekimab (anti-IL-33) in patients with moderate-to-severe chronic
obstructive pulmonary disease (COPD)**

Protocol number:	EFC16750, EFC16819
Compound number (INN/Trademark):	SAR440340/ itepekimab
Statistician:	[REDACTED]
	[REDACTED]
	[REDACTED]
Version #:	1.0
Date of issue:	05/07/2025

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1 Disease characteristics

1.1 Clarification on daily ICS dose at baseline

ICS use as controller medication at baseline will be identified using “CDGsn00010” code to search for corticosteroids in the ‘controller medication’ eCRF page, inhalation route (CMROUTE = “RESPIRATORY (INHALATION)”), and use of medication at the time of randomization.

The daily dose of the ICS is converted to fluticasone propionate following [Table 1](#) below:

Table 1- Equivalent dose for inhaled corticosteroids for adults

Inhaled corticosteroid	Equivalent dose (mcg) to 500 mcg Fluticasone propionate (DPI or HFA)
FLUTICASONE FUROATE	200*
BECLOMETASONE DIPROPIONATE	1000
BUDESONIDE (DPI)	800
CICLESONIDE (HFA)	320
MOMETASONE FUROATE	440
TRIAMCINOLONE ACETONIDE	2000

ADAPTED FROM GINA 2016 GUIDELINES

HFA=hydrofluoroalkane, DPI= Dry Powder Inhaler

* Fluticasone furoate (FF) dose ≥ 200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of $(FF \text{ dose} + 1) \times 2.5$; FF dose < 200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of $FF \text{ dose} \times 2.5$.

Example: A patient received 400 mcg budesonide (DPI) and 440 mcg mometasone furoate. They are equivalent to 250 mcg and 500 mcg fluticasone propionate correspondingly. The combined total daily dose is equivalent to 750 mcg fluticasone propionate and classified as high dose.

If the concomitant medication dose type is “Delivered” (CM DOSE TYPE = “Delivered”), the dose value will be further converted to the standard dose in “Metered” following the [Table 2](#) below:

Table 2 - Conversion for inhaled corticosteroids between different dose type

ICS Component	Conversion Factor from Delivered to Metered
BUDESONIDE	80/100
FLUTICASONE PROPIONATE	45/50
MOMETASONE FUROATE	100/110
FLUTICASONE FUROATE	90/100
BECLOMETASONE	40/50
CICLESONIDE	800/1000
TRIAMCINOLONE	75/100

2 Efficacy analyses

2.1 Clarification on endpoints related to AECOPD events

For the endpoints related to AECOPD events, including annualized rate and time to event endpoints on moderate or severe AECOPD events, severe AECOPD events, moderate AECOPD events and corticosteroid-treated AECOPD events, the primary analysis will be based on the adjudicated AECOPD events. The event start date will be based on the adjudicated date of

- For moderate event: first intake of systemic corticosteroids or systemic antibiotics.
- For severe event: first day of hospitalization, or emergency room visit, or death.

In addition, investigator reported events will also be analyzed for the annualized rate endpoints for above types of AECOPD events. As specified in the study SAP, for both moderate and severe events to be counted as separate events, they must be separated by at least 14 days between any course of systemic steroids/antibiotics or 14 days between discharge and new admission in case of hospitalization (severe events only). Therefore, two investigator-reported/adjudicated events within 14 days between the end date of the earlier event and the start date of the latter event will be merged. The start date of the merged event is the start date of the earlier event, and the end date of the merged event is the end date of the later end date of the two events. The severity will be the severity of the more severe event.

2.2 Clarification on the exploratory endpoint

- **Stated in SAP:** *Exploratory endpoint: Number of days on oral corticosteroids and antibiotics over the placebo-controlled treatment period*
- **Revised to:** *Exploratory endpoint: Number of days on systemic corticosteroids and antibiotics over the placebo-controlled treatment period*

This endpoint will be presented for systemic courses of corticosteroids and antibiotics, instead of only via oral routes as per protocol and SAP because most corticosteroids/antibiotics courses start with an IV route and then switch to oral, but sites often do not report them as separate courses.

Rules to identify systemic corticosteroids:

Use “CDGsn00010” code to search for corticosteroids in the ‘other medication’ eCRF page with CMONGO = Y or CMENDAT > MIN (EXSTDAT) (i.e. end date of the medication was after first IMP administration date or ongoing).

Rules to identify systemic antibiotics:

Use “CDGsn00892” code to search for antibiotics in the ‘other medication’ eCRF page with CMONGO = Y or CMENDAT > MIN (EXSTDAT) (i.e. end date of the medication was after first IMP administration date or ongoing). Please note that GENTAMICIN is excluded from the selection.

For both corticosteroids and antibiotics, only select systemic routes with the following terms:

- intradermal
- intracavernous
- Intravenous
- Intravenous bolus
- Intravenous drip
- Intravascular
- Irrigation
- Parenteral
- Perivenous
- Intramuscular
- Intramuscular or subcutaneous
- Subcutaneous
- Oral
- Perivenous
- Unknown
- Other
- missing routes

For the calculation of the days of medication intake, if medication **start date** is partially missing, missing day is imputed as the **first day** of the month. If medication **end date** is partially missing, missing day is imputed as the **last day** of month. If month is missing, month will not be imputed and the duration of medication intake will be considered as missing.

For outputs “**Analysis of systemic corticosteroids (SCS) duration over planned treatment period**” and “**Analysis of antibiotics (ABX) duration over planned treatment period**”, all SCS or ABX selected based on the above rules will be included, and the days and courses during the planned treatment period (from randomization start date to the end of the observation period) will be counted. For outputs “**Analysis of systemic corticosteroids (SCS) duration over planned treatment period for participants who took SCS for exacerbations**” and “**Analysis of antibiotics (ABX) duration over planned treatment period for participants who took ABX for exacerbations**”, SCS or ABX selected based on the above rules with additional condition: reason for treatment = “COPD exacerbations” will be included. Like above, the days and courses during the planned treatment period (from randomization start date to the end of the observation period) will be counted. If more than one SCS or more than one ABX records have overlapped start or end date, the overlapped days will only be counted once.

2.3 Additional exploratory analyses on efficacy

SGRQ

Additional responder analyses will be conducted for the Saint George's Respiratory Questionnaire (SGRQ) to evaluate the proportion of patients with improvement in SGRQ total score. The threshold of 10 (range: 9 to 11) was empirically derived prior to database lock on 80% of clean data (data cut 05Feb2025; n = 2078).

Therefore, the proportion of participants with SGRQ improvement (reduction) ≥ 6 , ≥ 8 , and ≥ 10 points at Week 24 and at Week 52, whether the participant is still on treatment or not, will be analyzed using a logistic regression model. The model will include treatment, screening eosinophil strata, region, controller therapy strata, and baseline SGRQ total score as covariates.

Participants with SGRQ improvement < 6 , < 8 , and < 10 points or missing change from baseline to Week 24 (or to Week 52) SGRQ total score will be considered as non-responders. The Week 52 analysis will be restricted to patients with a planned 52-week treatment period.

The odds ratio of being a responder, and risk difference comparing each itepekimab regimen to placebo will be provided along with the corresponding 95% CI and p-value. Descriptive statistics including number and percentage of responders will also be provided.

To assess the treatment effect when participants adhere to the study treatment as directed, the same analysis will be conducted in those participants in the ITT population who completed Week 24 or Week 52.

Of note, based on psychometric analyses conducted prior to database lock on 80% of clean data (data cut 05Feb2025; n = 2078), a between-group improvement threshold of 3.0 (range: 3.0 to 7.0) was empirically derived for the change from baseline in SGRQ total score.

E-RS:COPD

Responder analyses will be conducted for Evaluating Respiratory Symptoms in COPD (E-RS:COPD) to evaluate the proportion of patients with improvement in E-RS:COPD total score of ≥ 3.7 (range: 3.2 to 4.5), which was empirically derived prior to database lock on 80% of clean data (data cut 05Feb2025; n = 2078).

The proportion of participants with E-RS:COPD improvement (reduction) in total score ≥ 3.7 points at Week 24 and at Week 52, whether the participant is still on treatment or not, will be analyzed using a logistic regression model. The model will include treatment, screening eosinophil strata, region, controller therapy strata, and baseline E-RS:COPD total score as covariates.

Participants with E-RS:COPD improvement in total score < 3.7 points or missing change from baseline to Week 24 (or to Week 52) E-RS:COPD total score will be considered as non-responders. The Week 52 analysis will be restricted to patients with a planned 52-week treatment period.

The odds ratio of being a responder, and risk difference comparing each itepekimab regimen to placebo will be provided along with the corresponding 95% CI and p-value. Descriptive statistics including number and percentage of responders will also be provided.

To assess the treatment effect when participants adhere to the study treatment as directed, the same analysis will be conducted in those participants in the ITT population who completed Week 24 or Week 52.

This analysis will be repeated for RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms domains, using thresholds of 1.8, 1.4, 1.0, respectively (corresponding to empirically derived thresholds based on 80% of clean data).

Of note, based on psychometric analyses conducted prior to database lock on 80% of clean data (data cut 05Feb2025; n = 2078), between-group improvement thresholds were empirically derived for the total and domain scores:

- RS-Total: 1.4 (range: 1.4 to 1.7)
- RS-Breathlessness: 0.8 (no range could be estimated)
- RS-Cough and Sputum: 0.4 (no range could be estimated)
- RS-Chest Symptoms: 0.4 (no range could be estimated)

2.4 Additional subgroup analyses on primary and key secondary endpoints

To assess the consistency in treatment effects across subgroup levels, additional subgroup analyses will be conducted on the primary endpoint “Annualized rate of moderate or severe COPD exacerbation during the planned treatment period” and the key secondary endpoint “Change from baseline in pre-BD FEV1 at Week 24” for EFC16750 and EFC16819 with respect to:

- FEV1 reversibility (< 12% or < 200ml, ≥ 12% and ≥ 200ml; < 10%, ≥ 10%)

The < 12% or < 200ml, ≥ 12% and ≥ 200ml subgroups are defined based on the ERS/ATS 1991 criteria. Reversibility is calculated as (post-bronchodilator FEV1 (L) - pre-bronchodilator FEV1 (L)) x 100/ pre-bronchodilator FEV1 (L). It is positive if reversibility is ≥ 12% with an increase in FEV1 ≥ 200 mL after bronchodilator administration.

The < 10%, ≥ 10% subgroups are defined based on ERS/ATS 2022 criteria. Reversibility is calculated as (post-bronchodilator FEV1 (L) - pre-bronchodilator FEV1 (L)) x 100/predicted FEV1 (L). It is positive if reversibility is ≥ 10%.

3 Safety analyses

3.1 Clarification on the analysis of adverse events of special interest (AESIs) and other AEs of interest

The AESI “Anaphylactic or systemic allergic reaction requiring treatment” will be presented separately for “Anaphylactic reaction” and “Systemic allergic reaction/hypersensitivity” events, and search criteria updated for “Infection requires parenteral (IV, IM, SC) antimicrobial therapy” and “Malignancy” AESIs to improve the programming accuracy of the classifications. Changes from “Table 10 – Selections for AESIs and other AEs of interest” in the SAP are detailed and highlighted in yellow in the [Table 3](#) below.

Table 3 – Criteria for adverse events of special interest and other selected AE groupings

AE Grouping for analysis	Selection for analysis	AE Grouping in the SAP	Selection in SAP
AESI		AESI	
Significant ALT elevation	eCRF AECAT = ‘ALT increase’ is checked and AESIIN = ‘Y.’	Significant ALT elevation	eCRF AECAT = ‘ALT increase’ is checked and AESIIN = ‘Y.’
Anaphylactic reaction (medically reviewed)	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.	Anaphylactic or systemic allergic reaction requiring treatment (medically reviewed)	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 or systemic allergic reaction or not.
systemic allergic reaction/hypersensitivity (medically reviewed)	SMQ hypersensitivity (20000214) narrow search and with [AECONTRI =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.		

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AE Grouping for analysis	Selection for analysis	AE Grouping in the SAP	Selection in SAP
Severe injection site reactions (ISRs) that last longer than 24 hours	AE category = "Injection Site Reaction" and AESIIN = "Y"	Severe injection site reactions (ISRs) that last longer than 24 hours	AE category = "Injection Site Reaction" and AESIIN = "Y"
Serious infection	Primary SOC = 'Infections and infestations' and with serious status	Serious infection	Primary SOC = 'Infections and infestations' and with serious status.
Infection requires parenteral (IV, IM, SC) antimicrobial therapy	AE category = "Infection Event" and AESIIN = 'Y' and eCRF Infection Event Form question "Have any parenteral treatment (IV, Intramuscular, SC) been given for this event?" = "Y"	Infection requires parenteral (IV, IM, SC) antimicrobial therapy	AE category = "Infection Event" and AESIIN = 'Y'.
Infection requires oral antimicrobial therapy for longer than 2 weeks	eCRF Infection Event Form FAMEDYN= 'Y' and AESIIN = 'Y'.	Infection requires oral antimicrobial therapy for longer than 2 weeks	eCRF Infection Event Form FAMEDYN= 'Y' and AESIIN = 'Y'.
Parasitic infection	eCRF Infection Event Form Infection Type = 'Parasitic' and AESIIN = 'Y'.	Parasitic infection	eCRF Infection Event Form Infection Type = 'Parasitic' and AESIIN = 'Y'.
Opportunistic infection	eCRF Infection Event Form FAOPYN= 'Y' and AESIIN = 'Y'.	Opportunistic infection	eCRF Infection Event Form FAOPYN= 'Y' and AESIIN = 'Y'.
Malignancy	Sub-SMQ (20000091)– Malignant or unspecified tumors and AESIIN "Y"	Malignancy	Sub-SMQ (20000091)– Malignant or unspecified tumors
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)	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	Symptomatic Overdose is answered Yes, with Overdose of IMP answered Yes on AE eCRF.	Symptomatic overdose with IMP	Symptomatic Overdose is answered Yes, with Overdose of IMP answered Yes on AE eCRF.
Symptomatic overdose with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP answered Yes on AE eCRF.	Symptomatic overdose with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP answered Yes on AE eCRF.
Other selected AE Grouping		Other selected AE Grouping	
Injection site reaction	HLT = 'Injection site reactions'	Injection site reaction	HLT = 'Injection site reactions'
COVID-19 related AEs	SMQ [20000237] COVID-19 narrow search	COVID-19 related AEs	SMQ [20000237] COVID-19 narrow search

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AE Grouping for analysis	Selection for analysis	AE Grouping in the SAP	Selection in SAP
The list of terms may be adjusted according to MedDRA version changes			

4 Data handling

4.1 Analysis windows for time points

The analysis windows described in Tables 12 to 15 in the study SAP maps the scheduled and/or unscheduled visits to the analysis visits used in the by-visit summaries for efficacy, safety, PK and ADA variables.

For the scenario where subjects have their end of treatment (EOT) visit (premature EOT not included) out of visit window and > Day 379, their assessment measurements will be mapped to W52 analysis visit.

For Table 15 in the SAP, as post-BD spirometry, ECGs, SGRQ, EQ-5D-5L and ADA are not planned to be performed/collected in the 6 weeks after EOT follow up visit (F1), any measurement observed from D8 to D70 (inclusive) will be mapped to end of study (EOS) analysis visit.

For E-RS:COPD e-diary data, weekly average scores during the planned treatment period will be calculated as described in the Section 4.4.2.7 in the SAP. During the follow up period, for the EOT visit, the weekly average scores will be calculated using data from EOT date – 6 days to EOT date. For the FU1 visit, the weekly average scores will be calculated using data from EOT date + 36 days to EOT date + 42 days. For the EOS visit, the weekly average scores will be calculated using data from EOT date + 134 days to EOT date + 140 days. If fewer than 4 days of data are available in the above windows, the RS scores cannot be calculated and will be considered as missing.

4.2 Missing data

Handling of medications 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 month. If a medication date is missing, it will be considered a prior and concomitant medication. These data imputations are for categorization of prior/concomitant medication purpose only and will not be used in listings.

Handling of AEs with missing/partial date of onset

For individual CSR, missing or partial missing AE onset dates and times will be imputed so that 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 imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

For ISS, if an AE **start date** is partially missing, missing month is imputed with **January** and missing day is imputed as the **first day** of the month., if the imputed date is prior to the reference start date (RFSTDT). If only the date is missing, and the year and month are the same as the year and month for RFSTDT, the missing day will be imputed to RFSTDT. If the month and date are both missing, and the year is the same as the year for RFSTDT, the missing month and day will be imputed to the same as RFSTDT.

Handling of smoking with partial dates

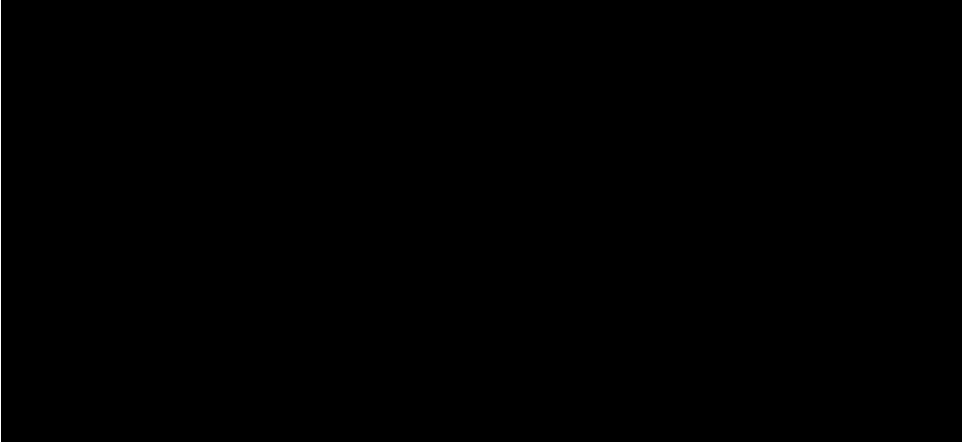
For the derivation of “time since cessation for former smokers” and “smoking duration”, if smoking **start date** is partially missing, missing month is imputed with **January** and missing day is imputed as the **first day** of the month. If smoking **end date** is partially missing, missing month is imputed with **December**, and missing day is imputed as the **last day** of the month.

Version History

Version Number	Summary of Changes
01	Initial version

Approvals

The signatures on this page indicate review and approval of this document.



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EFC16750-EFC16819- clarification of efficacy and safety analyses

Final Audit Report

2025-05-08

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-  [REDACTED] authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
[REDACTED]
-  [REDACTED] authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
[REDACTED]
-  Document e-signed by [REDACTED]
Signing reason: Approval
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[REDACTED]

✓ [REDACTED] authenticated with phone by verifying one-time code sent to the phone number [REDACTED]
[REDACTED]
Challenge: The user opened the agreement.
[REDACTED]

👤 Signer [REDACTED] entered name at signing as [REDACTED]
[REDACTED]

👤 Document e-signed by [REDACTED]
Signing reason: Approval
[REDACTED]

✓ Agreement completed.
[REDACTED]

✓ [REDACTED] authenticated with phone by verifying one-time code sent to the
phone number [REDACTED]
Challenge: The user completed the signing ceremony.
[REDACTED]

ERRATUM OF SAP SUPPLEMENTARY DOCUMENT FOR EFC16750 AND EFC16819 STUDIES

Randomized, double-blind, placebo-controlled, parallel-group Phase 3 study to evaluate the efficacy, safety, and tolerability of SAR440340/ REGN3500/itepekimab (anti-IL-33) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

Protocol number:	EFC16750, EFC16819
Compound number (INN/Trademark):	SAR440340/ itepekimab
Statistician:	[REDACTED]
	[REDACTED]
	[REDACTED]
Version #:	1.0
Date of issue:	09/05/2025

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Description of change and what is being changed

The **Table 1** of SAP supportive document (CLARIFICATIONS OF EFFICACY AND SAFETY ANALYSES AND PRE-SPECIFIED ADDITIONAL DATA ANALYSES BEFORE THE CORE DATABASE LOCK OF EFC16750 AND EFC16819 STUDIES) had a typo on the equivalent dose for Beclomethasone Dipropionate, 400 mg should have been reported instead of 1000 mg. The conversion based on 400 mg was used for the statistical analyses reported in the CSR.

Table 1- Corrected equivalent dose for inhaled corticosteroids for adults

Inhaled corticosteroid	Equivalent dose (mcg) to 500 mcg Fluticasone propionate (DPI or HFA)
FLUTICASONE FUROATE	200*
BECLOMETASONE DIPROPIONATE	400
BUDESONIDE (DPI)	800
CICLESONIDE (HFA)	320
MOMETASONE FUROATE	440
TRIAMCINOLONE ACETONIDE	2000

ADAPTED FROM GINA 2016 GUIDELINES

HFA=hydrofluoroalkane, DPI= Dry Powder Inhaler

* Fluticasone furoate (FF) dose ≥ 200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of $(FF \text{ dose} + 1) \times 2.5$; FF dose < 200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of FF dose $\times 2.5$.

Example: A patient received 400 mcg budesonide (DPI) and 440 mcg mometasone furoate. They are equivalent to 250 mcg and 500 mcg fluticasone propionate correspondingly. The combined total daily dose is equivalent to 750 mcg fluticasone propionate and classified as high dose.

The following cell:

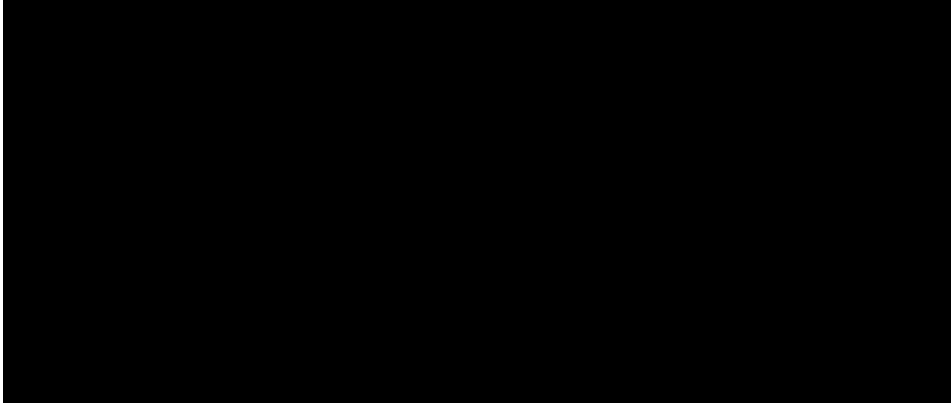
BECLOMETASONE DIPROPIONATE	1000
----------------------------	------

Is replaced with:

BECLOMETASONE DIPROPIONATE	400 ~~1000~~
----------------------------	---------------------

Approvals

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