

AMENDED CLINICAL TRIAL PROTOCOL 02

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)

Protocol number: EFC16819

Amendment number: 02

Compound number (INN/Trademark): SAR440340/REGN3500
itepekimab

Study phase: Phase 3

Short title: Study to assess the efficacy, safety, and tolerability of SAR440340/REGN3500/itepekimab in chronic obstructive pulmonary disease (COPD) (AERIFY-2)

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	26 September 2023, version 1.0 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	20 September 2022, version 1.0 (electronic 1.0)
Original Protocol		15 October 2020, version 1.0 (electronic 1.0)

Amended protocol 02 (26 September 2023)

This amended protocol 02 is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

A double-blind extension study (LTS18133) is planned to evaluate long-term safety and tolerability of itepekimab in participants who have completed the treatment period in this study. In order to minimize or avoid any interruption of their exposure to IMP, participants who will enter the LTS18133 study will transition from this study to the LTS18133 study prior to the 20-week post-treatment follow-up period. For these participants the End-of-Treatment visit (Visit 28) of this study will be combined with the first treatment Visit 1 of the LTS18133 study. Participants who will not enter the LTS18133 study will complete the 20-week post-treatment follow up period in this study, as originally planned.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of activities 4.1 Overall design	The following text: The treatment period will be followed by a 20-week safety follow-up period for all participants. Was replaced with: The treatment period will be followed by a 20-week safety follow-up period for participants not transitioning to the LTS18133 study.	To restrict the 20-week safety follow-up period to participants not transitioning to the LTS18133 study.
1.1 Synopsis 1.2 Schema 1.3 Schedule of activities 6.7 Continued access to intervention after the end of the study	Implementation of a long-term double-blinded extension study (LTS18133) All figures updated with a footnote for post-treatment period.	To allow participants of this study to transition to the LTS18133 study in order to receive active IMP during an additional period of 52 weeks.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities.	Footnotes have been reordered.	Footnotes reordered for consistency.
	Footnote text added to update visits of participants transitioning to the LTS18133 study.	Text added to describe participants transitioning to the LTS18133 study (visits 29, 30 and 31 are not applicable).
	Footnote text added to update End of IMP treatment (EOT) and the early treatment discontinuation (ETD) Visits.	Text added to describe the use of additional controller therapies for participants with inadequate control of the COPD at the end of IMP treatment (EOT) Visit and participants who prematurely discontinue from the study prior to completing the planned treatment period (ie, early treatment discontinuation) and will attend the early treatment discontinuation (ETD) visit.
	Footnote text added to update the treatment duration.	Text added to describe the treatment duration of the study (24-52 weeks) and the study visit schedule which should be adhered to within ± 3 days for the randomized IMP treatment period, and ± 5 days for the visits during the post-IMP treatment follow-up period.
	Footnote text added to describe non-clinic visits.	Footnote text added to update non-clinic visits by phone in case of IMP administration at the participant's home.
	Footnote text added to update information on early EOT visit.	Text updated to include sample size increase and pre-planned visits at Weeks 24,32,36,40 or 48.
	Footnote text added to update information on chest X-ray and MRI scan assessments.	Footnote text added to describe chest X-ray assessments and MRI scan assessments in case a chest X-ray is not feasible.
4.4 End of study definition	Footnote text added to update the eDiary data.	Footnote text added to include participants who transition to the LTS18133 study.
	Footnote text added to update inclusion criteria.	Inclusion criteria will be based on the CAT score.
4.4 End of study definition	Change in the end of study definition from "EOS Visit of the last participant" to "EOS Visit of the last participant except for participants who transition to the LTS18133 study, for whom the end of study will be the EOT visit."	End of study definition clarified for patients transitioning to the LTS18133 study.
1.1 Synopsis 6.7 Continued access to intervention after the end of the study	Text added to describe the availability of treatment extension through participation in the LTS18133 study in different countries.	Information updated to include the LTS18133 study in different countries.

Section # and Name	Description of Change	Brief Rationale
6.5 Concomitant therapy	The point regarding lung pneumonectomy reworded as "Lung pneumonectomy or lung volume reduction procedures (excluding lobectomies and resections smaller than lobectomies)"	Reworded for clarification
6.7 Continued access to intervention after the end of the study	Text added to describe the eligibility criteria of the LTS18133 participants. Participants having prematurely discontinued IMP or their participation to this study will not be eligible for LTS18133 study. Participants who completed their end-of-treatment visit (Visit 28) prior to approval of the protocol amendment 02 for EFC16819, and local approval of the LTS18133 study will not be eligible for entering the LTS18133 study either.	Information on availability and eligibility criteria of participants updated based on the completion of their End-of-treatment visit (Visit 28) after 24-52 weeks of treatment (depending upon time of inclusion) as per this study protocol.
1.1 Synopsis 9.2 Sample size Determination Table 12	"Approximately 3 months" replaced with "approximately 3 months or earlier".	Text amended in order to determine the sample size of part B.
9.4.7 Safety analyses	Text added to complement information on the IMP treatment period.	Text added to define the IMP treatment period as the time from the first administration of the IMP to the end of 20-week follow-up period (or last contact date in this study, whichever is earlier).
10.19 Contingency measures for a regional or national exceptional emergency situations	Information updated for post IMP treatment follow-up period visits.	Text added to include participants not transitioning to the LTS18133 study.
8.1.2.1.3 St. George's Respiratory Questionnaire (SGRQ) 11. References	3 new references were added (46, 47, 48) and following text added "A minimum change in score of 4 units was established as clinically relevant after participant and clinician testing." Reference 1 from the previous amendment has been reordered to reference 49.	References updated related to the use of SGRQ.
Throughout	Minor editorial, typographical error corrections and document formatting revisions	Minor, therefore, have not been summarized

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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)

Short title: Study to assess the efficacy, safety, and tolerability of SAR440340/REGN3500/itepekimab in chronic obstructive pulmonary disease (COPD) (AERIFY-2)

Rationale:

Chronic obstructive pulmonary disease (COPD) is a serious and life-threatening disease. It is the third leading cause of death worldwide and the fourth leading cause of death in the US, responsible for over 3 million deaths worldwide in 2016 and 160 000 deaths annually in the US (1, 2, 3). It is also the largest contributor to respiratory-related mortality. Chronic obstructive pulmonary disease is characterized by progressive decline in lung function and recurrent exacerbations of symptoms. The latter results in rapid disease progression and are associated with increased mortality, particularly following exacerbations that require hospitalization (4). Although smoking cessation in patients with established COPD slows the rate of lung function decline and reduces the risk of hospitalization and mortality, former smokers with COPD are still at high risk for exacerbations and substantial morbidity and risk of mortality remain, particularly when compared to former smokers without COPD (5). Currently available therapies have modest efficacy and/or important safety concerns. Data from the proof-of-concept (PoC)

Study ACT15104 in which itepekimab was studied versus placebo on top of approved standard of care (SoC) as background therapy provided preliminary clinical evidence that itepekimab has the potential to confer significant benefit beyond that provided by currently available therapies to participants with moderate-to-severe COPD who are former smokers. In Study ACT15104, participants with a smoking history of ≥ 10 packs-year, regardless of smoking status at screening, were recruited. However, one of the prespecified subgroup analyses conducted in this study was by smoking status at screening, where a clear effect was seen in former smokers. The data suggest that active smoking eliminated the beneficial effects of itepekimab. This effect in former smokers was consistent across a number of subgroups within the former smoker population, including subgroups by background controller therapy (double [inhaled corticosteroid {ICS} + long-acting beta-agonist {LABA}], ICS + long-acting muscarinic antagonist {LAMA}, or LABA + LAMA] or triple [ICS + LABA + LAMA] therapy) and regardless of blood eosinophil level or COPD Assessment Test (CAT) score at baseline. Improvement in FEV1 (forced expiratory volume in 1 second) was also seen in former smokers, specifically among those with blood eosinophil counts ≥ 250 cells/ μ L. These results contrast with those in the current smoker population, where minimal improvement of FEV1 was observed.

Two Phase 3 studies (EFC16750 and EFC16819) are planned to support registration of itepekimab in the proposed COPD indication. The objective of each study is to confirm the efficacy observed in the PoC study, assess the safety profile, and test 2 dose regimens of

itepekimab compared to placebo over 1 year, in participants with COPD who are former smokers and are in need of an additional treatment added to their current management. This study (EFC16819), in contrast to the EFC16750 study, will include a cohort of current smokers to further characterize the efficacy and safety profile in this population. All participants will receive SoC background controller medications and reliever medication on as needed basis throughout the study. The proposed study design provides the opportunity to assess the efficacy of itepekimab on multiple COPD domains including prevention of moderate and severe exacerbations, lung function, and symptom control.

Objectives and endpoints

Objectives	Endpoints/Estimand
Primary population (former smokers cohort)	
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 52-week placebo-controlled treatment period - The primary estimand will be a treatment policy/ while-on-treatment estimand (see Section 9.4.2).
Secondary	
- 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 occurrence of AECOPD in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on severe AECOPD in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on corticosteroid-treated AECOPD in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on respiratory symptoms in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on FEV1 slope in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on HRQoL as assessed by SGRQ 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 - Time to first moderate-or-severe AECOPD over the 52-week placebo-controlled treatment period - Annualized rate of severe AECOPD over the 52-week placebo-controlled treatment period - Time to first severe AECOPD over the 52-week placebo-controlled treatment period - Annualized rate of corticosteroid-treated AECOPD over the 52-week placebo-controlled treatment period - Change from baseline in E-RS: COPD total score at Week 24 and at Week 52 - Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4-12 weeks - 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

Objectives	Endpoints/Estimand
- Evaluate the safety and tolerability of itepekimab in former smokers with moderate-to-severe COPD - Evaluate the PK profile of itepekimab in former smokers with moderate-to-severe COPD - Evaluate immunogenicity to 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, 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
Secondary population (current smokers cohort)	
- Estimate 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 - Estimate the efficacy of itepekimab compared with placebo on pulmonary function in current smokers with moderate-to-severe COPD - Estimate the safety and tolerability of itepekimab in current smokers with moderate-to-severe COPD - Estimate the PK profile of itepekimab in current smokers with moderate-to-severe COPD - Estimate immunogenicity to itepekimab in current smokers with moderate-to-severe COPD	- Annualized rate of moderate-or-severe acute exacerbation of COPD (AECOPD)^a over the 52-week placebo-controlled treatment period - Change from baseline in pre-BD FEV1 at Week 52 - Incidence of TEAEs, AESIs, SAEs, and AEs leading to permanent treatment discontinuation - Incidence of potentially clinically significant laboratory, vital signs, and ECG 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

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; ECG=electrocardiogram; 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 will be recorded by the Investigator and are defined as acute worsening of respiratory symptoms that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations will be recorded by the Investigator and are defined as AECOPD that require hospitalization, observation for >24 hours in an emergency department/urgent care facility, or result 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).

Overall design:

EFC16819 is a multinational, randomized, double-blind, placebo-controlled, parallel-group 52-week, Phase 3 study to assess the efficacy, safety, and tolerability of itepekimab in 2 cohorts. One cohort consists of participants with moderate-to-severe COPD who are former smokers (primary population), and one cohort consists of participants with moderate-to-severe COPD who are current smokers (secondary population). All the participants from both cohorts will be receiving established triple (LAMA + LABA + ICS) or double controller therapy (LAMA + LABA or ICS + LABA). The aim of the study in the former smoker cohort is to evaluate the efficacy and assess the safety and tolerability of 2 dosing regimens of itepekimab. Study treatments for former smokers are itepekimab 300 mg every 2 weeks (Q2W), itepekimab

300 mg every 4 weeks (Q4W), or matching placebo administered subcutaneously during a 52 week treatment period for the first approximately 930 randomized participants and during a potential variable 24 to 52 week treatment period for any subsequent randomized participants (following an adaptive sample size increase described in [Section 9.2](#)). Former smoker participants enrolled into the potential variable 24-to-52-week treatment period will remain in the treatment period for a maximum of 52 weeks or until the last participant randomized completes a minimum treatment period of 24 weeks. In addition, the study will also estimate the efficacy, safety, and tolerability of a 300 mg Q2W dosing regimen of itepekimab compared to a matching placebo in the cohort of current smokers. Study treatments for current smokers are itepekimab 300 mg Q2W, or matching placebo administered subcutaneously during the 52-week randomized treatment period (2 treatment groups).

The treatment period will be followed by a 20-week safety follow-up period for participants not not transitioning to the LTS18133 study.

The primary efficacy endpoint is the annualized rate of moderate-or-severe acute exacerbations of COPD (AECOPD) over the placebo-controlled treatment period in former smokers. Moderate exacerbations will be recorded by the Investigator and are defined as acute worsening of respiratory symptoms that require either systemic corticosteroids (such as intramuscular [IM], intravenous [IV] or oral) and/or antibiotics. Severe exacerbations will be recorded by the Investigator and are defined as AECOPD that require hospitalization, observation for >24 hours in an emergency department/urgent care facility, or results in death. For both moderate and severe events to be counted as 2 separate events, they must be separated by at least 14 days between any course of systemic steroids/antibiotics or 14 days between discharge and new admission in case of hospitalization (severe events only).

For efficacy endpoint analysis, the primary population will be the intent-to-treat (ITT) population of the former smokers cohort (see [Section 9.3](#)). The efficacy analysis of subgroups defined by baseline characteristics will be detailed in the statistical analysis plan (SAP). In addition to the analysis in the current study, statistical analysis for subgroup with triple controller therapy only at baseline will be further conducted using the pooled data of Study EFC16750 and Study EFC16819; details will be provided in the SAP.

Separate randomizations will be performed for the former smoker cohort, which will be the primary population and the current smoker cohort, which will be a secondary population.

For the cohort of former smokers (primary population), participant randomization (to itepekimab 300 mg Q2W, itepekimab 300 mg Q4W, or matching placebo) will be stratified Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) by country (some countries might be pooled together), screening blood eosinophil counts ($<300/\text{mm}^3$ or $\geq 300/\text{mm}^3$), and controller therapy (double or triple) at baseline. The number of participants enrolled into each stratification group will be controlled and monitored as follows:

- Double controller therapy (LAMA + LABA or ICS + LABA): up to approximately 35% of participants.
- Eosinophils ≥ 300 cells/ mm^3 approximately 35% of participants.

For the current smokers cohort (secondary population), participant randomization (to itepekimab 300 mg Q2W or matching placebo) will be stratified (IVRS/IWRS) in the same way by country (some countries might be pooled together), screening blood eosinophil counts (<300 cells/mm³ or ≥ 300 cells/mm³), and controller therapy (double or triple) at baseline. The number of participants enrolled into each stratification group will be controlled and monitored as follows:

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

The study duration is outlined below:

- Screening period (3-5 weeks).
- Randomized investigational medicinal product (IMP) treatment period (52 weeks for first cohort of randomized former smoker participants [approximately n=930] and cohort of current smokers [approximately n=280], 24 to 52 weeks for additional randomized former smoker participants).
- Post-IMP treatment follow-up period (20 weeks) for participants not transitioning to the LTS18133 study.

Participants must have been on a SoC controller therapy for COPD for at least 3 months prior to Screening (Visit 1A) with a stable dose for controller therapy for ≥ 1 month prior to Screening (Visit 1A) and during the screening period. Participants must stay on their established controller medication for COPD throughout the duration of the study, with the exception of systemic steroids and antibiotics used for AECOPD.

Former smoker participants who satisfy the eligibility criteria will be randomized (1:1:1) to one of the following IMP treatment groups to be administered for the planned treatment duration:

- Ittepekimab 300 mg, administered as a single subcutaneous (SC) injection Q2W.
- Ittepekimab 300 mg, administered as a single SC injection Q4W with alternating SC injection of matching placebo at the 2-week interval between active IMP.
- Placebo matching to ittepekimab, administered as a single SC injection Q2W.

Current smoker participants who satisfy the eligibility criteria will be randomized (1:1) to one of the following IMP treatment groups to be administered for 52 weeks:

- Ittepekimab 300 mg, administered as a single SC injection Q2W.
- Placebo matching to ittepekimab, administered as a single SC injection Q2W.

Disclosure Statement: This is an intervention model, treatment study with 3 arms (former smokers) and 2 arms (current smokers) that is blinded/masked related to allocated treatment for participants, Investigators, and outcomes assessors.

Number of participants:

An approximate total of 1210 participants who are either former smokers (n=930) or current smokers (n=280) will be enrolled and randomized separately into different cohorts in this Phase 3 study.

Approximately 930 former smoker participants will be randomized 1:1:1 into the 3 treatment arms. Approximately 310 participants will be randomized per arm to receive either itepekimab 300 mg Q2W, itepekimab 300 mg Q4W, or matching placebo to itepekimab.

For the former smoker, an adaptive sample size increase is planned, based upon the unadjusted, blinded, investigator-reported exacerbation rate observed in former smokers, approximately 3 months or earlier prior to the last participant being enrolled, to compensate for any loss of power induced by the lower than expected rate of AECOPD (see [Section 9.2](#)).

Approximately 280 current smoker participants will be randomized, with approximately 140 participants in each arm receiving either itepekimab 300 mg Q2W or matching placebo to itepekimab.

Intervention arms and duration:

For former smokers, there are 3 treatment arms:

- Arm A: Itepekimab 300 mg SC Q2W.
- Arm B: Itepekimab 300 mg SC Q4W.
- Arm C: Matching placebo SC Q2W.

Participants will be treated for 52 weeks for the first 930 randomized participants, and a minimum of 24 weeks for potential additional randomized former smoker participants.

For current smokers, there are 2 treatment arms:

- Arm A: Itepekimab 300 mg SC Q2W.
- Arm B: Matching placebo SC Q2W.

Participants will be treated for 52 weeks.

Study intervention(s)

Investigational medicinal product(s)

Sterile itepekimab or matching placebo to itepekimab.

Sterile itepekimab or matching placebo will be provided in prefilled syringes for SC administration. Each prefilled syringe contains a deliverable volume of 2 mL with an itepekimab concentration of 150 mg/mL (active) or 0 mg/mL (placebo).

- Formulation: 2 mL solutions for injection (150 mg/mL).

- Route(s) of administration: SC.
- Dose regimen: All participants will receive Q2W dosing to maintain the blind. Former smoker participants on Q4W dosing regimen will receive alternating doses of active IMP and placebo Q2W.

Noninvestigational medicinal products(s)

Participants must continue on their established controller therapy.

- Formulation: Dry powder inhaler (DPI), metered dose inhaler (MDI), or nebulizer.
- Route(s) of administration: oral inhalation for LAMA, LABA, ICS, LAMA + LABA, ICS + LABA, or LAMA + LABA + ICS.
- Dose regimen: As per prescribed (not to be provided by Sponsor).

For other information related to COPD controllers including safety precautions please consult prescription labels for the products.

Reliever medication (albuterol/salbutamol, levalbuterol/levosalbutamol, ipratropium, ipratropium/albuterol)

Participants may administer albuterol/salbutamol, levalbuterol/levosalbutamol, ipratropium, or ipratropium/albuterol as reliever medication as needed during the study.

- Formulation: DPI, MDI, nebulizer.
- Route(s) of administration: oral inhalation, nebulization.
- Dose regimen: As needed, per prescribed (not to be provided by Sponsor).

For other information related to COPD relievers including safety precautions please consult the prescription labels for the products.

Medical devices

Medical devices will not be supplied for this study.

Post-trial access to study medication

A long-term double-blinded extension study (LTS18133) will be implemented to allow participants in this study to continue receiving active IMP for an additional period.

Only participants completing their End-of-Treatment (Visit 28) visit as per this study protocol will be offered to participate in the LTS18133 study. Participants having prematurely discontinued IMP or discontinued their participation in this study will not be eligible for the LTS18133 study.

Availability of treatment extension through participation in the LTS18133 study may differ from country to country and will depend upon local regulations, review and approval by the health authority and the IRB/IEC before the study is initiated.

Statistical considerations:

- Primary endpoint

The primary analysis of the annualized rate of moderate-or-severe AECOPD during the 52-week placebo-controlled treatment period in former smokers will be performed following the ITT principle. The primary estimand is a treatment policy estimand (which includes all moderate-or-severe AECOPD events during the treatment period). The observation duration will be from randomization to Visit 28 (Week 52) for participants with a 52-week planned treatment period and from randomization to Visit 14 (Week 24) up to Visit 28 (Week 52) for former smoker participants with a potential variable 24-52 week planned treatment period. Participants who permanently discontinue IMP will be asked and encouraged to return to the clinic for all remaining study visits, all off-treatment moderate-or-severe AECOPD during the planned 52-week 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. No imputation will be performed for the unobserved events that may happen after study discontinuation and up to the end of the planned treatment period. 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 (placebo, itepekimab 300 mg SC Q2W, itepekimab 300 mg SC Q4W), region (pooled country), screening eosinophil strata (<300 cells/mm³, ≥ 300 cells/mm³), controller therapy (double, triple) strata, baseline disease severity (as % predicted post-bronchodilator (BD) FEV1 used as continuous variable), and 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. The treatment comparisons with placebo will be performed using a step-down procedure to compare itepekimab 300 mg SC Q2W versus placebo first; only if it is statistically significant, will the comparison of itepekimab 300 mg SC Q4W versus placebo be performed.

This estimand compares the rate of moderate-or-severe AECOPD for the participants randomly assigned to an itepekimab regimen versus placebo, regardless of what treatment the participants actually receive or whether the treatment regimens have been adhered to. It assesses the benefits of the treatment policy or strategy relative to placebo (6). The estimated annualized event rate for each treatment group and its 2-sided 95% confidence intervals (CIs) will be derived from the negative binomial model. The event rate ratio (RR) of each itepekimab regimen versus placebo, and the corresponding 2-sided 95% CI and p-value will also be provided.

An on-treatment analysis in all participants in a supportive analysis to assess the efficacy of itepekimab excluding data measured when participants do not adhere to the treatment regimen also be performed and be used to estimate the benefit when adhering to itepekimab treatment. In this analysis, only the AECOPD events observed during the on-treatment period (from first administration of IMP to last administration of IMP +14 days) will be included. 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 occurring during the

on-treatment period as the response variable and the log-transformed duration of the treatment period will be the offset variable. This approach defines the estimand to evaluate the efficacy of itepekimab while on treatment.

- Key secondary endpoints

Change from baseline in pre-BD FEV1 at Week 24:

The main analysis of change from baseline in pre-BD FEV1 at Week 24 is to assess the efficacy of itepekimab on pulmonary function in former smokers. Similar to the primary endpoint, the primary estimand is a treatment policy estimand. 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 Week 24 as response variables, and treatment, age (continuous variable [years]), sex, baseline height (continuous variable), region (pooled country), screening eosinophil strata, controller therapy strata (double or triple), visit, treatment by-visit interaction, and baseline pre-BD FEV1 value (continuous variable) and baseline pre-BD FEV1-by-visit interaction as covariates. Participants who discontinue IMP before Week 24 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 up through Week 24 will be included in the analysis. 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. No imputation will be performed for missing values in this analysis. This estimand compares the change from baseline in pre-BD FEV1 for the participants randomly assigned to an itepekimab regimen versus the participants randomly assigned to the placebo arm, regardless of the treatment participants actually received. It assesses the benefits of the treatment policy or strategy relative to placebo (6).

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 least squares (LS) mean change from baseline, the corresponding 95% CI and p-value will be provided for comparison of each itepekimab regimen against placebo.

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 through Week 24 as response variables. A pre-BD FEV1 value is considered as on-treatment if it is measured on or before the last dose date +14-days.

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design - Initial 930 former smokers

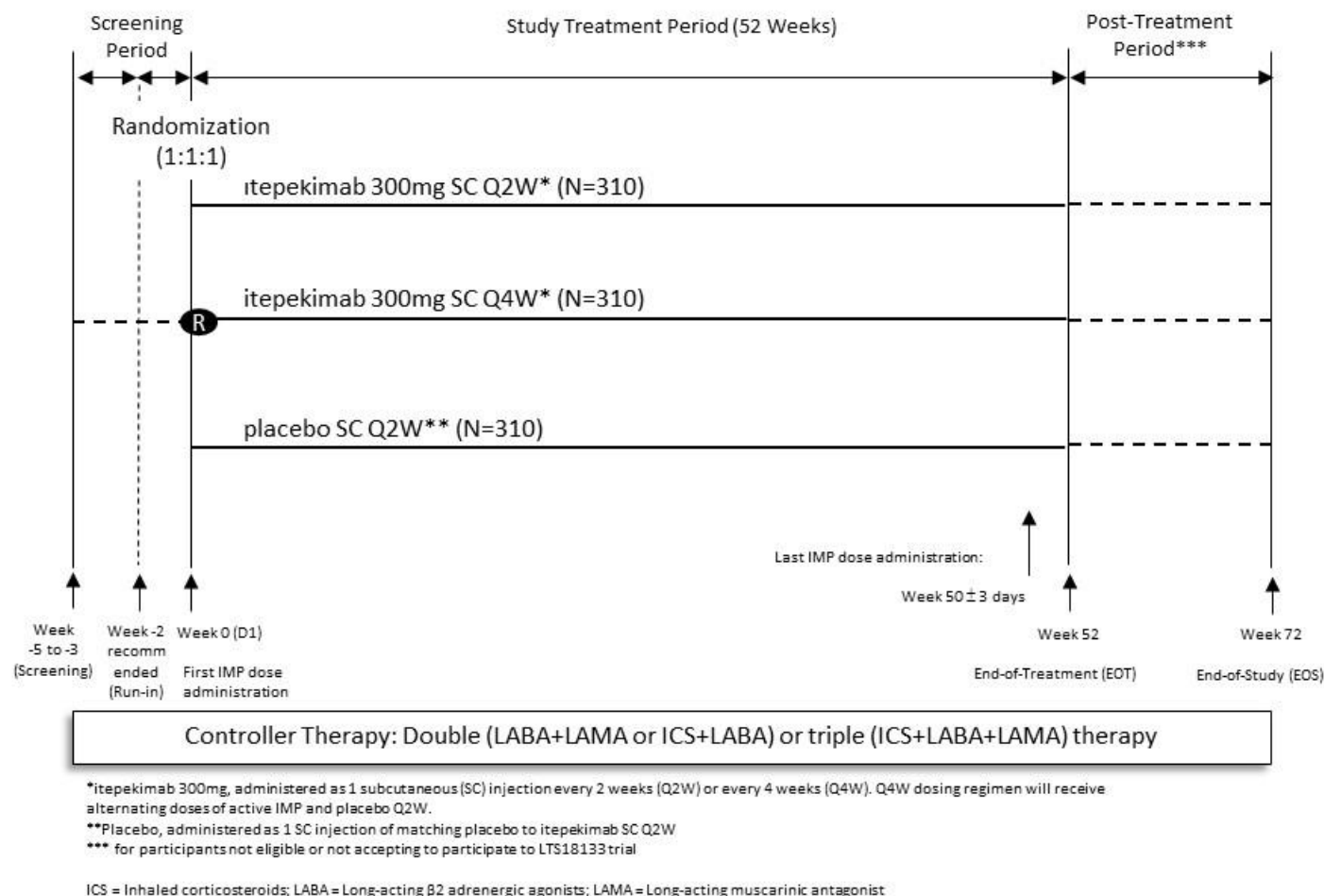
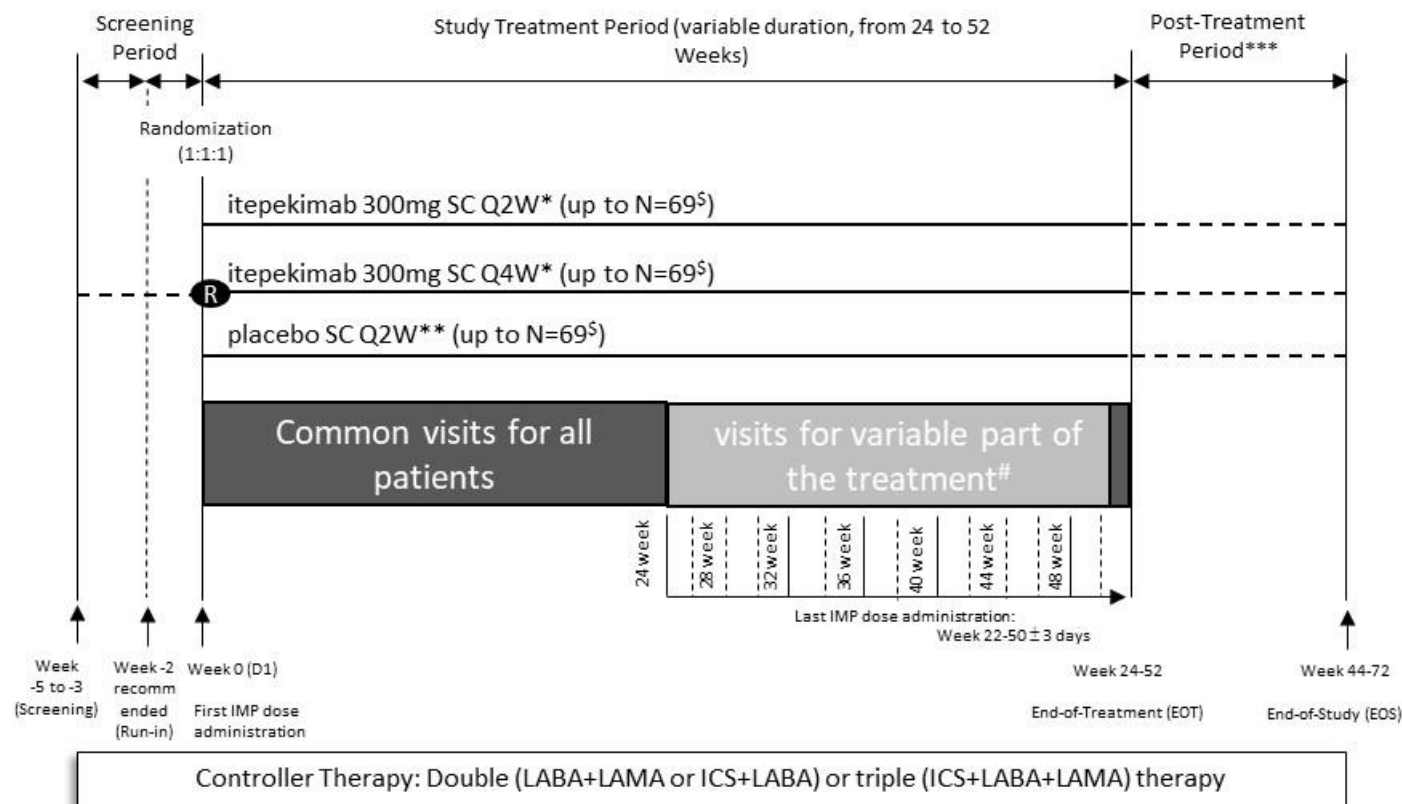


Figure 2 - Graphical study design - adaptive additional former smokers (up to n=207)



*itepekimab 300mg, administered as 1 subcutaneous (SC) injection every 2 weeks (Q2W) or every 4 weeks (Q4W)

**Placebo, administered as 1 SC injection of matching placebo to itepekimab SC Q2W

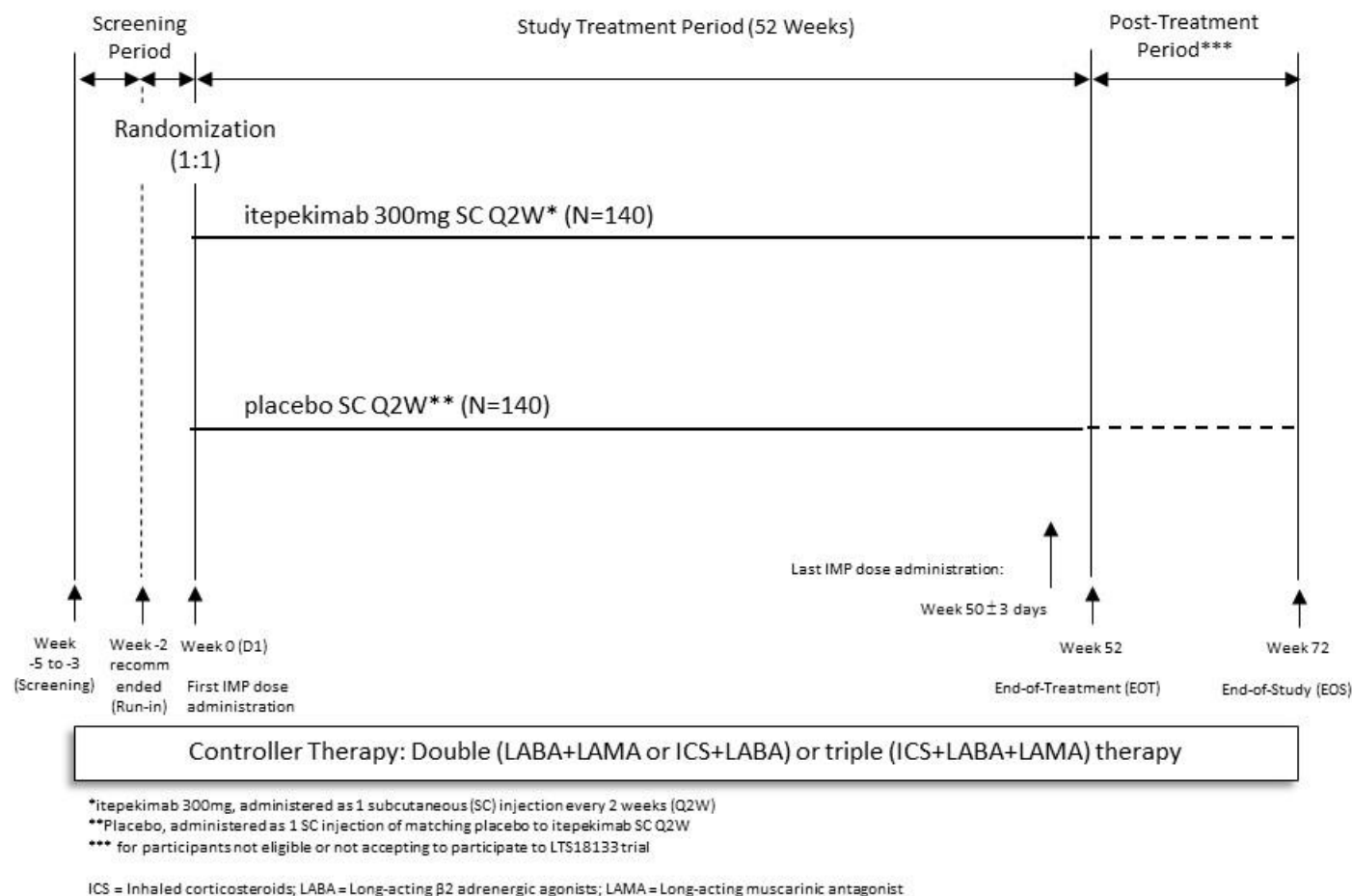
*** for participants not eligible or not accepting to participate to LTS18133 trial

[#]Variable treatment period. The initial cohort of 960 randomized participants will have a 52 weeks treatment period. Participants randomized in addition, following an adaptive sample size adjustment as described in Section 9.2, will remain in the treatment period until the last participant completes a minimum treatment of 24 weeks. (see Section 4.1.). At that date, all patient still on treatment will have their End of Treatment (EOT) visit, which will occur 2 weeks after last administration of IMP.

[§] up to 3 x 69 = 207 patients will be randomized following an optional sample size adjustment as described in Section 9.2

ICS = Inhaled corticosteroids; LABA = Long-acting β_2 adrenergic agonists; LAMA = Long-acting muscarinic antagonist

Figure 3 - Graphical study design - current smoker cohort (n=280)



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening (3-5 weeks)		Interventional treatment period (up to 52 weeks)																												Follow-up period (20 weeks) ^a		
	Screen- ing	Run-in ^b	Randomization/ Baseline																										EOT ^c		EOS		
VISIT	1A	1B	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29 ^a	30 ^a	31 ^a	
WEEK ^d	W-5 to -3	W -2 recommen- ded ^b	0	2	4	6 ^e	8	10 ^e	12	14 ^e	16	18 ^e	20 ^e	22 ^e	24 ^f	26 ^e	28 ^e	30 ^e	32	34 ^e	36	38 ^e	40	42 ^e	44 ^e	46 ^e	48	50 ^e	52	EOT +6 wee- ks	EOT +14 wee- ks	EOT+ 20 week- s	
Informed consent	X																																
Participant demographics	X																																
Previous medical and surgical history	X																																
Chest X-ray ^g		X																															
Inclusion/exclusion criteria	X		X																														
CAT ^h	X		X																														
Participant-reported smoking status	X		X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X	X	X ^e	X	
Prior and concomitant medications	X		X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X	X	X ^e	X	
Study treatment administration																																	
IVRS/IWRS	X		X	X	X		X		X		X				X				X		X		X				X		X			X	
Randomization			X																														
IMP administration ⁱ			X	X	X	X ^j	X	X ^j	X	X ^j	X	X ^j	X ^j	X ^j	X	X ^j	X ^j	X ^j	X	X ^j	X	X ^j	X	X ^j	X ^j	X ^j	X	X ^j					

	Screening (3-5 weeks)		Interventional treatment period (up to 52 weeks)																												Follow-up period (20 weeks) ^a		
	Screen- ing	Run-in ^b	Randomization/ Baseline																										EOT ^c		EOS		
VISIT	1A	1B	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29 ^a	30 ^a	31 ^a	
WEEK ^d	W-5 to -3	W -2 recommen- ded ^b	0	2	4	6 ^e	8	10 ^e	12	14 ^e	16	18 ^e	20 ^e	22 ^e	24 ^f	26 ^e	28 ^e	30 ^e	32	34 ^e	36	38 ^e	40	42 ^e	44 ^e	46 ^e	48	50 ^e	52	EOT +6 week- s	EOT +14 week- s	EOT+ 20 week- s	
Dispense or review of eDiary ^k		X	X	X	X		X		X		X				X				X		X		X				X		X			X	
Safety																																	
Physical examination ^l	X		X						X						X						X								X			X	
Vital signs ^m	X		X	X	X		X		X		X				X				X		X		X				X		X	X		X	
Electrocardiogram, (12-lead) ⁿ	X		X ⁿ												X														X			X	
Hematology, clinical chemistry, urinalysis ^o	X		X	X	X		X		X						X						X								X	X		X	
Routine urine cotinine dipstick test	X		X	X	X		X		X		X				X				X		X		X				X		X	X		X	
High-sensitivity urine cotinine/anabasine test (former smokers only)	X														X														X				
Hepatitis and HIV serology tests ^p	X																																
TB Assessment ^q	X																																

	Screening (3-5 weeks)		Interventional treatment period (up to 52 weeks)																												Follow-up period (20 weeks) ^a		
	Screen- ing	Run-in ^b	Randomization/ Baseline																										EOT ^c			EOS	
VISIT	1A	1B	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29 ^a	30 ^a	31 ^a	
WEEK ^d	W-5 to -3	W -2 recommen- ded ^b	0	2	4	6 ^e	8	10 ^e	12	14 ^e	16	18 ^e	20 ^e	22 ^e	24 ^f	26 ^e	28 ^e	30 ^e	32	34 ^e	36	38 ^e	40	42 ^e	44 ^e	46 ^e	48	50 ^e	52	EOT +6 wee- ks	EOT +14 wee- ks	EOT+ 20 week- s	
Pregnancy (β-HCG blood) test ^r	X																																
Urine pregnancy test ^r			X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X		X	
SARS-CoV-2 (COVID-19) test ^s	X																																
Adverse event reporting, including SAEs	X	X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X	X ^e	X	X ^e	X ^e	X ^e	X ^e	X	X ^e	X	X	X ^e	X
Pharmacokinetics and ADA																																	
Serum PK samples for itepekimab concentration ^t			X	X	X		X		X						X						X								X	X		X	
Anti-itepekimab antibody ^t			X					X							X														X			X	
Biomarkers																																	
Total IL-33			X		X				X						X														X	X		X	
Whole blood RNA (optional)			X						X						X						X								X				
DNA pharmacogenomic (optional) ^u			X																														

	Screening (3-5 weeks)		Interventional treatment period (up to 52 weeks)																												Follow-up period (20 weeks) ^a		
	Screen- ing	Run-in ^b	Randomization/ Baseline																										EOT ^c		EOS		
VISIT	1A	1B	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29 ^a	30 ^a	31 ^a	
WEEK ^d	W-5 to -3	W -2 recommen- ded ^b	0	2	4	6 ^e	8	10 ^e	12	14 ^e	16	18 ^e	20 ^e	22 ^e	24 ^f	26 ^e	28 ^e	30 ^e	32	34 ^e	36	38 ^e	40	42 ^e	44 ^e	46 ^e	48	50 ^e	52	EOT +6 week- s	EOT +14 week- s	EOT+ 20 week- s	
Serum/plasma for archival samples (optional) ^v			X						X						X														X				
Efficacy																																	
COPD exacerbation reporting by the Investigator			X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X ^e	X ^e	X	X ^e	X	X ^e	X	X ^e	X ^e	X ^e	X ^e	X	X ^e	X	X	X ^e	X
Spirometry (pre-BD) ^w	X		X	X	X		X		X		X				X				X		X		X				X		X	X		X	
Spirometry (post-BD) ^w	X		X	X	X		X		X						X						X								X			X	
SGRQ ^k			X						X						X						X								X			X	
E-RS:COPD ^k		X (daily)	X (daily)																									X				X	
PGIC ^k															X														X				
PGIS ^k			X												X														X				
BODE Index score, includes 6-minute walk test, and mMRC; pulse oximetry ^{m, x}			X																										X				

	Screening (3-5 weeks)		Interventional treatment period (up to 52 weeks)																												Follow-up period (20 weeks) ^a		
	Screen- ing	Run-in ^b	Randomization/ Baseline																										EOT ^c		EOS		
VISIT	1A	1B	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29 ^a	30 ^a	31 ^a	
WEEK ^d	W-5 to -3	W -2 recommen- ded ^b	0	2	4	6 ^e	8	10 ^e	12	14 ^e	16	18 ^e	20 ^e	22 ^e	24 ^f	26 ^e	28 ^e	30 ^e	32	34 ^e	36	38 ^e	40	42 ^e	44 ^e	46 ^e	48	50 ^e	52	EOT +6 wee- ks	EOT +14 wee- ks	EOT+ 20 week- s	
Health economic evaluation																																	
EQ-5D-5L ^k			X																										X			X	
Healthcare resource utilization ^k			X		X		X		X		X				X				X		X		X				X		X	X		X	

6MWD = 6-Minute Walking Distance; ADA = antidrug antibody; AESI = adverse event of special interest; ERS/ATS = European Respiratory Society/American Thoracic Society; β -hCG = human chorionic gonadotropin-beta; BD = bronchodilator(y); BODE Index = Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; BP = blood pressure; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; COVID 19 = coronavirus disease 2019; CRP = C-reactive protein; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eDiary = electronic diary; EOS = End of Study; EOT = End of treatment; EQ-5D-5L = EuroQol 5-dimension 5-level quality-of-life questionnaire; E-RS:COPD = Evaluating Respiratory Symptoms in COPD; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin; IL = interleukin; IMP = investigational medicinal product; ISR = injection site reaction; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LABA = long-acting β 2 agonists; LAMA = Long-acting muscarinic antagonist, mMRC = modified Medical Research Council Dyspnea Scale; PGIC = Participant Global Impression of Change; PGIS = Participant Global Impression of Severity; PK = pharmacokinetic(s); RNA = ribonucleic acid; SABA = short-acting β -agonists; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St. George's Respiratory Questionnaire; TB = tuberculosis; W = week.

- a For participants transitioning to the LTS18133 study, visits 29, 30 and 31 are not applicable. See [Section 6.7](#).
- b Run-in visit is recommended to be scheduled 2 weeks prior to the Baseline/Randomization Visit. The E-RS:COPD score over 7 days needs to be obtained prior to Baseline/Randomization (Visit 2).
- c End of IMP treatment (EOT) Visit: After EOT, if a participant's COPD cannot be adequately controlled by the prescreening background therapy, additional controller therapies may be prescribed based on the Investigator's clinical judgment. Participants who prematurely discontinue from the study prior to completing the planned treatment period (ie, early treatment discontinuation), will attend the early treatment discontinuation (ETD) visit and follow the assessments for EOT as shown in this table and will attend the remaining follow-up visits per the protocol schedule with a $\pm$ 5-day window until the end of the study.
- d The study has a treatment duration of up to 52 weeks. The study visits occur on the planned dates (relative to the first injection of the study drug), as scheduled. The visit schedule should be adhered to within $\pm$ 3 days for the randomized IMP treatment period, and $\pm$ 5 days for the visits during the post-IMP treatment follow-up period.
- e By telephone in case of IMP administration at the participant's home. Nonclinic visit headings are in light grey color.
- f An early EOT visit will be planned 52 weeks after the last of the first 1210 participants is randomized, or alternatively 24 weeks after the last potential additional randomized participants, if the sample size is increased as per Section 9.2, whichever is later. In that case, a pre-planned clinic visit at Week 24, 32, 36, 40 or 48 will be replaced by an early EOT visit for potential additional randomized participants who are still on treatment.
- g Chest X-ray to be performed unless a <6-month-old chest X-ray/chest CT scan/chest MRI scan is available. In case a chest X-ray is not feasible due to local regulations, an MRI scan will be performed.
- h Inclusion criteria will be based on the CAT score.
- i IMP (itepekimab or placebo) to be administered every 2 weeks. The last dose will be given 2 weeks prior to the planned EOT Visit (ranging from Week 24 to Week 52), except if the participant enters the extension study LTS18133. Participants should be monitored for at least 30 minutes after administration of all IMP injections. The monitoring period may be extended as per country-specific requirements.

- j Starting from Visit 5 (Week 6), IMP will be administered by the participant, caregiver, or healthcare professional at the participant's home or in a healthcare facility depending on what is chosen, according to treatment allocation. If IMP is administered at home, the site should verify the IMP compliance/administrations with the participants during the scheduled telephone contacts and at next on-site visit check the completed eDiary. See [Section 6.1](#) for more details. If the participant or Investigator decides not to administer IMP at home, the IMP injections can be performed at the site for these visits.
- k An eDiary will be used to record participant's answers to the EQ-5D-5L, SGRQ, PGIC, PGIS, and E-RS: COPD questionnaires, , number of puffs of controller/reliever medication. This device will be dispensed at Run-in (Visit 1B) (including instructions for use) and recorded information will be downloaded from this device on indicated days. At the EOS Visit the eDiary data will be downloaded and the device will be returned to the site. Healthcare resource utilization/productivity will be recorded in the eCRF. For participants who enter the LTS18133 study, the eDiary data will be downloaded and the device will be returned to the site at EOT visit (Week 52).
- l Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Height (cm) will be measured and recorded at Screening (Visit 1A) only. Body weight (kg) will be measured and recorded at Screening (Visit 1A), Baseline/Randomization (Visit 2), Week 24 (Visit 14), and EOT and EOS Visits.
- m Vital signs, including systolic and diastolic BP (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate (breaths per full minute) will be measured at Screening (Visit 1A), Baseline/Randomization (Visit 2), and at every subsequent on-site visit.
- n Single 12-lead ECGs will be collected and centrally read. ECGs to be preferably performed prior to laboratory assessments and spirometry measurement in order to prevent potential effect of albuterol/salbutamol or levalbuterol/levosalbutamol administration on ECG tracing. ECG at Baseline/Randomization (Visit 2) will only be required if the ECG for screening was performed >6 weeks prior to Baseline (Week 0).
- o Hematology will include hemoglobin, hematocrit, platelet count, total red blood cell count, and total white blood cell count with differential (including neutrophils and eosinophils). Serum clinical chemistry will include creatinine, blood urea nitrogen, glucose (fasting), lactate dehydrogenase, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, bicarbonate C-reactive protein, and creatine phosphokinase). Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen, and bilirubin. If any urinalysis parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement. If urinalysis sample is abnormal for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory. For China: If local regulations restrict use of sponsor provided dipstick, a urine sample can be sent for urinalysis to the central laboratory.
- p Clinical laboratory testing at Screening (Visit 1A) will include a hepatitis screen covering hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb IgM and Total), hepatitis C virus antibodies (HCVAb), HIV screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBs Ag (negative), and HBc Ab Total (positive), HBV DNA testing will be performed prior to randomization to rule out a false positivity to clarify the serological status. In case of results showing HCV Ab (positive), HCV RNA testing will be performed to rule out a false positivity.
- q TB assessment per local guidelines or, if not available, in central laboratory using a Quantiferon® test.
- r Only for women of childbearing potential: a serum pregnancy test will be performed at Screening (Visit 1A); urine pregnancy tests will be performed at the visits listed in the SoA table. A negative result must be obtained at Visit 1A and at Visit 2 prior to randomization. In case of a positive urine test, the study treatment will be withheld and a serum pregnancy test performed as soon as possible to confirm the pregnancy. Pregnancy will lead to definitive treatment discontinuation in all cases. Pregnancy urine test at Week 20, 28, and 44 (home IMP administration/telephone visits) will be performed by the participant at home. The outcome will be recorded. Participant will be instructed to not administer next IMP in case of suspected/confirmed pregnancy and contact the site.
- s Nasopharyngeal/oropharyngeal swabs and a quantitative polymerase chain reaction or antigen test will be performed to detect SARS-CoV-2 infection at either local or central laboratory.
- t Systemic drug concentration and ADA samples are to be collected prior to dosing. 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.
- u Optional DNA sample may be collected once during the study.
- v Optional archived samples may be used for research purposes related to respiratory diseases such as COPD or inflammatory diseases (eg, exploratory biomarkers of disease or drug effect), pathway biology, additional drug safety assessments, or development and validation of bioassay methods beyond those defined in the present protocol.
- w Spirometry will be performed at clinical sites according to ERS/ATS 2005 guidance. Pre-BD spirometry will be performed during a washout period of BDs according to their action duration following the guidance of the ERS/ATS 2019 guidance. For example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of ipratropium for at least 12 hours, withholding the last dose of LABA for at least 24 hours, and finally the last dose of ultralong-acting LABA (like vilanterol) or the last dose of LAMA should be withheld for at least 36 hours). This will be verified before performing the measurements. Note: When both pre- and post-BD spirometry are assessed, the post-BD spirometry should be performed after 4 actuations of SABA (albuterol, salbutamol) with post-BD reversibility performed at least 15 minutes following the last actuation).
- x The mMRC will be measured as part of the BODE Index. Oxygen saturation using pulse oximetry and respiratory rate will be measured at the start of the 6MWD, and at the conclusion of the test (See [Section 8.1.2.1.5](#) for details). The CAT score and mMRC result will be captured in the eCRF. The score of each domain of the BODE Index score must be recorded in the source documents and eCRF. Body-mass index (BMI) should be calculated at Screening (Visit 1A) (for eligibility), and at Baseline/Randomization (Visit 2) and EOT Visit (ranging from Week 24 up to Week 52) for the BODE Index. Pulse oximetry will be measured at Baseline/Randomization (Visit 2) and EOT Visit as part of the BODE Index. If the participant is using supplemental oxygen, this should be continued at the same rate.

1.3.1 Reduced schedule of activities (SoA) for participants after early treatment discontinuation

	ETD ^a	Interventional treatment period (up to 52 weeks)																											Follow-up period (20 weeks)		
VISIT		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 (EOT)	29	30	31 (EOS)	
WEEK ^a		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	EOT+ 6 weeks	EOT+ 14 weeks	EOT+20 weeks	
BODE Index score, includes 6-minute walk test, and mMRC; pulse oximetry																											X				
Smoking status	X		X		X		X		X				X				X		X		X				X		X	X	X ^a	X	
Prior and concomitant medications	X		X		X		X		X				X				X		X		X				X		X	X	X ^a	X	
IVRS/IWRS	X																													X	
Dispense or review of eDiary ^b	X		X		X		X		X				X				X		X		X				X		X			X	
Physical examination ^c	X						X						X						X								X			X	
Vital signs ^d	X		X		X		X		X				X				X		X		X				X		X	X		X	
Electrocardiogram, (12-lead) ^e													X														X			X	
Hematology, clinical chemistry, urinalysis ^f	X						X						X						X								X	X		X	
Routine urine cotinine dipstick	X						X						X						X								X			X	
High-sensitivity urine cotinine/anabasine test (former smokers only)													X														X				
Urine pregnancy test	X						X						X						X								X			X	
Adverse event reporting, including SAEs	X	X	X		X		X		X				X				X		X		X				X		X	X	X ^a	X	
Serum PK samples for itepekimab concentration	X						X						X						X								X	X		X	

	ETD ^a	Interventional treatment period (up to 52 weeks)																											Follow-up period (20 weeks)			
VISIT		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 (EOT)	29	30	31 (EOS)		
WEEK ^a		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	EOT+ 6 weeks	EOT+ 14 weeks	EOT+20 weeks		
Anti-itepekimab antibody	X						X						X														X			X		
Total IL-33	X		X				X						X														X	X		X		
Whole blood RNA (optional)	X																										X					
Serum/plasma for archival samples	X																															
COPD exacerbation reporting by the Investigator	X	X	X		X		X		X				X				X		X		X				X		X	X	X ^a	X		
Spirometry (pre-BD) ^g	X		X		X		X		X				X				X		X		X				X		X	X		X		
Spirometry (post-BD) ^g	X		X		X		X						X						X								X			X		
SGRQ ^b	X						X						X						X								X			X		
E-RS:COPD ^b		X (daily)																												X		X
PGIC ^b													X														X					
PGIS ^b	X												X														X					
EQ-5D-5L ^b	X																										X			X		
Health care utilization ^b	X		X		X		X		X				X				X		X		X				X		X	X		X		

BD = bronchodilator(y); BODE Index = Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ECG = electrocardiogram; eDiary = electronic diary; EOS = End of Study; EOT = End of Treatment; EQ-5D-5L = EuroQol 5-dimension 5-level quality-of-life questionnaire; E-RS:COPD = Evaluating Respiratory Symptoms in COPD; ETD = Early Treatment Discontinuation; IL = interleukin; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LABA = long-acting β_2 agonists; LAMA = Long-acting muscarinic antagonist, mMRC = modified Medical Research Council Dyspnea Scale; PGIC = Participant Global Impression of Change; PGIS = Participant Global Impression of Severity; PK = pharmacokinetic(s); RNA = ribonucleic acid; SABA = short-acting β -agonists; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire;

- a* Participants who withdraw from study treatment (prior to completing the planned duration of IMP treatment) will perform, as soon as possible, the ETD Visit. Once the ETD Visit is performed, participants should follow the assessments scheduled in the ETD SOA based on the original visit numbers and the visits scheduled should be adhered to within ± 5 days. Visits which are in light grey can be skipped after early treatment discontinuation except for Visit 30 (Week 66) which is a telephone visit.
- b* An eDiary will be used to record participant's answers to the EQ-5D-5L, SGRQ, PGIC, PGIS, and E-RS:COPD questionnaires, number of puffs of controller/reliever medication. This device will be dispensed at Run-in (Visit 1B) (including instructions for use) and recorded information will be downloaded from this device on indicated days. At the EOS Visit the eDiary data will be downloaded and the device will be returned to the site. Healthcare resource utilization/productivity will be recorded in the eCRF.
- c* Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Body weight (kg) will be measured and recorded at EOT and EOS Visits.
- d* Vital signs will include systolic and diastolic BP (mmHg), pulse rate (beats per minute), body temperature ($^{\circ}\text{C}$), and respiratory rate (breaths per full minute). Pulse oximetry will be measured at the EOT Visit (ranging from Week 24 up to Week 52) as part of the BODE Index.
- e* Single 12-lead ECGs will be collected and centrally read.
- f* Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count with differential (including neutrophils and eosinophils), and total red blood cell count. Serum clinical chemistry will include creatinine, blood urea nitrogen, glucose (fasting), lactate dehydrogenase, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, bicarbonate), C-reactive protein, and creatine phosphokinase. Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen and bilirubin. If any urinalysis parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement. If a urinalysis sample is abnormal for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory. For China, if local regulations restrict use of sponsor provided dipstick, a urine sample can be sent for urinalysis to the central laboratory.
- g* Spirometry will be performed at clinical sites according to ERS/ATS 2005 guidance but measured. Pre-BD spirometry will be performed during a washout period of BDs according to their action duration following the guidance of the ERS/ATS 2019 guidance. For example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of ipratropium for at least 12 hours, withholding the last dose of LABA for at least 24 hours, and finally the last dose of ultralong-acting LABA (like vilanterol) or the last dose of LAMA should be withheld for at least 36 hours. This will be verified before performing the measurements. Note: When both pre and post-BD spirometry are assessed, the post-BD spirometry should be performed after 4 actuations of SABA (albuterol, salbutamol) with post-BD reversibility performed at least 15 minutes following the last actuation).

2 INTRODUCTION

Itepekimab (also known as REGN3500 or SAR440340) is a human immunoglobulin (Ig) G 4^P monoclonal antibody (mAb) that binds interleukin (IL) 33 with subnanomolar affinity and thereby inhibits IL-33 signaling. Itepekimab is under development as a potential novel treatment for COPD. A PoC study (ACT15104) in participants with moderate-to-severe COPD on controller therapy of LAMA, LABA, and/or ICS therapy was recently conducted to demonstrate the impact of blocking the IL-33 pathway on exacerbations and lung function.

In Study ACT15104, itepekimab 300 mg Q2W showed an acceptable safety profile in participants with COPD who are either current or former smokers, and compelling preliminary clinical evidence for the efficacy of itepekimab as an add-on to standard of care (SoC) background therapy in participants with COPD who are former smokers. The aim of this Phase 3 study is to evaluate the benefit-risk profile of 2 dose regimens of itepekimab in participants with COPD who are former smokers. In addition, the aim of this study is also to evaluate the efficacy and safety of one dose of itepekimab in participants with COPD who are current smokers.

2.1 STUDY RATIONALE

Chronic obstructive pulmonary disease is a serious and life-threatening disease. It is the third leading cause of death worldwide and the fourth leading cause of death in the US, responsible for over 3 million deaths worldwide in 2016 and 160 000 deaths annually in the US (1, 2, 3). It is also the largest contributor to respiratory-related mortality. Chronic obstructive pulmonary disease is characterized by progressive decline in lung function and recurrent exacerbations of symptoms. The latter results in rapid disease progression and are associated with increased mortality, particularly following exacerbations that require hospitalization (4). Tobacco smoke is the major contributor to COPD (2). Although smoking cessation in patients with established COPD slows the rate of lung function decline and reduces the risk of hospitalization and mortality, former smokers with COPD are still at high risk for exacerbations and substantial morbidity and risk of mortality remain, particularly when compared to former smokers without COPD (5). Currently available therapies have modest efficacy and/or important safety concerns.

Itepekimab is a human IgG 4^P mAb that binds IL-33 with subnanomolar affinity and thereby inhibits IL-33 signaling. Interleukin-33 is a proinflammatory cytokine localized to the nuclei of a variety of cell types, including epithelial cells, endothelial cells, and fibroblasts (7). When epithelial cells are damaged by exposure to airborne allergens, viruses, cigarette smoke, or air pollutants, IL-33 is released locally and proposed both to initiate and to amplify innate and adaptive inflammatory pathways (8). The IL-33 binds to its cognate receptor, suppression of tumorigenicity 2 (ST2), and subsequently engages the IL-1 receptor accessory protein (IL-1RAcP) as a co-receptor to initiate signaling and activation of both innate and adaptive immune cells. The IL-33 signaling initiates and amplifies downstream inflammatory pathways characteristic of both Type 1 and Type 2 inflammation. Based on the proximal position of IL-33 to external inflammatory insults (ie, IL-33 is stored in epithelial cells) and its ability to initiate and amplify multiple downstream inflammatory pathways, IL-33 may be a common amplifier in diseases featuring epithelial inflammation.

Accumulating clinical and nonclinical data also implicate IL-33 in the pathogenesis of COPD. The IL-33 protein expression is increased in bronchial epithelial cells of patients with COPD compared to non-COPD controls and correlates with excess airway mucus production and mucin gene expression (9). The IL-33 protein expression in lung homogenates from patients with COPD correlates with COPD severity and is negatively correlated with FEV1 (10). IL-33 levels in exhaled breath condensate, sputum, and serum samples of patients with COPD are elevated compared with that in healthy nonsmokers and healthy smoker controls (11). Plasma IL-33 levels in patients with stable COPD are elevated compared to healthy controls and are related to blood eosinophil count and the chronic bronchitis phenotype (12).

These reports are also consistent with a study from the Regeneron Genetics Center that examined whether previously reported genetic variants near IL-33 (*rs1342326*) and IL1 receptor-like 1 (*IL1RL1*) (*rs1420101*) associated with asthma and eosinophilia, a hallmark of Type 2 inflammatory disease, were also associated with lifetime median electronic health record (EHR)-documented eosinophil count, asthma, COPD, and asthma-COPD overlap syndrome (ACOS) in a hospital patient population of predominantly European ancestry from the Geisinger Health System (GHS). The results of this study provide genetic evidence linking the IL-33 pathway to eosinophilic forms of asthma, COPD, and ACOS through an allelic series that includes both risk-increasing common alleles and risk-decreasing rare predicted loss of function alleles (further information is provided in the Investigator's Brochure (IB) and the REGN3500-MX-16094 study report).

Chronic exposure to cigarette smoke, pollutants, and airborne contaminants are the major drivers of the pathogenesis of COPD. Pharmacology studies have evaluated the impact of cigarette smoke on the IL-33 pathway. Cigarette smoke induces IL-33 protein expression in bronchial epithelial cells in mice (10) and humans (13). Pharmacology models have demonstrated that IL-33 expression in lungs of mice exposed to house dust mites (HDMs) remains elevated, even when allergen exposure is stopped for prolonged periods of time (14). These chronic in vivo models suggest that chronic insults to the lung induce IL-33 and that this cytokine can persist even in the absence of the initial trigger. However, the role of IL-33 in COPD in smokers versus patients who are former smokers is not understood in the field.

Data from the PoC Study ACT15104 in which itepekimab was studied versus placebo on top of approved SoC as background therapy provided preliminary clinical evidence that itepekimab has the potential to confer significant benefit beyond that provided by currently available therapies to former smokers with moderate-to-severe COPD. As noted above, Study ACT15104 studied participants with COPD who were current or former smokers as defined in the electronic case report form (eCRF). The study did not enroll patients with a smoking history of <10 packs/year as these participants are likely to have other causes of chronic airflow obstruction, such as bronchiectasis, rather than COPD. In the overall study population, itepekimab reduced the risk of experiencing moderate-to-severe AECOPD compared to placebo by 19.2% over a treatment period of up to 52 weeks, although the difference did not reach statistical significance (RR: 0.808, 95% CI 0.613 to 1.065; p=0.1296). One of the prespecified subgroup analyses conducted in this study was by smoking status, where a clear effect was seen in former smokers. The data suggest that active smoking eliminated the beneficial effects of itepekimab. In this analysis, itepekimab demonstrated a relative risk reduction (RRR) in former smokers compared to placebo in moderate-to-severe AECOPD of 42.5% (RR 0.575, 95% CI 0.388 to 0.853, nominal p=0.0061). This effect was consistent across a number of subgroups within the former smoker population, including

subgroups by controller therapy (double [ICS + LABA, ICS + LAMA, or LABA + LAMA] or triple [ICS + LABA + LAMA] therapy) and regardless of blood eosinophil level or CAT score at baseline. Improvement in FEV1 was also seen in former smokers, specifically among those with blood eosinophil counts ≥ 250 cells/ μ L. These results contrast with the results in the current smoker population, where minimal improvement of FEV1 was observed. In that population, itepekimab did not demonstrate a reduction in the rate of moderate-to-severe AECOPD (-9.4%, RR 1.094, 95% CI 0.743 to 1.612, nominal $p=0.6472$), and consistent with this finding, did not demonstrate any benefit in other endpoints evaluated in the study.

The objectives of the current study are 1) to further evaluate the efficacy and assess the safety and tolerability of itepekimab 300 mg administered SC Q2W or Q4W as compared to placebo in moderate-to-severe COPD participants who are former smokers and are in need of an additional treatment added to their current COPD management, and 2) to further characterize the efficacy and safety of itepekimab using dose regimen of itepekimab 300 mg SC Q2W compared to placebo over one year in participants with COPD who are current smokers.

2.2 BACKGROUND

Chronic obstructive pulmonary disease is a common, chronic progressive lung disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities associated with an abnormal inflammatory immune response in the lung to noxious particles and gases (15). Chronic inflammation causes structural changes, narrowing of the small airways, destruction of the lung parenchyma, and reduced lung elastic recoil, resulting in progressive airflow obstruction. The main cause of COPD in the US is tobacco smoke, but multiple additional causes, such as air pollution, exposure to biomass fuel combustion, occupational exposures, and genetic susceptibility, contribute to the risk of COPD. However, individual risk factors have not been correlated with unique COPD phenotypes. The most common respiratory symptoms include chronic dyspnea, cough, and sputum production. Chronic obstructive pulmonary disease is characterized by exacerbations, which are typically caused by either viral or bacterial infections of the lungs that trigger an inflammatory response, tissue destruction, and promote rapid disease progression (measured by the rate of lung function decline over time). Exacerbations are associated with increased mortality, particularly following severe exacerbations (those that require hospitalization) (4). Medical comorbidities, such as cardiovascular disease, diabetes, lung cancer, skeletal muscle dysfunction, osteoporosis, mental health disorders, and metabolic syndrome, are common among patients with COPD and occur across the spectrum of disease severity (16).

The prevalence of COPD is projected to grow rapidly over the coming decades due to past and/or continued exposure to risk factors and an aging population, increasing the substantial economic and social burden of COPD (15, 17, 18). Based on the Burden of Obstructive Lung Diseases (BOLD) study and other epidemiological studies, it is estimated that there were 384 million cases of COPD globally in 2010 (15). In the US alone, there are approximately 16 million diagnosed patients (2), of whom more than 38% were current smokers (19). Although smoking cessation in patients with established COPD slows the rate of decline of lung function and reduces the risks of hospitalization and mortality, former smokers with COPD are still at high risk for exacerbations and substantial morbidity and risk of mortality remain (5). In one study, former smokers had an

exacerbation rate of 22.8 per 1000 person-years, as compared with 27.4 per 1000 person-years among current smokers (20). Healthcare costs attributable to COPD increase with increasing disease severity and frequency of hospitalizations (which are linked to exacerbations); the annual costs attributable to COPD were \$32.1 billion in 2010 and are projected to increase to \$49 billion in 2020 (18, 21). The results from the PoC study performed with itepekimab (ACT15104, presented herein), show a similar rate of exacerbations between former and current smokers who received placebo. There remains a high unmet need for additional therapies that reduce exacerbations, improve lung function, and improve symptoms in patients with COPD who are former smokers. Data from Study ACT15104 provide preliminary clinical evidence that itepekimab has the potential to confer significant benefit to former smokers with moderate-to-severe COPD beyond that provided by available therapies.

For current smokers, smoking cessation is the critical first step in modifying the clinical course of COPD and reducing the rate of lung function decline (5, 18, 21). Currently available therapies which are approved for the treatment of COPD include LAMA, LABA, ICS, roflumilast (phosphodiesterase type 4 [PDE-4] inhibitor), and theophylline. The SoC for COPD starts with inhaled BDs (LAMA and/or LABA). As the disease progresses, BDs are often combined with other drugs approved for the treatment of COPD (ICS, roflumilast, and in some cases, theophylline) (22, 23, 24). Use of ICS in combination with LABA has been found to be more effective than either component alone, and triple therapy (ICS + LABA + LAMA) is more effective than double therapy (ICS + LABA or ICS + LAMA) in controlling symptoms and reducing exacerbations. The major limitations of these existing treatments for COPD include modest efficacy that may be limited to patients with high blood eosinophils and, for ICS, an increased risk of pneumonia, hoarseness of voice, and oral candidiasis. Oral or systemic corticosteroids are reserved for the treatment of exacerbations given their unacceptable long-term safety profile in the COPD population. The use of roflumilast, a PDE-4 inhibitor, has been limited due to its modest efficacy in only a subset of patients with severe COPD associated with chronic bronchitis and frequent exacerbations and concerns about side effects, including gastrointestinal and psychiatric adverse effects and weight loss.

The differential efficacy between current smokers and participants who are former smokers observed in Study ACT15104 is not without precedent. Recent studies have indicated that a number of therapies have greater efficacy in COPD in former smokers (as compared to current smokers) Firstly, ICS has shown improved efficacy in the subset of patients with COPD who are former smokers (25, 26, 27, 28). For example, addition of ICS to LAMA + LABA was associated with a 30% reduction in exacerbations in former smokers compared to a 14% reduction in current smokers in the IMPACT study (25). The SUMMIT study found that ICS + LABA reduced exacerbations by 36% compared to placebo among former smokers and by only 19% compared to placebo among current smokers (27). A similar difference in the effect of ICS on FEV1 was also found in the SUMMIT study. These reports are consistent with the fact that cigarette smoking is well known to lead to corticosteroid resistance in asthma and COPD (26, 29, 30).

While macrolides are not approved for the treatment of COPD, and are therefore not considered available therapy, there are reports which have shown reductions in exacerbations with long-term use of macrolides in patients with COPD which are of interest given the differential results seen between former and current smokers (31, 32). A secondary analysis of a large randomized long-term trial of macrolide therapy was conducted to identify subgroups that most effectively

respond to long-term treatment with azithromycin; it was noted that the reduction in exacerbation risk with azithromycin was strongest among former smokers, and azithromycin had relatively little effect among current smokers (31). The mechanisms underlying this finding are not well understood (33). Macrolides can also cause hearing loss and resistant bacterial colonization, limiting their long-term use (31).

Currently, no targeted treatments addressing the immunological underpinnings of COPD are approved, and none have demonstrated efficacy outside of the population with high eosinophil levels. The anti-IL-5 mAb mepolizumab showed an 18% to 20% reduction of exacerbations as add-on therapy to ICS plus BD(s) in patients with COPD with high blood eosinophils, and a 2% reduction of exacerbations in the overall population regardless of blood eosinophil count (34). Mepolizumab also demonstrated a greater exacerbation risk reduction in never/former smokers when compared to current smokers (21% versus 13%, respectively) (35). Additionally, the anti-IL-5 receptor mAb benralizumab showed similar mixed results as add-on therapy to ICS and BD(s), with reduction of exacerbations in patients with COPD with high blood eosinophils ranging from 4% worsening to 17% improvement, depending on the dose (36).

Given the high prevalence and serious and life-threatening nature of COPD, there is a great need for continued research and the development of novel therapeutic strategies to improve treatment for patients who suffer from this disease. Many patients are underserved by currently available therapies, which have significant limitations. Data from Study ACT15104 provide preliminary clinical evidence that itepekimab has the potential to confer significant benefit beyond that provided by currently available therapies in patients with COPD who are former smokers. Therefore, it is anticipated that itepekimab may be an effective and safe alternative to available treatment options in this population.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of itepekimab may be found in the IB.

2.3.1 Risk assessment

The current AE profile emerging from our clinical studies suggest that itepekimab is generally well-tolerated in participants with COPD (regardless of smoking status) and asthma and has identified no new safety concerns. In general, administration of mAbs is associated with the potential risk of systemic hypersensitivity reactions (including immunogenicity). Based upon the mechanism of action of itepekimab as an antagonist of IL-33, an epithelial cytokine which triggers downstream inflammatory pathways in the setting of epithelial damage, serious infections including opportunistic infections are considered important potential risks for itepekimab in particular. Potential risks for itepekimab are managed in this clinical study through careful participant selection, close monitoring, and early recognition and treatment of AEs. Risk minimization, monitoring, and management plans are in place and are outlined in the IB. The safety data and other potential risks for itepekimab are also summarized in the IB.

Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of itepekimab on the fetus and newborn are unknown. Monoclonal antibodies can cross the placenta and may cause harm to the fetus. In Cynomolgus monkeys, there were no effects on microscopic findings in male and female reproductive organs after 26 weeks of treatment and no effects on surrogate parameters of fertility. Risk minimization measures are in place within the study. Females who are lactating, breastfeeding or who are pregnant are excluded. Women of childbearing potential (WOCBP; pre-menopausal female biologically capable of becoming pregnant) are only eligible if they employ by one of the acceptable forms of highly effective contraception method specified in this protocol (see inclusion criterion I 10).

Male contraception is not required in the study. Extremely low levels of itepekimab are expected to reach the fetus via seminal fluid. Monoclonal antibodies have physicochemical characteristics that limit their passive transmission through biological membranes. In order to reach the fetus, any therapeutic antibody present in seminal fluid would need to undergo vaginal absorption, which presents a significant barrier. Using the highest dose of itepekimab being tested in Study R3500-HV-1551 (10 mg/kg IV), applying conservative assumptions (37, 38) and assuming that 100% of maternal exposure is transferred to the fetus, the highest potential exposure to a fetus of itepekimab through seminal transfer would be [REDACTED] µg/mL. This value is approximately [REDACTED] than the pharmacologically active concentration measured in vitro.

In early human clinical studies, itepekimab was well-tolerated by healthy adult subjects during the completed first-in-human single ascending dose study assessing single IV doses of 0.3, 1, 3, 10 mg/kg, and 150 mg SC itepekimab or matching placebo (Study R3500-HV-1551), as well as by participants with moderate asthma during the completed first-in-participant multiple ascending dose study assessing 75 mg or 150 mg SC once every week (QW) doses of itepekimab or placebo for 4 weeks (R3500-AS-1619). No deaths and no serious adverse events (SAEs) were reported.

In Study ACT15102, itepekimab 300 mg Q2W monotherapy or coadministered with dupilumab 300 mg Q2W was well-tolerated in participants with moderate-to-severe asthma. The percentage of participants with at least 1 treatment-emergent adverse event (TEAE) was well balanced across treatment groups. In Study ACT15104, the percentage of participants with at least 1 treatment-emergent SAE was balanced across treatment groups: 24 (14.0%) participants in the itepekimab group and 26 (15.2%) participants in the placebo group. There were no itepekimab treatment-related antidrug antibody (ADA) in Studies ACT15102 and ACT15104. The full safety data and other potential risks for itepekimab are also summarized in the IB.

Considering the high mortality of patients with COPD, all deaths will be adjudicated. Considering that cardiovascular disease is a frequent and important comorbidity of COPD, cardiac events will also be adjudicated throughout the study. The program will have an Adjudication Committee for the aforementioned events and a Data Monitoring Committee (DMC), which will review the benefit-risk including the cardiac safety on a regular basis.

Table 1 presents a summary of the potential risks of study participation and mitigation strategies.

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Systemic hypersensitivity reactions, including events associated with immunogenicity	There were no preclinical findings suggestive of systemic hypersensitivity reactions. The occurrence of immunogenicity to itepekimab was low, with anti-itepekimab antibodies detected in 5% and 2% of itepekimab-treated animals in the single-dose (REGN3500-PK- 15053) and repeat-dose (REGN3500- TX-15034) studies, respectively. In the repeat-dose toxicology study in Cynomolgus monkeys (REGN3500-TX-15034), 1 monkey (out of 48 monkeys receiving itepekimab) receiving the 100 mg/kg IV dose had a positive ADA assay during the recovery period that was 8.6-fold greater than the baseline sample, which is suggestive of a moderate response. In the ACT15102 study, the incidence of systemic hypersensitivity AESIs was slightly higher in the itepekimab and itepekimab + dupilumab groups compared to placebo and dupilumab groups (3 [4.1%] participants each in the itepekimab and itepekimab + dupilumab groups, and 1 [1.4%] participant each in the dupilumab and placebo groups). All cases of systemic hypersensitivity were mild or moderate in intensity and none was serious. All participants with systemic hypersensitivity recovered. In the ACT15104 study, incidence of systemic hypersensitivity AESIs was similar between itepekimab and placebo, 1 [0.6%] in placebo and 2 [1.2%] participants in the itepekimab arm. All cases of systemic hypersensitivity were moderate in intensity and none was serious. All participants with systemic hypersensitivity recovered. In Studies R3500-HV-1551, R3500-AS-1619, ACT15102, ACT15104, R3500-AD-1798, R3500- AD-1805 and PKM16966, no treatment emergent ADA were detected.	Protocol exclusion criteria: - Participants with a history of a systemic hypersensitivity reaction to a monoclonal antibody. Monitoring: - Participants should be monitored for any signs or symptoms of a hypersensitivity reaction for at least 30 minutes for all IMP injections that are administered. The monitoring period may be extended as per country specific or local site requirements. Management of hypersensitivity: - The study protocols provide detailed instructions on how to manage reactions during the infusion or following injection. ADA level measurements using a validated assay. Correlation of ADA status with safety and efficacy data.
Serious infections, including opportunistic infections	There were no preclinical findings suggestive of infections. In ACT15102, infection SAEs were similar between the 4 groups: 0 events Placebo, 1 event itepekimab 300mg Q2W, 1 event in itepekimab 300mg Q2W + dupilumab 300 mg Q2W, and 1 event in dupilumab 300md Q2W. There were no reported cases of opportunistic infections.	Protocol exclusion criteria: - Subjects with recent bacterial, protozoal, viral, or parasite infection requiring systemic treatment. - Subjects with a history of tuberculosis or systemic fungal diseases. Subjects are screened for tuberculosis. - Subjects with HIV infection or HIV seropositivity at Screening (Visit 1A).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	In ACT15104, 19 participants with events of infection SAEs were report during the study: 10 in placebo and 9 in itepekimab. One participant each in the placebo group and 2 participants in the itepekimab group experienced an opportunistic infection: herpes zoster. All cases were of mild-moderate intensity and led to protocol predefined permanent treatment discontinuation. Neither were considered serious or related to IMP by the Investigator. Both events were resolved at the time of data cut-off. It is not yet known whether itepekimab will pose additional risk for participants in the context of the current COVID-19 pandemic. There were no identified cases suggestive of SARS-CoV-2 infections in the ACT15104 study. For the overall susceptibility for serious and/or opportunistic infection, refer to the relevant section in this table. With increasing severity of COPD the risk of respiratory tract infection in general is known to be increased. Adequate treatment for COPD may result in the reduction of exacerbations which are largely of infectious etiology.	- Subjects with a positive hepatitis B surface antigen or core antibody or hepatitis C antibody at Screening (Visit 1A). - Active or latent tuberculosis infection. Protocol exclusion criteria: - Suspicion of, or confirmed, COVID-19 infection or in contact with a known exposure to COVID-19 at Screening (Visit 1A) or during the screening period; known history of COVID-19 infection within 4 weeks prior to Screening (Visit 1A); history of requiring mechanical ventilation or ECMO secondary to COVID-19 within 3 months prior to Screening (Visit 1A); participants who have had a COVID-19 infection prior Screening (Visit 1A) who have not yet sufficiently recovered to participate in the rigors of a clinical trial. Monitoring and Management: Participants should be monitored for any signs or symptoms of a SARS-CoV-2 infection and tested/treated as per local/international guidelines. Itepekimab/placebo can temporarily be withheld after a confirmed symptomatic SARS-CoV-2 infection based upon clinical judgement, and guidelines for resumption of therapy must be followed as per clinical protocol (Section 7.2). Similar to all participants with COPD, it is important to minimize the risk of exposure of participants to SARS-CoV-2 at the site, following prevention and mitigation guidelines.

Study intervention(s) Itepekimab

Study procedures

None

Other

None

ADA = antidrug antibody; AESI = adverse event of special interest; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus; IMP = investigational medicinal product; IV = intravenous; PK = pharmacokinetic(s); Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

2.3.2 Benefit assessment

In Study ACT15104, in the overall study population, itepekimab reduced the risk of experiencing moderate-to-severe AECOPD compared to placebo by 19.2% over a treatment period of up to 52 weeks, although the difference did not reach statistical significance (RR: 0.808, 95% CI 0.613 to 1.065; p=0.1296). One of the prespecified subgroup analyses conducted in this study was by smoking status, where a clear effect was seen in former smokers. The data suggest that active

smoking ameliorated the efficacy of itepekimab. In this analysis, itepekimab demonstrated an RRR in former smokers compared to placebo in moderate-to-severe AECOPD of 42.5% (RR 0.575, 95% CI 0.388 to 0.853, nominal $p=0.0061$). This effect was consistent across a number of subgroups within the former smoker population, including subgroups by controller therapy (double [ICS + LABA, ICS + LAMA, or LABA + LAMA] or triple [ICS + LABA + LAMA] therapy) and regardless of blood eosinophil level or CAT score at baseline. Improvement in FEV1 was also seen in former smokers, specifically among those with blood eosinophil counts ≥ 250 cells/ μ L. These results contrast with the results in the current smoker population. In that population, itepekimab did not demonstrate a reduction in the rate of moderate-to-severe AECOPD (-9.4%, RR 1.094, 95% CI 0.743 to 1.612, nominal $p=0.6472$), and consistent with this finding, did not demonstrate any benefit in other endpoints evaluated in the study. The results of Study ACT15104 support continued evaluation of itepekimab as a potential agent for treatment of moderate-to-severe COPD in participants who are former smokers.

In the PoC study in participants with moderate-to-severe asthma not well controlled on ICS + LABA therapy (ACT15102), itepekimab 300 mg Q2W monotherapy or coadministered with dupilumab 300 mg Q2W significantly reduced the odds of experiencing loss of asthma control (LOAC) and improved pre-BD FEV1 compared with that for placebo.

The objectives of the current study are 1) to further evaluate the efficacy and assess the safety and tolerability of itepekimab 300 mg administered SC Q2W or Q4W as compared to placebo in moderate-to-severe COPD participants who are former smokers and are in need of an additional treatment added to their current COPD management, and 2) to further characterize the efficacy and safety of itepekimab, using a dose regimen of itepekimab 300 mg administered SC Q2W compared to placebo over one year in participants with COPD who are current smokers.

The placebo arm is appropriate for the objectives of this study. Having a placebo group will provide the most robust assessment of the efficacy and safety of itepekimab. As all participants included in the study must be on a stable controller double or triple therapy (containing LAMA + LABA, ICS + LABA, or LAMA + LABA + ICS) for COPD, participants in the placebo arm are not limited to placebo treatment only.

2.3.3 Overall benefit: risk conclusion

Taking into account measures to minimize risk to study participants, the potential risks identified in association with itepekimab are justified by the anticipated benefits for the overall population that may be afforded to participants with moderate-to-severe COPD. The results from the PoC study (ACT15104) suggest that itepekimab may not be beneficial for participants with COPD who are current smokers. However, due to relatively small number of current smokers in the PoC study (ACT15104), the current study will help to understand better the efficacy and safety of itepekimab in participants with COPD participants who are current smokers, and to confirm whether there is no relevant efficacy.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints/Estimands
Primary population (former smokers cohort)	
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 52-week placebo-controlled treatment period - The primary estimand will be a treatment policy/ while-on-treatment policy estimand (see Section 9.4.2).
Secondary	
- 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 occurrence of AECOPD in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on severe AECOPD in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on corticosteroid-treated AECOPD in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on respiratory symptoms in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo on FEV1 slope in former smokers with moderate-to-severe COPD - Evaluate the efficacy of itepekimab compared with placebo HRQoL as assessed by SGRQ in former smokers with moderate-to-severe COPD - Evaluate the safety and tolerability of itepekimab in former smokers with moderate-to-severe COPD - Evaluate the PK profile of itepekimab 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 - Time to first moderate-or-severe AECOPD over the over the placebo-controlled treatment period - Annualized rate of severe AECOPD over the placebo-controlled treatment period - Time to first severe AECOPD over the placebo-controlled treatment period - Annualized rate of corticosteroid-treated AECOPD over the placebo-controlled treatment period - Change from baseline in E-RS:COPD total score at Week 24 and at Week 52 - Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4-12 weeks - 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 - Incidence of TEAEs, AESIs, SAEs, and AEs leading to permanent treatment discontinuation - Incidence of potentially clinically significant laboratory test, vital signs, and ECG abnormalities in the treatment-emergent period - Functional itepekimab concentrations in serum from baseline to end of study

Objectives	Endpoints/Estimands
Evaluate immunogenicity to itepekimab in former smokers with moderate-to-severe COPD	Incidence of treatment-emergent anti-itepekimab antibodies responses throughout the study
Secondary population (current smoker cohort)	
- Estimate 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 - Estimate the efficacy of itepekimab compared with placebo on pulmonary function in current smokers with moderate-to-severe COPD - Estimate the safety and tolerability of itepekimab in current smokers with moderate-to-severe COPD - Estimate the PK profile of itepekimab in current smokers with moderate-to-severe COPD - Estimate immunogenicity to itepekimab in current smokers with moderate-to-severe COPD	- Annualized rate of moderate-or-severe acute exacerbation of COPD (AECOPD)^a 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
Primary population (former smokers cohort)	
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 ≥100mL 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/Estimands
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 will be recorded by the Investigator and are defined as acute worsening of respiratory symptoms that require either systemic corticosteroids (such as intramuscular, intravenous, or oral) and/or antibiotics. Severe exacerbations will be recorded by the Investigator and are defined as AECOPD that require hospitalization, observation for >24 hours in an emergency department/urgent care facility, or result 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 the PGIS, PGIC, and EQ-5D-5L will be described in the SAP.

3.1 APPROPRIATENESS OF MEASUREMENTS

The primary and key secondary efficacy and safety assessments used in this study are standard for the evaluation of therapy in participants with COPD, and have been used or are being used in similar designed Phase 3 studies using mepolizumab, benralizumab and dupilumab (NCT03930732) (34, 36).

4 STUDY DESIGN

4.1 OVERALL DESIGN

EFC16819 is a multinational, randomized, double-blind, placebo-controlled, parallel-group, 52-week, Phase 3 study to evaluate the efficacy and assess the safety and tolerability of 2 dosing regimens of itepekimab in a cohort of participants with moderate-to-severe COPD who are former smokers (primary population). All participants are on an established triple or double background controller therapy (containing LAMA + LABA + ICS, LAMA + LABA or ICS + LABA). Study treatments are itepekimab 300 mg Q2W, itepekimab 300 mg Q4W, or matching placebo administered during the 52-week treatment period for the first approximately 930 randomized former smoker participants and during a potential variable 24-to-52-week treatment period for any subsequent randomized former smoker participants (following an adaptive sample size increase described in [Section 9.2](#)). Former smoker participants enrolled into the potential variable 24-to-52-week treatment period will remain in the treatment period for a maximum of 52 weeks or until the last former smoker randomized completes a minimum treatment period of 24 weeks. Another single dosing regimen of itepekimab 300 mg Q2W or matching placebo will be tested in a cohort of participants with moderate-to-severe COPD who are current smokers (secondary population) during a 52-week treatment period. The treatment period will be followed by a 20-week safety follow-up period for participants not transitioning to the LTS18133 study.

The primary endpoint is the annualized rate of moderate-or-severe AECOPD over the placebo-controlled treatment period in former smokers. Moderate exacerbations will be recorded by the Investigator and are defined as acute worsening of respiratory symptoms that require either systemic corticosteroids (such as IM, IV, or oral) and/or antibiotics. Severe exacerbations will be recorded by the Investigator and are defined as AECOPD that require hospitalization, observation for >24 hours in an emergency department/urgent care facility or result in death. For both moderate and severe events to be counted as 2 separate events, they must be separated by at least 14 days between any course of systemic steroids/antibiotics or 14 days between discharge and new admission in case of hospitalization (severe events only).

For efficacy endpoint analysis, the main analysis population will be the ITT population of the former smokers cohort (see [Section 9.3](#)). The efficacy analysis of subgroups defined by baseline characteristics will be detailed in the SAP. In addition to the analysis in the current study, statistical analysis for subgroup with triple controller therapy only at baseline will be further conducted using the pooled data of Study EFC16750 and Study EFC16819, and the details will be provided in the SAP.

Separate randomizations will be performed for the former smokers cohort, which will be the primary population, and the current smokers cohort, which will be the secondary population; randomization will be stratified (IVRS/IWRS) by country (some countries might be pooled together), screening blood eosinophil counts (<300 cells/mm³ or ≥ 300 cells/mm³), and controller therapy (double or triple) only at baseline. During the randomization procedure, the eosinophil count at Screening (Visit 1A) must be entered in the interactive response technology (IRT) system. The unit used is/mm³ (eg, 420/mm³); this is important for correct stratification. The

number of participants enrolled into each stratification group will be controlled and monitored as follows:

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

In all participants on double therapy, the reasons for use of double therapy will be obtained and documented in the eCRF.

The study duration is outlined below:

- Screening period (3-5 weeks).
- Placebo-controlled treatment period (52 weeks for the first randomized former smoker participants [approximately n=930] and current smokers [approximately n=280], 24 to 52 weeks for potential additional randomized former smoker participants).
- Post-IMP treatment follow-up period (20 weeks), for participants not transitioning to the LTS18133 study.

Participants must have been on a SoC controller therapy for COPD for at least 3 months prior to Screening (Visit 1A) with a stable dose for controller therapy for ≥ 1 month prior to Screening (Visit 1A) and during the screening period. Participants must stay on their established controller medication for COPD throughout the duration of the study, with the exception of systemic steroids and antibiotics used for AECOPD.

Former smoker participants who satisfy the eligibility criteria will be randomized (1:1:1) to one of the following IMP treatment groups to be administered for up to 52 weeks (study duration as described above):

- Itepekimab 300 mg, administered as a single SC injection Q2W.
- Itepekimab 300 mg, administered as a single SC injection Q4W with alternating SC injection of matching placebo at the 2-week interval between active IMP.
- Placebo matching to itepekimab, administered as a single SC injection Q2W.

Current smoker participants who satisfy the eligibility criteria will be randomized (1:1) to one of the following IMP treatment groups to be administered for up to 52 weeks:

- Itepekimab 300 mg, administered as a single SC injection Q2W.
- Placebo matching to itepekimab, administered as a single SC injection Q2W.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, placebo-controlled study design where the effects of the IMP is assessed on top of SoC background therapy is considered to be the most appropriate design to examine the efficacy and safety of a novel biologic therapy in COPD. Annualized rate of moderate-to-severe AECOPD was selected as the primary endpoint as it is generally considered to be the most clinically relevant

outcome in COPD. Chronic obstructive pulmonary disease exacerbations have major short-term and long-term effects on patients and are an important measure of the clinical burden of COPD. They determine disease-associated morbidity, mortality, resource burden and healthcare costs. Exacerbations in patients with COPD are also associated with more rapid disease progression (rate of lung function decline over time). Severe exacerbations account for the majority of hospital admissions. They may be associated with acute respiratory failure which is an important predictor of mortality (Global Initiative for Chronic Obstructive Lung Disease [GOLD]). Hospitalizations, which are driven by exacerbations, are the largest contributor to COPD-related healthcare expenditure in major European Union (EU) countries, representing up to 54% of total direct costs. Similar study designs and endpoints have been employed for recent studies with other biologics and are considered “state-of-the-art” for studies in COPD (NCT03930732) (34, 36). The selection of the dose of IMP is explained in Section 4.3. The presence of a placebo arm is appropriate for the objectives of this study, as it will provide the most robust assessment of the efficacy and safety of itepekimab. The 1-year duration of this study allows for assessment of the broad range of short-term and mid-term effects itepekimab may have on AECOPD, lung function, HRQoL, and symptom control, while reducing the impact of seasonal variations observed in exacerbations.

This study includes an inclusion criterion stating that a smoking history of 10 pack-years is a requirement for inclusion (I 03) for both former and current smokers. The reason for this is that because tobacco smoke is the key factor in the development and progression of COPD, allowing patients in the study who have no substantial smoking history will likely increase the heterogeneity of the patient population. However, there is no reason to believe itepekimab will work differently in patients with COPD with former exposure by eg, biomass fuel combustion. In the ACT15104 PoC study, the definition of ‘former’ smoker was a participant with a smoking cessation date ≥ 8 days prior to screening. However, the majority of participants quit smoking long time before enrolling in the study (mean smoking cessation: 11.8 years prior to screening). A post-hoc analysis of the ACT15104 study data using a definition of former smokers as those with a smoking history of ≥ 10 pack-years and a smoking cessation date > 6 months prior to screening (n=178), compared to the inclusion criterion of former smokers with a smoking cessation date ≥ 8 days prior to screening (n=187), was performed and yielded similar results. For the current study a smoking cessation of ≥ 6 months prior to screening for former smokers was chosen because on the one hand it is generally believed that majority of reversible alteration in the lung has a recovery period of a few weeks after smoking cessation. (39, 40) On the other hand, the risk of resuming smoking after smoking cessation is the highest shortly after cessation and reduces over time. Six months of abstinence is generally considered to be a reasonable estimate of life-long abstinence (41).

Based on the inclusion criteria for this study, all study participants will meet criteria for “Group D COPD” according to GOLD 2020 guidelines. The GOLD guidelines recommend one of the following regimens for initial management of Group D participants: LAMA monotherapy, LABA + LAMA double therapy, or ICS + LABA double therapy. Clinicians are guided to select a regimen that is tailored to each individual participant. For example, participants who have severe symptoms (eg, CAT score ≥ 20), LABA + LAMA may be appropriate as initial therapy instead of LAMA monotherapy. Alternatively, for participants with blood eosinophil counts ≥ 300 cells/ μ L, ICS + LABA is recommended as initial therapy. Also in follow-up pharmacological treatment either early after initial treatment or after years of follow-up, double therapy (LABA + LABA or ICS + LABA), either with or without roflumilast or azithromycin are

recommended treatment options besides triple therapy after the participant has experienced 1 or more new exacerbations. Secondly, some participants might have AEs or contraindications associated with ICS, LABA, or LAMA and can therefore not be treated with triple therapy. Therefore, the study will allow for the use of triple or double controller therapy. In all participants on double therapy, the reasons for use of double therapy will be obtained and documented in the eCRF. Secondly, the number of participants on double therapy is limited up to approximately 35% (see [Section 4.1](#)). After 1 severe or 2 moderate exacerbations of COPD, adjustments in baseline controller therapy will be permitted for symptom control and as needed for the remainder of the study period and will be documented. If these conditions are met, a step up from double therapy to triple therapy is allowed, if needed.

4.2.1 Participant input into design

A participant input meeting took place in February 2020. During these interactions, the design and endpoints were discussed with a participant as well as a representative from the US COPD foundation. Prior to this, a participant advisory panel was organized in April 2018 related to the EFC15804 study of dupilumab in COPD of similar design (NCT03930732). This feedback was revisited too. Among other minor textual changes to the protocol, home administration was endorsed by the participant input and was included as an option for visits from Week 6 onwards in the current protocol.

4.3 JUSTIFICATION FOR DOSE

The dose regimen of itepekimab 300 mg SC Q2W was well-tolerated in Phase 2 clinical studies when administered for 12 weeks in participants with moderate-to-severe asthma (Study ACT15102; itepekimab 300 mg Q2W [N=73], itepekimab Q2W + dupilumab Q2W [N=74]) and for 24 to 52 weeks in participants with moderate-to-severe COPD (Study ACT15104; n=172). In participants with moderate-to-severe asthma, itepekimab 300 mg Q2W monotherapy demonstrated a significant reduction in LOAC (primary endpoint) and a significant improvement in pre-BD FEV1 (secondary endpoint) compared with that for placebo at Week 12 in the overall population (Study ACT15102). In former smokers with moderate-to-severe COPD but not in current smokers with COPD, itepekimab 300 mg Q2W demonstrated a substantial and nominally significant reduction in the risk of experiencing a moderate-or-severe AECOPD and a meaningful and nominally significant improvement in pre-BD FEV1 compared with that for placebo (Study ACT15104).

The itepekimab pharmacokinetic (PK) profile in healthy subjects, participants with asthma, and participants with COPD is described by a 2-compartment population PK (Pop PK) model with first order absorption and linear elimination. Body weight was the primary factor responsible for itepekimab PK variability in which higher body weight was associated with faster clearance of drug. In a preclinical pharmacology study, a concentration of ■■■ mg/L was shown to be associated with maximum in vivo efficacy in a chronic exposure to HDM asthma model in mice.

Based on the totality of clinical data and the PK and PK-PD analysis results, 2 dosing regimens of itepekimab 300 mg Q2W and itepekimab 300 mg Q4W for the Phase 3 program in participants with COPD who are former smokers were selected. The 300 mg Q2W regimen provided substantial efficacy in the former smoker population in Study ACT15104 and was selected for use in the current study for confirmation. Both dose regimens of 300 mg SC Q2W and Q4W are expected to achieve a mean [REDACTED]

[REDACTED]. Based on this information, the less frequent dosing regimen may provide a similar benefit/risk ratio in the former smoker COPD participants. For current smokers, only 300 mg Q2W dose regimen is included to replicate the ACT15104 study dose.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study.

The end of the study is defined as the date of the EOS Visit of the last participant in the study, except for participants who transition to the LTS18133 study. For participants who enter the LTS18133 study, the last visit in this study will be the EOT Visit (Visit 28).

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 40 to 85 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with a physician diagnosis of COPD for at least 1 year (based on GOLD definition (15)).

I 03. Participants with a smoking history of ≥ 10 pack-years,

- For former smokers: participants who report that they are not currently smoking and smoking cessation must have occurred ≥ 6 months prior to Screening (Visit 1A) with an intention to quit permanently. Note: Urine cotinine levels will be tested at Screening (Visit 1A) and each subsequent visit during the study. Please see E 02.
- For current smokers: participants who report that they are currently smoking tobacco (participant smoked at least 1 cigarette per day on average during the past 7 days) at Screening (Visit 1A) and who are not currently participating in or planning to initiate a smoking cessation intervention at Screening (Visit 1A) or during screening period.

I 04. Participants with moderate to severe COPD with post-BD FEV1/FVC ratio < 0.70 and a post-BD FEV1 % predicted $\geq 30\%$ and $< 80\%$ at Screening (Visit 1A) and at Baseline/Randomization (Visit 2).

I 05. Participants with COPD Assessment Test (CAT) score ≥ 10 at Screening (Visit 1A) and Baseline/Randomization (Visit 2).

I 06. Participant-reported history of signs and symptoms of chronic bronchitis (chronic productive cough for at least 3 months in the year prior to screening in a participant in whom other causes of chronic cough [eg, inadequately treated gastroesophageal reflux or chronic rhinosinusitis; or clinical diagnosis of bronchiectasis] has been excluded).

I 07. Participants with a documented history of high exacerbation risk defined as having had ≥ 2 moderate or ≥ 1 severe exacerbations within the year prior to Screening (Visit 1A), with at least 1 exacerbation treated with systemic corticosteroids. At least 1 exacerbation must have occurred while participants were on their current controller therapy:

- Moderate exacerbations will be recorded by the Investigator and are defined as acute worsening of respiratory symptoms that requires either systemic corticosteroids

(IM, IV, or oral) and/or antibiotics (however, use of antibiotics alone does not qualify as a moderate exacerbation unless documentation is available that use of antibiotics was necessary for treatment of worsening symptoms of COPD).

- Severe exacerbations will be recorded by the Investigator and are defined as AECOPD that require hospitalization or observation for >24 hours in emergency department/urgent care facility.

I 08. Participants with SoC controller therapy, for ≥ 3 months prior to Screening (Visit 1A) and at a stable dose of controller therapy for at least 1 month prior to the screening AND during the screening period, including either:

- Double therapy: LAMA + LABA or ICS + LABA
OR
- Triple therapy: LAMA + LABA + ICS.

Weight

I 09. Body mass index (BMI) ≥ 18.0 kg/m² or BMI ≥ 16.0 kg/m² for participants enrolled in East-Asian countries (Japan, South Korea, Singapore, China including Taiwan and Hong-Kong).

Sex

I 10. Male or female

- a) Male participants: No contraceptive measures required for this study.
- b) Female participants: Contraceptive use by WOCBP should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4], not breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP as defined in Appendix 4 (Section 10.4).
OR
- A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the intervention period and for at least 20 weeks after the last dose of study intervention.

Informed Consent

I 11. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

- E 01. Participants with current diagnosis of asthma according to the Global Initiative for Asthma (GINA) guidelines, or documented history of asthma unless asthma resolved before 18 years of age and has not recurred.
- E 02. For former smokers: Active smoking or vaping of any products (eg, nicotine, tetrahydrocannabinol [THC]) within 6 months prior to Screening (Visit 1A). Former smokers only: Participants with a confirmed positive cotinine test at Screening (Visit 1A) or Baseline/Randomization (Visit 2), in the absence of nicotine replacement therapy (NRT) with negative anabasine test at Screening (Visit 1A), are to be excluded from the study.

For current smokers: vaping of any products (eg, nicotine, [THC]) within 6 months prior to Screening (Visit 1A).
- E 03. Clinically significant new abnormal electrocardiogram (ECG) within 6 months prior to, or at Screening (Visit 1A) that may affect the participant's participation in the study in the judgment of the Investigator.
- E 04. Clinically significant and current pulmonary disease other than COPD, eg, sarcoidosis, interstitial lung disease, bronchiectasis (clinical diagnosis), diagnosis of α -1 anti-trypsin deficiency, or another diagnosed pulmonary disease.
- E 05. Diagnosis of cor pulmonale, evidence of right cardiac failure, or moderate-to-severe pulmonary hypertension.
- E 06. Long-term treatment with oxygen >4.0 L/min *OR* if a participant requires more than 2.0 L/min in order to maintain oxygen saturation $>88\%$.
- E 07. Hypercapnia requiring bilevel positive airway pressure (BiPAP).
- E 08. Moderate-or-severe exacerbation of COPD (AECOPD, as defined above in [I 07](#)) within 4 weeks prior to Screening (Visit 1A) or during the screening period.
- E 09. Prior history of/planned: lung pneumonectomy for any reason, or lung volume reduction procedures (including bronchoscopic volume reduction) for COPD.

Note: Surgical biopsy, segmentectomy, wedge resection, or lobectomy for other diseases would not be excluded.
- E 10. Participants with a history of clinically significant renal, hepatic, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, or other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. A specific example includes, but is not limited to, poorly controlled insulin- dependent diabetes.

- E 11. Unstable ischemic heart disease, including acute myocardial infarction within the past 1-year prior to Screening (Visit 1A), or unstable angina in the 6 months prior to Screening (Visit 1A), or during the screening period.
- E 12. Cardiac arrhythmias including paroxysmal (eg, intermittent) atrial fibrillation, are excluded. Note: Participants with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (ie, selective β blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) and stable appropriate level of anticoagulation for at least 6 months, may be considered for inclusion. Note: Participants with isolated premature ventricular contractions (PVCs) or premature atrial contractions (PACs) may be considered for inclusion.
- E 13. Cardiomyopathy, as defined by Stage III-IV (New York Heart Association) cardiac failure, or other relevant cardiovascular disorder that in Investigator's judgment may put the participant at risk or affect the study.
- E 14. Uncontrolled hypertension (ie, systolic blood pressure [BP] >180 mm Hg or diastolic BP >110 mm Hg with or without use of anti-hypertensive therapy).
- E 15. Participants with active tuberculosis (TB), latent TB, a history of incompletely treated TB, suspected extrapulmonary TB infection (TBI), or who are at high risk of contracting TB (such as close contact with individuals with active or latent TB) or received Bacille-Calmette-Guérin (BCG)-vaccination within 12 weeks prior to Screening (Visit 1A). (See Appendix 2 [[Section 10.2](#)]).

Note: TB testing is mandatory to rule out active/latent TB and should be performed and assessed according to local guidelines. If no local guidelines are available or are not able to be performed at the site, a blood sample for Quantiferon testing should be sent to the central laboratory. Participants with confirmed positive TB test are excluded from the study unless all of the following conditions are met:

- Have a history of prior documented completed chemoprophylaxis for latent TBI (with a treatment regimen as per local guidelines), OR treated for active TBI,

AND

- Have obtained consultation with a specialist to rule out or treat active TBI,

AND

- For whom review and approval from Sponsor have been granted are eligible.

- E 16. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at Screening (Visit 1A).
- E 17. Participants with any of the following result at Screening (Visit 1A): Positive (or indeterminate) hepatitis B surface antigen (HBsAg) or positive IgM hepatitis B core antibody (HBcAb) or positive total hepatitis B core antibody (HBcAb) confirmed by positive hepatitis B virus (HBV) deoxyribonucleic acid (DNA) or positive hepatitis C virus total antibody (HCVAb) confirmed by positive hepatitis C virus (HCV) ribonucleic acid (RNA).

- E 18. Suspicion of, or confirmed, coronavirus disease 2019 (COVID-19) infection or in contact with known exposure to COVID-19 at Screening (Visit 1A) or during the screening period; known history of COVID-19 infection within 4 weeks prior to Screening (Visit 1A); history of requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) secondary to COVID-19 within 3 months prior to Screening (Visit 1A); participants who have had a COVID-19 infection prior Screening (Visit 1A) who have not yet sufficiently recovered to participate in the procedures of a clinical trial.
- E 19. Diagnosed active parasitic infection (eg, helminth), suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.
- E 20. Evidence of acute or chronic infection requiring systemic treatment with antibacterial, antiviral, antifungal, antiparasitic, or antiprotozoal medications within 4 weeks before Screening (Visit 1A) or during the screening period, significant viral infections within 4 weeks before Screening (Visit 1A) or during the screening period that may not have been treated with antiviral treatment (eg, influenza receiving only symptomatic treatment).
- E 21. Participants with active autoimmune disease or participants using immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis).
- E 22. History of malignancy within 5 years before Screening (Visit 1A), or during the screening period, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.
- E 23. Participants with a history of a systemic hypersensitivity reaction to a mAb.
- E 24. Known allergy to itepekimab excipients.
- E 25. Clinically significant laboratory tests at Screening (Visit 1A):
- Alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) >2 times upper limit of normal range (ULN).
 - Hemoglobin <10 g/100 mL for male and <9 g/100 mL for female.
 - Neutrophils <1500/mm³ (<1000/mm³ for those of African descent).
 - Platelets <100 000/mm³.
 - Creatinine ≥150 µmol/L.

Prior/concomitant therapy

- E 26. Previous use of itepekimab.
- E 27. Live-attenuated vaccine(s) within 4 weeks prior to Screening (Visit 1A) or plans to receive such vaccines during the study (see Appendix 9 [[Section 10.9](#)]).

- E 28. Anti-IgE therapy (eg, omalizumab) within 130 days prior to Screening (Visit 1A) or any other immune-directed biologic therapy (eg, anti-IL5, anti-IL5R, anti-IL4ra, etc) or systemic immunosuppressant (eg, methotrexate, any anti-tumor necrosis factor [TNF] mAbs, B- and/or T- cell targeted immunosuppressive therapies, janus kinase [JAK] inhibitors) within 2 months or 5 half-lives prior to Screening (Visit 1A), whichever is longer.
- E 29. Exposure to another investigative drug (monoclonal antibodies as well as small molecules) prior to Screening (Visit 1A), within the period specified as follows: an interval of less than 6 months or <5 PK half-lives for investigative monoclonal antibodies, and an interval of less than 30 days or <5 PK half-lives, whichever is longer, for investigative small molecules.
- E 30. Initiation of allergen immunotherapy within 3 months prior to Screening (Visit 1A), or a dose change from 1 month prior to Screening (Visit 1A), or a plan to begin allergen immunotherapy, or to change its dose during the screening period or the randomized treatment period.
- E 31. Participants requiring nonselective β -1 adrenergic receptor blockers for any reason. Participants receiving medications or therapy that are prohibited as concomitant medications.
- E 32. Prohibited medications (see [Section 6.5](#)) within 4 weeks before Screening (Visit 1A) or during the screening period.

Note: The following concomitant medications are prohibited (other than those covered by other exclusion criteria):

- Systemic steroids (except systemic steroids to treat acute COPD exacerbations).
- Roflumilast (unless on stable therapy for >6 months prior to Screening [Visit 1A]).
- Macrolides (eg, azithromycin) therapy (unless on stable therapy for >6 months prior to Screening [Visit 1A]).
- Methylxanthines (eg, theophylline, aminophylline).
- Lipxygenase inhibitors.
- Cromones.
- Leukotriene receptor antagonists (LTRA).
- IVIG therapy.

Other exclusions

- E 33. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.
- E 34. Any country-related specific regulation that would prevent the participant from entering the study (see Appendix 8 [[Section 10.8](#)]).
- E 35. Participants not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

- E 36. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation [ICH])-Good Clinical Practice [GCP] Ordinance E6).
- E 37. Any specific situation during study implementation/course that may raise ethics considerations.
- E 38. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.3.1 Meals and dietary restrictions

Not applicable.

5.3.2 Caffeine, alcohol, and tobacco

For former smokers, use of tobacco products will not be allowed from 6 months prior to Screening (Visit 1A) until after the final follow-up visit. If abstinence is difficult for the participants, the participants may seek medical help and receive supportive treatment with NRT. For all study participants, vaping is not allowed from 6 months prior to Screening (Visit 1A). One hour prior to spirometry the current smoker participant should refrain from smoking. Use of alcohol and caffeine is allowed. However, 8 hours prior to spirometry, no alcohol should be consumed (for details, refer [Section 8.1.1.2](#)).

5.3.3 Activity

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Participants who are eligible for rescreening may be rescreened once for any reason, except for failing to meet [I 04](#) (spirometry), which will lead to screen failure. Participants who fail any of the other inclusion or meet any exclusion criteria may be rescreened during the open screening period

of the study; a different participant identification number will be issued. There is no requirement for a waiting period between the screen-failure date and the rescreen.

In the case of technical malfunction of equipment during spirometry, the participant may be rescreened. A participant who is unable to complete a successful spirometry effort as defined by ERS/ATS criteria can be retested one additional time during the screening period of the study. If a participant is unable to perform an attempt of adequate quality 2 times in a row, it needs to be assessed if the participant is good candidate for the study. A participant who fails to meet [I 04](#) during a successful spirometry effort as defined by ERS/ATS, cannot be rescreened.

If certain dynamic laboratory tests do not meet the inclusion criteria at Screening (Visit 1A), these laboratory assessments may be repeated, at the discretion of the Investigator, if the parameter result is judged to be likely to return to acceptable range for study inclusion within the screening period prior to Baseline/Randomization (Visit 2). There is no need to screen fail such participants if the test finally meets the inclusion criteria. Re-testing of blood eosinophil values is allowed up to three times during the screening period to meet inclusion criteria for showing blood eosinophil count <300 or ≥ 300 cells/mm³ before randomization, ie, in case of premature stratum closure.

It is intended to include approximately 65% of participants with blood eosinophils <300 cells/mm³ and 35% of participants with blood eosinophils ≥ 300 cells/mm³ in each of the 2 cohorts (former smoker cohort [primary population] and current smoker cohort [secondary population]). By including approximately 35% of participants with high blood eosinophils, it is expected to have adequate power to evaluate treatment effects in this important subgroup of COPD participants. If one of the stratification groups is filled, the IRT will close enrollment in this group. As other studies are recruiting participants with blood eosinophils ≥ 300 cells/mm³, there will be increased competition for this subset of participants. Having this control measure in place, this should guarantee sufficient number of participants in both blood eosinophil count subgroups. Participants who are in the screening period at that moment will not be guaranteed randomization, even if they meet all inclusion criteria and none of the exclusion criteria, because over recruitment will not be allowed. New participants should be prescreened based on their historical eosinophil value that needs to be confirmed at Screening (Visit 1A). Retesting of the eosinophil count is allowed up to 3 times during the screening period if needed. If a participant does not finally meet the required eosinophil count before randomization the participant should be screen failed. It is intended to include up to approximately 35% of participants on double controller therapy (LAMA + LABA or ICS + LABA). The site will receive updates related to both caps. Once this stratification group is filled, the enrollment will be closed in this group. Screened participants on double controller therapy should be screen failed and new participants should be prescreened for controller therapy.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION

For exceptional emergency situations (examples are provided in Appendix 19) where the site is unable to adequately follow protocol-mandated procedures, contingency measures proposed in Appendix 19 ([Section 10.19](#)) should be considered for temporarily delaying screening/enrollment/randomization/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

The IMP is to be administered every 14 ± 3 days (Q2W: former and current smokers) (up to 26 doses) or 28 ± 3 days (Q4W: former smokers only) (up to 13 doses) with placebo injection in between during the 52-week treatment period (Table 3). Each prefilled syringe contains a deliverable volume of 2 mL with an itepekimab concentration of 150 mg/mL (active) or 0 mg/mL (placebo).

The IMP will be administered by the Investigator/designee, participants/caregivers (under the supervision of the investigator/delegate or after sufficient training), or health care professional (in case of exceptional circumstances) following clinic procedures and blood collection (if applicable). Participants should be monitored for at least 30 minutes after administration of all IMP injections. The monitoring period may be extended as per country specific or local site-specific requirements.

The SC injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive visits.

To train participants or their caregivers how to prepare and inject IMP the Investigator will first train the participant at an on-site visit during the treatment period. At this visit, the participant will perform the injection under the supervision of the Investigator or delegate. At subsequent study visits, participants will be trained to self-inject IMP or caregivers will be trained to inject IMP to the participant, and they are allowed to inject IMP at home after a minimum of 2 self-administered injections at investigational site from Visit 5 (Week 6) onwards. All training shall be documented in the participant's study file as well as the determination and clearance for the participant's and/or caregiver's to complete an injection at home. Prior to Visit 5 (Week 6) injections cannot be administered at home by a participant or caregiver, but in exceptional circumstances this will be allowed by a health care professional. The participant or caregiver should only perform the injection in the abdomen or upper thighs. The caregiver can perform the injection in upper thighs, the abdomen and upper arms. The site of administration during the previous site visit should be taken into consideration (the same site should not be injected twice during consecutive visits). The participant or caregiver should also be instructed to monitor for any reaction for at least 30 minutes following injection (or longer per country specific or local site-specific requirements). The start date for home administration by participant or caregiver can be postponed temporarily or indefinitely if this is considered necessary by the Investigator or preferred by the participant or caregiver. In that case, the participant will be asked to return to the investigational site for their IMP injections or have IMP administered by a home nurse (if appropriate).

The DTP supply of itepekimab/placebo from the Sponsor to the participant can be used, where allowed by local regulations and agreed upon by the participant.

For doses not given at the study site, electronic diary (eDiary) will be provided to record information related to the injections. The eDiary will be kept as source data in the participant's study file. During scheduled telephone contacts as per SoA, the site should verify the IMP compliance/administrations with the participant and at next on-site visit check the completed eDiary.

Table 3 - Overview of study interventions administered

ARM name	300 mg Q2W	300 mg Q4W	Placebo
Intervention name	Itepekimab	Itepekimab	Placebo matching itepekimab
Type	Biologic	Biologic	Biologic
Dose formulation	prefilled syringe	prefilled syringe	prefilled syringe
Unit dose strength(s)	150 mg/mL	150 mg/mL	0 mg/mL
Dosage level(s)	300 mg Q2W	300 mg Q4W with alternating placebo administration at the 2-week interval between active IMP	0 mg/mL Q2W
Route of administration	SC injection	SC injection	SC injection
Use	experimental	experimental	placebo-comparator
IMP and NIMP	IMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in prefilled syringes. Each prefilled syringe will be labeled as required per country requirement.	Study intervention will be provided in prefilled syringes. Each prefilled syringe will be labeled as required per country requirement.	Study intervention will be provided in prefilled syringes. Each prefilled syringe will be labeled as required per country requirement.
Current name	Itepekimab	Itepekimab	Not applicable
Targeted cohort(s)	Former + Current smoker cohort	Former smoker cohort only	Former + Current smoker cohort

Between the protocol-scheduled on-site visits, interim visits may be required to dispense IMP. As an alternative to these visits, itepekimab may be supplied from the site to the participant via a Sponsor-approved courier company, where allowed by local regulations and agreed upon by the participant. For exceptional emergency situation (examples are provided in Appendix 19) that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 19 ([Section 10.19](#)).

Non-investigational medicinal products

Participants must continue their established controller therapy. Participants must continue the controller therapy regimen and continue to use the same dose (see [Section 6.6](#)).

- Formulation: DPI, MDI, nebulizer.
- Route(s) of administration: oral inhalation for LAMA, LABA, ICS, LAMA + LABA, ICS + LABA, or LAMA + LABA + ICS.
- Dose regimen: As per prescribed (not to be provided by Sponsor).

For other information related to COPD controllers including safety precautions please consult the prescription labels.

6.1.1 Medical devices

Medical devices for therapeutic interventions will not be supplied for this study. Medical devices for diagnostic interventions (eg, spirometry, ECG) are not considered as ‘medical devices’ in the context of this study.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff (or participant/caregiver after formal training) may administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see [Section 8.3.9](#)).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for Direct-to-Participant [DTP] shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will be randomly assigned to a study intervention using a central IRT. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. For screen failures, see [Section 5.4](#). The IVRS will not allow randomization if the applicable stratum or study cohort (former smokers and current smokers) is already full.

Study intervention will be dispensed at the study visits summarized in the schedule of activities (SOA; [Section 1.3](#)).

Returned study intervention should not be redispensed to the participants.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

Methods of blinding

Itepekimab and placebo will be provided in identically matched 2-mL prefilled syringes. To protect the blind, each treatment kit of 2-mL (itepekimab/placebo) glass prefilled syringes will be prepared such that the treatments (itepekimab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number.

In accordance with the double-blind design, study participants, Investigators, and study site personnel will remain blinded to study treatment and will not have access to the randomization scheme or to the IMP content (itepekimab or placebo) except under circumstances described in [Section 6.3](#).

6.4 STUDY INTERVENTION COMPLIANCE

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person who administers the study intervention. During scheduled telephone contacts as per SoA, the site should verify the IMP compliance/administrations with the participant and at next on-site visit check the completed eDiary.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, if medically relevant) that the participant had received within 1-year prior to the time of enrollment or receives during the study must be recorded along with the following details:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The following treatments are not permitted during the screening and treatment periods:

- Any COPD-controller medication other than those used at study entry.

- Systemic steroids (oral or parenteral [IV, IM, SC]), except when used to treat acute COPD exacerbations. Note: 1 short-term course of systemic corticosteroids (up to 6 days) is permitted in the 52-week treatment period, when medically necessary for reasons not related to AECOPD exacerbation, eg, in the case of severe poison ivy exposure. Please also note that intra-articular steroids are considered as systemic steroids.
- New chronic use of macrolide antibiotics (eg, azithromycin) for other conditions except to AECOPD, in which case macrolides may be used up to 28 days. Stable, chronic use for >6 months prior to Screening (Visit 1A) is allowed.
- New use of PDE-4 inhibitors (roflumilast) during the course of the study. Stable, chronic use for >6 months is allowed when started prior to Screening (Visit 1A).
- Methylxanthines (eg, theophylline, aminophylline).
- Lipoxygenase inhibitors.
- Cromones.
- Leukotriene receptor antagonists (LTRA).
- Anti-IL5 or IL5R mAb (eg, benralizumab; mepolizumab).
- Anti-IgE therapy (eg, omalizumab).
- Anti-IL4 receptor mAb (eg, dupilumab).
- Systemic immunosuppressants (eg, methotrexate, any anti-TNF mAbs, B- and/or T-cell targeted immunosuppressive therapies, JAK inhibitors).
- IV Ig therapy.
- Live-attenuated vaccines: refer to the Appendix for List of Prohibited Live-Attenuated Vaccines, Appendix 9 ([Section 10.9](#)).
- β -adrenergic receptor blockers (except for a selective β -1 adrenergic receptor blocker used with dose stable 1 month prior to Screening (Visit 1A)).
- Allergen immunotherapy, except in the case of initiation of allergen immunotherapy 3 months or more and stable dose 1 month or more prior to Screening (Visit 1A).
- Other investigational drugs.
- Lung pneumonectomy or lung volume reduction procedures (excluding lobectomies and resections smaller than lobectomies).
- New nonpharmacologic management, such as pulmonary rehabilitation, except if part of the participant's chronic management program (established for ≥ 8 weeks prior to screening).

The following treatments are not recommended during the study period:

- COPD symptom relievers other than salbutamol/albuterol, levosalbutamol/levalbuterol, ipratropium, or ipratropium/albuterol: In case of use in exceptional circumstances (eg, prescribed by a physician not involved in the study), their use must be documented in the participant's file and reported in the eCRF.

The following is a list of permitted concomitant medications during the study:

- Antihistamines are permitted.
- NRT that is not inhaled (eg, vaping is not allowed in the former and current smoker cohort).
- Ocular, intranasal, and topical corticosteroids.
- Inactivated and other nonlive-attenuated vaccines (including any future nonlive-attenuated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines).

6.5.1 Reliever medicine

The reliever medication will not be dispensed or supplied by the Sponsor.

Participants may administer albuterol/salbutamol, levalbuterol/levosalbutamol, ipratropium, or ipratropium/albuterol as reliever medication as needed during the study.

If a nebulizer is used, the dose administered via nebulizer must be converted by the study staff to puffs using the nebulizer-to-puff conversion factor (Table 4 to Table 6) and entered in the eDiary. For Respimat® no conversion is required.

Salbutamol/albuterol nebulizer, levosalbutamol/levalbuterol nebulizer, and ipratropium nebulizer use will be converted as shown in the following tables:

Table 4 - Conversion of salbutamol/albuterol nebulizer solution dose to number of puffs

Salbutamol/albuterol nebulizer solution -total daily dose (mg)	Number of puffs*
2.5	4
5.0	8
7.5	12
10	16

*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs

Example of salbutamol/albuterol nebulizer-to-puff conversion: Participant received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 AM and 11 AM. Total daily = 7.5 mg or 12 puffs.

Table 5 - Conversion of levosalbutamol/levalbuterol nebulizer solution dose to number of puffs

Levosalbutamol/levalbuterol nebulizer solution -total daily dose (mg)	Number of puffs*
0.63	2
1.25/1.26	4
1.89	6
2.5/2.52	8
3.15	10
3.75/3.78	12
5/5.04	16

*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs

Example of levosalbutamol/levalbuterol nebulizer-to-puff Conversion: Participant received 3 levosalbutamol/levalbuterol nebulizer treatments (1.25 mg/treatment) between 7 AM and 11 AM. Total daily =3.75 mg or 12 puffs.

Table 6 - Conversion of ipratropium or ipratropium/short-acting β -agonists (SABA) nebulizer solution dose to number of puffs

Ipratropium or ipratropium/short-acting β -agonists (SABA) nebulizer solution -total daily dose (mg)	Number of puffs*
0.5	4
1.0	8
1.5	12
2.0	16

*Conversion factor: Ipratropium nebulizer solution (0.5 mg Ipratropium) corresponds to 4 puffs

6.6 DOSE MODIFICATION

No dose modification or interval modification is allowed for IMP. After 1 severe or 2 moderate exacerbations of COPD, adjustments in baseline controller therapy will be permitted for symptom control and as needed for the remainder of the trial period and will be documented. Reliever medication dose and interval may be modified as needed.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

A long-term double-blinded extension study (LTS18133) will be implemented to allow participants in this study to continue receiving active IMP for an additional period.

Only participants completing their End-of-Treatment (Visit 28) after 24-52 weeks of treatment (depending upon time of inclusion) per this study protocol will be offered to participate in the LTS18133 study. Participants having prematurely discontinued IMP or their participation in this study will not be eligible for LTS18133 study. Participants who completed their end-of-treatment visit (Visit 28) prior to approval of the protocol amendment 02 for EFC16819, and local approval of the LTS18133 study will not be eligible for transitioning to the LTS18133 study either.

Availability of treatment extension through participation in the LTS18133 study may differ from country to country and will depend upon local regulations, review and approval by the health authority and the IRB/IEC before the study is initiated.

6.8 TREATMENT OF OVERDOSE

Symptomatic overdose is an AESI (defined in [Section 8.3.8](#)). No antidote is available for itepekimab.

In the event of an overdose (symptomatic or asymptomatic), the Investigator/treating physician should:

1. Contact the Sponsor or Sponsor representative(s) immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Obtain a serum sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Sponsor or Sponsor representative(s) (determined on a case-by-case basis).
4. Document appropriately in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor or Sponsor representative(s) based on the clinical evaluation of the participant.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will have an early treatment discontinuation (ETD) visit with all assessments planned for the EOT Visit. See the SoA for data to be collected at the time of discontinuation of study intervention (see [Section 1.3.1](#)).

Definitive (permanent) discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP whatever the reason.

The participants may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

Participants must be permanently withdrawn from the study treatment for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the participant's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Pregnancy.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Appendix 10 [[Section 10.10](#)]).
- Diagnosis of a malignancy during study, excluding squamous or basal cell carcinoma of the skin.
- Any situation that meets permanent discontinuation rule as outlined in Appendix 6 ([Section 10.6](#)).
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (Appendix 11 [[Section 10.11](#)]).

- Serum alanine aminotransferase (ALT) $>3 \times$ upper limit of normal (ULN) and total bilirubin >2 ULN (see Appendix 6 [Section 10.6]).
- Serum ALT $>5 \times$ ULN if baseline ALT $\leq 2 \times$ ULN or ALT $>8 \times$ ULN if baseline ALT $>2 \times$ ULN (see Appendix 6 [Section 10.6]).

See the SoA (Section 1.3.1) for data to be collected at the time of definitive intervention discontinuation and follow-up and for any further evaluations that need to be completed. Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (within 48 hours) before making a decision of definitive discontinuation of the IMP for the concerned participant.

Note: if a former smoker participant, despite strong recommendations, resumes smoking (as indicated by interview and/or urine cotinine testing), this should be reported in the eCRF, but it does not necessitate withdrawal from the study treatment. The participant may receive help to quit smoking as clinically indicated (eg, NRT and or other smoking cessation support). If a current smoker ceases smoking, this should be reported in the eCRF, but it does not necessitate withdrawal from the study treatment either.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol 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.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for ETD Visit.

In addition, and to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study treatment visits and participate in all safety follow-up assessments according to the visit schedule with a ± 5 -day window. For such participants the assessment schedule will be reduced, and some visits conducted by telephone (See SoA for participants after permanent treatment discontinuation [Section 1.3.1]). For site visits, under exceptional circumstances when a participant cannot come to the site for a scheduled visit, a telephone contact can be made. During the telephone contact, at least information about AEs, concomitant medications, and COPD exacerbation events should be collected.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Appendix 6 (Section 10.6) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 Temporary discontinuation

Temporary treatment discontinuation may be considered by the Investigator because of AEs suspected to be related to IMP, or disruption of the clinical trial due to an exceptional emergency situation (Appendix 19 [[Section 10.19](#)]). For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF. Following a temporary interruption or missed dose(s), the IMP treatment should be reinitiated at the next visit, maintaining the original dose.

7.1.4 Rechallenge

Reinitiating of intervention with the IMP after a potential allergic reaction will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the permanent discontinuation criteria for the study are not met (see [Section 7.1.1](#) and Appendix 10 [[Section 10.10](#)]).

7.1.4.1 Study intervention restart or rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an ETD Visit should be conducted, as shown in the SoA. See SoA ([Section 1.3.1](#)) for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

If possible, the Investigators should discuss with the participant key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- If a participant continues to be unreachable and has been withdrawn from the study, the site should continue to try to obtain a vital status update (death) via available resources, if possible.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 ([Section 10.1.9](#)).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA ([Section 1.3](#)). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA ([Section 1.3](#)), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA ([Section 1.3](#)).
- In case a study procedure is not performed, or not performed in time due to COVID-19, it is important to capture this specific deviation related information in the eCRF and explain the basis of the missing or delayed data, including the relationship to COVID-19.

It is recommended that assessments/procedures at a site visit are performed in the following order if applicable and possible:

- Participant-reported outcomes (PROs) and other questionnaires.
- ECG.
- Procedures:
 - Spirometry pre-BD.
 - Spirometry post-BD.
 - eDiary download.
- Safety and laboratory assessments.
- Administration of IMP.

Sanofi or a designee will provide standard study supplies to the sites for the execution of trial-related activities. These supplies include the following:

- eDiaries.
- ECG machines.
- Spirometry devices.
- Laboratory kits including tubes, needles, dipsticks.
- IMP transportation material as described in the Pharmacy Manual.

Instructions on material supply, tracking, return and destruction will be provided in vendor manuals.

Since January 2020, a worldwide COVID-19 pandemic is ongoing. The SARS-CoV-2 causes the illness COVID-19, which may lead to mild to severe respiratory problems. These symptoms may mean people with COPD have a higher risk of more severe illness from COVID-19 due to their existing lung problems. A pandemic public health emergency (like COVID-19) may impact the conduct of this clinical trial. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19. These challenges may lead to difficulties in performing protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing (see Appendix 19 [[Section 10.19](#)]).

8.1 EFFICACY ASSESSMENTS

8.1.1 Disease-specific efficacy measures

8.1.1.1 Severity of COPD exacerbations as defined by the protocol

Moderate exacerbations will be recorded by the Investigator and are defined as acute worsening of respiratory symptoms that require either systemic corticosteroids (such as IM, IV or oral) and/or antibiotics. Severe exacerbations will be recorded by the Investigator and are defined as AECOPD that require hospitalization, observation for >24 hours in emergency department/urgent care facility, or result in death.

All other exacerbations will be classified as “mild”.

For both moderate and severe events to be counted as 2 separate events, they must be separated by at least 14 days between any course of systemic steroids/antibiotics or 14 days between discharge and new admission in case of hospitalization (severe events only). In all other cases, it should be counted as 1 ongoing event.

Clinical symptoms of exacerbations of COPD

In addition to the protocol-defined exacerbations of COPD listed above, clinical signs and symptoms of exacerbations of COPD will be captured in the exacerbation eCRF (including, but not limited to, increase in dyspnea, increase in wheezing, increase in cough, increase in sputum volume and/or increase in sputum purulence).

Management of exacerbations of COPD

Exacerbations of COPD should be treated as deemed necessary by the Investigator taking into account, if possible, the list of non-permitted concomitant medications (see [Section 6.5](#)). After successful management of an acute exacerbation of COPD (eg, with oral corticosteroids and/or antibiotics), all efforts should be made to resume the initial controller COPD treatment regimen if this is medically acceptable in the Investigator’s opinion. After 1 severe or 2 moderate exacerbations of COPD, adjustments in controller therapy will be permitted for symptom control and as needed for the remainder of the trial period. The treatment of the exacerbation of COPD

will be captured on the exacerbation page in the eCRF (including, but not limited to requiring use of systemic corticosteroids [such as IM, IV or oral], requiring use of antibiotics, requiring hospitalization, or emergency room (ER) visit, or resulting in death).

Protocol-defined moderate and severe COPD exacerbation events are collected as efficacy endpoints via the exacerbation page in the eCRF. These moderate and severe events do not need to be reported as AEs unless they fulfill a seriousness criterion. Mild COPD exacerbations are not collected as efficacy endpoints, nor will they need to be reported as AE.

8.1.1.2 Spirometry

Spirometry at clinical site visits should be performed in accordance with the European Respiratory Society/American Thoracic Society (ERS/ATS) 2005 guidelines and prior to administration of investigational product (42).

For pre-BD measured/calculated parameters, including FEV1, FVC, and forced expiratory flow (FEF) 25% to 75%, spirometry will be performed after a washout period of BDs according to their action duration following the guidance of the ERS/ATS 2019 guidance (43). For example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of ipratropium for at least 12 hours, withholding the last dose of LABA for at least 24 hours, and finally the last dose of ultralong-acting LABA (like vilanterol) or the last dose of LAMA should be withheld for at least 36 hours). This will be verified before performing the measurements.

Note: When both pre- and post-BD spirometry are assessed, the post-BD spirometry should be performed after 4 actuations of short-acting β -agonist (SABA; albuterol, salbutamol) with post-BD reversibility performed at least 15 minutes following the last actuation.

At all visits, spirometry will be performed preferably in the morning; afternoon/evening is allowable in the exceptional circumstance when morning spirometry cannot be performed; spirometry should be done at approximately the same time at each visit throughout the study. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits, and whenever possible, the same person should perform the measurements.

Prior to any spirometry, the following activities should be avoided:

- For current smokers, smoking within 1 hour before testing (to avoid acute bronchoconstriction due to smoke inhalation) Note: For the former smoker cohort, smoking is an exclusion criterion (E 02) and resuming smoking is strongly discouraged.
- Consuming intoxicants within 8 hours before testing (to avoid problems with coordination, comprehension, and physical ability).
- Performing vigorous exercise within 1 hour before testing (to avoid potential exercise-induced bronchoconstriction).
- Wearing clothing that substantially restricts full chest and abdominal expansion (to avoid external restrictions on lung function).

At least 3 measurements fulfilling the ERS/ATS acceptability and repeatability criteria should be obtained at every visit, if possible. In very rare cases it can happen that a participant is already randomized into the study after immediate results of spirometry, and later an alert notification is received mentioning that the inclusion criteria on pre-BD FEV1 was not met (after manual central reading by a vendor registered respiratory therapist). In that case, these participants do not have to be withdrawn from the study and do not have to stop study treatment.

Further details on spirometry will be available in a separate Operational Manual provided to the sites.

8.1.2 Clinical outcome assessments

8.1.2.1 Participant-reported outcome questionnaires

At Run-in (Visit 1B), participants will be issued an eDiary. Participants will be instructed and trained by members of the clinical staff on the use of the device, and written instructions on the use of the eDiary will be provided to the participants. Recorded information will be downloaded from this device on the other indicated days ([Section 1.3](#)).

On a daily basis during screening and treatment, the participant will use an eDiary to:

- Respond to the COPD exacerbation and symptom scale questions of the EXAcacerbations of Chronic Pulmonary Disease Tool (EXACT) instrument. Record use of established controller and reliever inhalation therapy. Record use of corticosteroids or antibiotics.

If use of any corticosteroids and/or antibiotics are recorded in the eDiary by a participant, an alert will be sent to the site. The Investigator should contact the participant in order to verify if he/she has had a COPD exacerbation. When there is low compliance for the EXACT instrument, an alert will be sent to the site as well.

The eDiary will be used for other participant-reported questionnaires such as Participant Global Impression of Severity (PGIS), Participant Global Impression of Change (PGIC), St. George's Respiratory Questionnaire (SGRQ), and EuroQol 5-Dimension 5-Level Quality-of-Life Questionnaire (EQ-5D-5L). In addition, healthcare resource utilization/productivity data will be captured at specific time points ([Section 1.3](#)) in the eCRF.

In the follow-up period, the participant's responses in the eDiary will not be recorded daily; electronic questionnaires will only be administered at on-site visits as outlined in the SoA.

Participant-reported outcome questionnaires at a site/visit should be completed prior to any other assessments or procedures.

8.1.2.1.1 COPD Assessment Test (CAT)

The CAT ([44](#)) is a questionnaire that is designed for participants with COPD to measure the effects of the disease on their wellbeing and daily life. The CAT™ is an 8-item self-administered questionnaire which has been developed for use in routine clinical practice to measure the health status of participants with COPD (see Appendix 12: COPD Assessment Test, [Section 10.12](#)).

The CAT™ score ranges from 0 to 40, a higher score indicating a higher impact on health status. The test comprises items relating to cough, phlegm, chest tightness, dyspnea, activity limitation, confidence, sleep, and energy (45). Participants scored questions from 1-5 according to the degree of impact felt for each item (ie, 0 = no impact; 5 = high degree of impact).

8.1.2.1.2 *Evaluating Respiratory Symptoms in COPD (E-RS:COPD)*

The Evaluating Respiratory Symptoms in COPD (E-RS:COPD) is administered as a part of the 14-item EXACT instrument (see Appendix 14 [Section 10.14] and Appendix 15 [Section 10.15]) and is completed on a daily basis. The 11-item E-RS:COPD assesses severity of respiratory symptoms overall and severity of individual symptoms such as breathlessness, cough and sputum, and chest symptoms. The total score of E-RS:COPD ranges from 0 to 40, with higher values indicating more severe respiratory symptoms. Additionally, 3 domain scores including RS-Breathlessness score (Range 0-17), RS-Cough and Sputum score (Range 0-11) and RS-Chest Symptoms score (Range 0-12) can also be computed. The E-RS:COPD utilizes the 11 respiratory symptom items contained in the 14-item of the daily EXACT instrument displaying in the following:

- Breathlessness (5 items),
- Cough and sputum (2 items),
- Chest symptoms (3 items),
- Difficulty bringing up sputum (1 item),
- Tired or weak (1 item),
- Sleep disturbance (1 item), and,
- Scared or worried (1 item).

Development and validation history of the tool is consistent with guidelines proposed by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and well-known measurement principles.

8.1.2.1.3 *St. George's Respiratory Questionnaire (SGRQ)*

The SGRQ is a 50-item questionnaire designed to measure and quantify health status in adult participants with chronic airflow limitation (39, 40, 46, 47). A global score ranges from 0 to 100. Scores by dimension are calculated for 3 domains: Symptoms, Activity and Impacts (Psycho-social) as well as a total score. A lower score indicates better health status (see Appendix 12 [Section 10.12]). A minimum change in score of 4 units was established as clinically relevant after participant and clinician testing (48).

The first part ("Symptoms") evaluates symptomatology, including frequency and severity of cough, sputum production, wheeze, breathlessness, and the duration and frequency of attacks of breathlessness or wheeze. The second part has 2 components: "Activity" and "Impacts". The "Activity" section addresses disturbances to participants' daily physical activities. The "Impacts" section covers a range of effects that chest troubles may have on participants' daily life and psycho-social functions (eg daily life activities and functioning, employment, physical

functioning, emotional impact, stigmatization, and participants' perceptions when treated). The recall period of the questionnaire is over the past 4 weeks.

Psychometric testing has demonstrated its repeatability, reliability, and validity. Sensitivity has been demonstrated in clinical trials. A minimum change in score of 4 units is established as clinically relevant after participant and clinician testing. The SGRQ has been used in a range of disease groups including asthma, COPD, and bronchiectasis.

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

The EQ-5D-5L 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. The EQ-5D-5L is designed for self-completion by participants. The EQ-5D-5L consists of a descriptive system and the EuroQol (EQ) visual analog scale (VAS). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ VAS records the participant's self-rated health on a vertical VAS (see Appendix 15 [Section 10.16]).

8.1.2.1.5 Other clinical outcome assessments

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

The BODE Index (Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index) is a composite measure composed of a performance outcome measure, a participant-reported outcome measure and a biomarker. The BODE Index is a multidimensional grading system to assess the respiratory and systemic expressions of COPD (41).

It comprises 4 domains: degree of pulmonary impairment (FEV1); participant's perception of symptoms (modified Medical Research Council Dyspnea Scale [mMRC]); and 2 independent domains: the 6 Minute Walking Distance (6MWD) and the 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 Appendix 16 [Section 10.17]). A >1 point decrease (= improvement) in BODE Index is considered a surrogate measure of improved survival in therapeutic trials in severe COPD. For degree of pulmonary impairment (FEV1), site should choose the post-bronchodilator FEV1 as a percent of the predicted value.

For the 6MWD, the site should ensure the participant can walk on a continuous route as much as possible with a minimum number of turns. Furthermore, the same tract/path should be used for each participant in their clinic, where possible, to closely approximate the original BODE is strongly encouraged. A 100-foot corridor is not required.

The following order of tests is suggested:

1. Spirometry
2. mMRC

3. BMI
4. Oxygen saturation using pulse oximetry and respiratory rate at baseline
5. 6MWD
 - a) In order to minimize variability between two 6MWD tests/visits, the following guidance should be followed:
 - i. The 6MWD has to be done at the same time of the day,
 - ii. The tests should always be done in the above specified order,
 - iii. Participants should rest for 15 minutes before commencing the test,
 - iv. Participants must not have exercised vigorously within 2 hours of beginning the test.
6. Oxygen saturation using pulse oximetry and respiratory rate at end.

A reference for the 6MWD may be found at the following link - procedures should adhere as closely as possible to those specified in the guidance document:

<https://www.thoracic.org/statements/resources/pfet/sixminute.pdf>

The score of each domain of the BODE Index score must be recorded in the source documents and eCRF.

8.1.2.1.5.2 Participant Global Impression of Change (PGIC) and Participant Global Impression of Severity (PGIS)

The PGIC 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”.

The PGIS is a 1-item questionnaire that asks participants to provide the overall self-assessment of their COPD symptom severity on a 4-point scale for the past week. Response choices are: 1 = “None”, 2 = “Mild”, 3 = “Moderate”, 4 = “Severe” (see Appendix 18 [Section 10.18]).

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Height and weight will also be measured and recorded at screening (the participant is allowed to wear indoor, daytime clothing with no shoes). Weight will also be measured and recorded at the Baseline/Randomization (Visit 2), Week 24 (Visit 14), and EOT and EOS visits.

- Investigators should pay special attention to clinical signs related to previous serious illnesses and pay special attention to signs or symptoms of infection or malignancy.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- Body temperature (route of measurement [oral/tympanic/rectal/axillary/temporal]) will be recorded (°C), pulse rate (beats per minute), respiratory rate (breaths per full minute), and systolic and diastolic BP (mmHg) will be assessed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3 Electrocardiograms

- Single 12-lead ECGs will be obtained as outlined in the SoA (see [Section 1.3](#)) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. The ECGs will be obtained prior to laboratory assessments and prior to spirometry. A qualified Investigator or appropriate designee (qualified physician) should review the ECGs in a timely manner to determine if there are any safety concerns and for clinical management of the participant. In case of abnormal findings identified by the qualified Investigator or appropriate designee (qualified physician), the ECG should be provided to the cardiologist for further confirmation and description of findings. The Investigator must always date and sign the ECG and comment on the assessment before filing this in the medical records. In the event of any clinically significant abnormal findings that meet the definition of an AE ([Section 8.3](#)) the Investigator will continue to monitor the participant with additional ECGs until the ECG findings return to baseline ECG findings or the Investigator determines that follow-up is no longer necessary.
- Any clinically significant ECG related to a pre-existing condition at Screening (Visit 1A) that does not affect the conduct of the study per the Investigator's judgment will need to be well documented in the source documentation.
- Further details related to ECG, including alert criteria, will be provided in a separate Manual, which will be provided by the vendor.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 ([Section 10.2](#)) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated (either by central or local laboratory) until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor or Sponsor representative(s).
 - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
 - All protocol-required laboratory assessments, as defined in Appendix 2 ([Section 10.2](#)), must be conducted in accordance with the Laboratory Manual and the SoA.
 - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.
 - Critical values alerts are linked to extremely high or low laboratory test values which are considered to be potentially life threatening. In the event a critical value is reported, PPD will contact the site.
 - Special procedures for collection, storage, and shipping of serum are described in the Central Laboratory Manual.

At screening, hepatitis serology testing is performed in order to rule out active or chronic infection. Guidance on hepatitis serology eligibility interpretation is provided in [Table 7](#).

Table 7 - Hepatitis serology testing

Hepatitis serology result	Protocol action
HBsAg: positive or indeterminate	Excluded
HBsAb positive, HBsAg negative, HBcAb: negative	Eligible
HBcAb IgM: positive	Excluded
HBcAb Total: positive (with or without HBsAb positive)	Test for HBV DNA If HBV DNA Positive: Excluded If HBV DNA Indeterminate: Eligible
HCV antibody: positive	Test for HCV RNA If HCV RNA Positive: Excluded If HCV RNA Indeterminate: Eligible

DNA = deoxyribonucleic acid; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin.

8.2.5 Pregnancy testing

Pregnancy testing will be performed in all WOCBP at screening with a blood test using a central laboratory, and at all subsequent clinic visits using Sponsor-provided urine tests, or locally-provided urine test (China only). Pregnancy urine test at Week 20, 28, and 44 (home IMP administration/telephone visits) will be performed by the participant at home. The outcome will be recorded. Participant will be instructed to not administer next IMP in case of suspected/confirmed pregnancy and contact the site.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see [Section 6.8](#)).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the EOS visit at the time points specified in the SoA ([Section 1.3](#)).

All AEs will be collected from the signing of the ICF at the time points specified in the SoA ([Section 1.3](#)).

All SAEs and adverse events of special interest (AESI) will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 ([Section 10.3](#)). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 ([Section 10.3](#)).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs, and AEs of special interest (as defined in [Section 8.3.8](#)), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 7.3](#)). Further information on follow-up procedures is provided in Appendix 3 ([Section 10.3](#)).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 20 weeks after last dose of IMP.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 ([Section 10.4](#)).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in [Section 8.3.4](#). While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Adjudication Committee

Adjudication will be performed by experts independent of the Sponsor, for the evaluation of whether deaths and (potential) cardiovascular SAEs meet criteria for certain safety endpoints.

A separate confirmatory adjudication will occur for AECOPD exacerbations. Adjudicators will adjudicate these events in a consistent and unbiased manner throughout the study.

The goal of the adjudication is to ensure that all events reported by the site are judged uniformly, using prespecified criteria by a group independent of the Sponsor. Adjudication Committee members will be blinded to treatment allocation. Adjudication Committee members' responsibilities and the process for data review are described in the Adjudication Committee Charter/Manual of Operation.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected. Specifically, for participants with COPD, worsening of underlying condition is not considered an AE unless it meets serious criteria as defined in Appendix 3 ([Section 10.3](#)).

Any COPD exacerbations are disease-related events (DREs) that are common in participants with moderate-to-severe COPD and they will not be reported according to the standard process for reporting of AEs unless the event meets the definition of a SAE.

Once the Investigator has become aware of any COPD exacerbation events, they will record details of the events on the corresponding exacerbation page in the eCRF only if the events meet AECOPD definition of moderate-or-severe AECOPD (see [Section 8.1.1](#)).

8.3.8 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
 - In the event of pregnancy in a female participant, IMP should be discontinued.
 - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP/noninvestigational medicinal product (NIMP).
 - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose during an interval of <8 days.
 - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the maximum prescribed daily dose, within the intended therapeutic interval.
- Significant ALT elevation
 - $ALT > 3 \times \text{the ULN}$ associated with total bilirubin $> 2 \times \text{ULN}$;
 - or
 - $ALT > 5 \times \text{the ULN}$ if baseline $ALT \leq 2 \times \text{ULN}$;
 - $ALT > 8 \times \text{ULN}$ if baseline $ALT > 2 \times \text{ULN}$.
- Other project specific AESI(s)
 - Anaphylactic reactions or systemic allergic reactions that require treatment (see Appendix 10 [Section 10.10]).
 - Severe injection site reactions (ISRs) that last longer than 24 hours.

Note: A severe ISR (for AE reporting) is any event that meets one of the following criteria:

 - With a diameter of at least 10 cm.
 - Impacting daily activities.
 - With ulceration or necrosis.
 - For which operative intervention is required.

Note: adverse event intensity should be reported as “severe” if ISR is reported as “severe ISR AESI”.
- Any infection meeting at least one of the following criteria:
 - Any serious infection (SAE).
 - Requires parenteral (IV, IM, SC) antimicrobial therapy. Note: antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.

- Requires oral antimicrobial therapy for longer than 2 weeks.
- Is a parasitic infection.
- Is an opportunistic infection (see Appendix 11 [[Section 10.11](#)]).
- Malignancy.

The definitions of an AE or SAE can be found in Appendix 3 ([Section 10.3](#)).

Any AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see [Section 6.8](#)).

8.3.9 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

Blood samples will be collected for determination of functional itepekimab concentrations in serum as specified in the SoA ([Section 1.3](#)). Samples may be collected at additional time points during the study if warranted (see Appendix 6, [Section 10.6](#)). Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. The actual date and time (24-hour clock time) of each sample will be recorded. The sample types for PK samples are described in [Table 8](#).

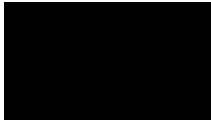
Table 8 - Summary of handling procedures for PK samples

Sample type	PK (itepekimab)
Matrix	
Blood sample volume	
Blood handling procedures	
Serum aliquot split	
Serum shipment condition	

PK = pharmacokinetic(s).

The bioanalytical methods for pharmacokinetics are summarized in [Table 9](#).

Table 9 - Summary of bioanalytical methods for PK samples

Analyte	PK (itepekimab)
Matrix	
Analytical technique	
Site of bioanalysis	

; PK: pharmacokinetic(s).

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Note: If an SAE or AESI (anaphylaxis, systemic hypersensitivity reaction, and severe ISR lasting 24 hours) occurs in a participant, additional blood samples may be collected for determination of functional itepekimab concentration at or near the onset of the occurrence of the event. An unscheduled systemic drug concentration page in the eCRF must be completed as well.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5 GENETICS

For those participants who consent to the optional pharmacogenetic/pharmacogenomic sample collection in the corresponding section of the ICF, blood samples for exploratory genetic analysis of DNA will be collected and stored for possible future use. Specific procedures for collection, storage and shipping of pharmacogenetic/pharmacogenomic samples will be provided in a Laboratory Manual.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Appendix 5 ([Section 10.5](#)) for information regarding genetic research.

8.6 BIOMARKERS

- Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA ([Section 1.3](#)):
 - Blood eosinophil and neutrophil counts will be measured as part of the standard 5-part white blood count (WBC) differential cell count on a hematology auto analyzer.
 - Serum C-reactive protein (CRP) level.
 - Total IL-33 will be measured with a quantitative immunoassay.

- Optional samples for biomarker research that should be collected from participants who signed the optional pharmacogenetic/pharmacogenomic informed consent are the following:
 - Whole blood messenger RNA for sequencing (RNAseq) or whole transcriptome analysis.
- An optional collection of serum/plasma samples that will be archived for other biomarker research is also part of this study.
 - The archived samples may be used for research purposes related to respiratory diseases such as COPD or inflammatory diseases (eg, exploratory biomarkers of disease or drug effect), pathway biology, additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol.
 - Samples (including unused samples or leftover samples after testing) may also be used for research to develop methods, assays, prognostics and/or companion diagnostics related to IL-33, disease process, pathways associated with disease state, and/or mechanism of action of the study intervention.
 - Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis.

More detailed information on the collection, handling, transport, and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate Laboratory Manual.

8.7 IMMUNOGENICITY ASSESSMENTS

Blood samples will be collected for determination of antibodies to itepekimab in serum as specified in the SoA ([Section 1.3](#)). In addition, blood samples will be collected at the final visit from participants who discontinued IMP or were withdrawn from the study. Samples may be collected at additional time points during the study if warranted (see Appendix 6, [Section 10.6](#)). Special procedures for the collection and handling of samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. The sample types for immunogenicity samples are described in [Table 10](#).

Table 10 - Summary of handling procedures for ADA samples

Sample type	ADA
Matrix	
Blood sample volume	
Blood handling procedures	
Serum aliquot split	
Serum shipment condition	

ADA = antidrug antibody

The bioanalytical method for antidrug antibody is summarized in [Table 11](#).

Table 11 - Summary of bioanalytical methods for ADAs

Analyte	ADA
Matrix	
Analytical technique	
Site of bioanalysis	

ADA = antidrug antibody [REDACTED].

Note: 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 ADA assessment at or near the onset of the occurrence of the event. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled page in the eCRF must be completed as well.

If necessary, for safety monitoring, additional ADA samples may be drawn after the EOS Visit until resolution of SAE/AESI. Samples positive in the ADA assay may be further characterized for the presence of neutralizing activity. More details will be provided in the SAP.

8.8 HEALTHCARE RESOURCE UTILIZATION

Healthcare resource utilization data, associated with medical encounters due to participant’s COPD, will be collected in the eCRF. Protocol-mandated procedures, tests, and encounters are excluded. The data will include healthcare resource utilization during exacerbations and outside of exacerbations.

The data collected may be used to conduct exploratory economic analyses and will include:

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8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Appendix 1 [[Section 10.1.3](#)]) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of samples will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Appendix 1 [[Section 10.1.4](#)]).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such cases, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The statistical hypotheses to be tested on the primary endpoint of annualized rate of moderate-to-severe COPD exacerbations over the 52-week treatment period in former smokers 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 statistical hypotheses to be tested on the key secondary endpoint of change from baseline in pre-BD FEV1 at Week 24 in former smokers are as follows:

- Null hypothesis: $c_{itepekimab} = c_{placebo}$
- Alternative hypothesis: $c_{itepekimab} \neq c_{placebo}$

Where $c_{itepekimab}$ represents change from baseline in pre-BD FEV1 at Week 24 for itepekimab 300 mg Q2W or Q4W, $c_{placebo}$ represents change from baseline in pre-BD FEV1 at Week 24 for placebo.

The statistical hypotheses to be tested on other secondary endpoints such as change from baseline in pre-bronchodilator FEV1 at Week 52, change from baseline in post-bronchodilator FEV1 at Weeks 24 and 52, annualized rate of severe COPD exacerbations over the placebo-controlled 52-week treatment period, change from baseline in SGRQ total score at Weeks 24 and 52, and change from baseline in E-RS:COPD total score at Weeks 24 and 52, can be specified similarly as those for the primary or key secondary endpoint. For the time to first moderate-to-severe AECOPD or time to first severe AECOPD endpoint, the null hypothesis is the hazard ratio between itepekimab 300 mg Q2W or Q4W and placebo is equal to 1, while the alternative hypothesis is the hazard ratio is unequal to 1. For the proportion of participants with SGRQ improvement ≥ 4 points at Weeks 24 and 52, the null hypothesis is the odds ratio of response between itepekimab 300 mg Q2W or Q4W and placebo group is equal to 1, while the alternative hypothesis is the odds ratio is unequal to 1.

The study will be declared positive if the null hypothesis for annualized rate of moderate-or-severe AECOPD for itepekimab 300 mg Q2W versus placebo is rejected in former smokers.

9.2 SAMPLE SIZE DETERMINATION

In the Phase 2a Study ACT15104 in participants with moderate-to-severe COPD, a relative reduction of 41.9% (95% CI: 14.2% to 60.6%) in the annualized rate of moderate-or-severe AECOPD between itepekimab 300 mg Q2W and placebo was observed in the former smoker subpopulation. Furthermore, the dispersion parameter was around [REDACTED].

The original sample size calculation for the 52 week treatment duration portion of this study is based on the primary comparison between itepekimab 300 mg SC Q2W/Q4W versus placebo with regard to annualized rate of moderate-or-severe AECOPD over the 52-week treatment period in former smokers. Taking into account the prior data from Study ACT15104 and the objectives of the current study, 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]; details are provided in [Section 9.5](#)).
- 1:1:1 randomization.
- Average treatment duration per participant of [REDACTED] years to account for minimal loss of follow-up due to early study discontinuation.
- 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 former smoker participants (310 participants per arm) in the 52 week treatment duration portion, study was designed to have a 90% power to detect a 30% relative reduction in the annualized rate of moderate-or-severe AECOPD for itepekimab 300 mg Q2W or Q4W versus placebo in the ITT population of former smokers. The minimum detectable risk reduction was [REDACTED].

Based on the significance level of 0.049, The study also had a 90% power to detect an 80 mL difference in the change from baseline in pre-BD FEV1 at Week 24 (or at Week 52) for itepekimab 300 mg Q2W or Q4W versus placebo in the ITT population of former smokers assuming a common standard deviation of [REDACTED] mL. The minimum detectable difference between groups is approximately [REDACTED] mL.

During the COVID-19 pandemic, a lower-than-expected rate of exacerbations has been observed in participants with COPD. This is likely the result of social distancing and/or mask wearing leading to fewer respiratory infections, a known trigger for COPD exacerbations (49).

The blinded annualized rate of moderate or severe exacerbations in the former smokers at the time of protocol amendment 01 suggests a lower placebo exacerbation rate compared to the original assumption of an AECOPD rate of [REDACTED] in placebo. To preserve the power of the study, an adaptive sample size increase of the former smoker cohort will be based upon a blinded exacerbation rate observed approximately 3 months or earlier prior to the last of the planned 930 former smoker participants being randomized.

If the observed blinded exacerbation rate is ■■■ or higher, the sample size will not be adjusted. If the blinded exacerbation rate is below ■■■, a sample size adaptation will be made to the former smoker cohort, based on the blinded rate of a moderate or severe investigator-reported exacerbation observed approximately 3 months or earlier prior to the randomization of the last of the planned 930 former smoker participants. Details are provided in [Table 12](#). The number of additional former smoker participants will not exceed approximately 207. All additional former smoker participants randomized as part of this sample size adaptation will have a variable treatment duration (minimum of 24 weeks, maximum of 52 weeks). In [Section 4.1](#) the variable treatment duration is described in more detail. More details will be provided in the SAP.

Table 12 - Summary of sample size adaptation based upon blinded AECOPD rate in former smokers

Observed blinded AECOPD rate approx.. 3 months or earlier prior to LPI*	Assumed AECOPD rate in Placebo group	Additional participants to be randomized to a 24-52 week treatment period	Power to detect a 30% risk reduction in the annualized rate of AECOPD
1.0 or above	≥1.25	0	≥87.3%
≥0.95 - <1.0	1.19	9	86.9%
≥0.9 - <0.95	1.13	36	86.9%
≥0.85 - <0.9	1.06	75	86.9%
≥0.80 - <0.85	1	108	86.7%
≥0.75 - <0.8	0.94	150	86.6%
<0.75	0.88	207	86.7%

*LPI = Last participant in of the planned 930 former smoker participants

In addition to the primary population of former smoker participants, the study will also enroll a secondary population of participants who are current smokers. The targeted enrollment for the current smoker cohort is approximately a total of 280 current smokers (N=140 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, with 280 participants there is an 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 30% (95% CI half-width).

In this study, separate randomization will be performed for former smokers cohort, which will be the primary population and the current smokers cohort, which will be a secondary population, and each stratified by country (some countries might be pooled together), screening blood eosinophil count (<300 cells/mm³ or ≥300 cells/mm³), and controller therapy (double or triple). It is noted that due to smaller sample size in current smokers, using the same stratification factors and levels as those in former smokers may result in incomplete stratum. Its impact on data analysis will be further assessed and addressed in the SAP.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined ([Table 13](#)):

Table 13 - Populations for analyses

Population	Description
Former smoker cohort (primary population for efficacy and safety analyses)	All participants with a history of ≥ 10 pack-years who report that they are not currently smoking at Screening (Visit 1A) and smoking cessation must have occurred ≥ 6 months prior to Screening (Visit 1A).
Current smoker cohort (secondary population for efficacy and safety analyses)	All participants with a history of ≥ 10 pack-years who report that they are currently smoking (participants who smoked at least 1 cigarette per day on average during the past 7 days) at Screening (Visit 1A).
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.
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. The ITT/efficacy analysis population will be used for the AECOPD related endpoints, and the endpoints assessed at Week 24 (such as change from baseline in pre-BD FEV1, post-BD FEV1, E-RS:COPD, or SGRQ at Week 24).
ITT-Week 52 population	The ITT/Week 52 population includes all the participants who have the opportunity to complete 52 weeks of treatment period based on their randomization date, regardless of whether the participant is enrolled in the 52 weeks treatment duration portion, or in the potential additional variable treatment duration portion. All participants in the ITT-Week 52 population have a planned treatment duration of 52 weeks. The ITT/Week 52 population is the analysis population for the endpoints that assess change from baseline at Week 52 (such as change from baseline in pre-BD FEV1, post-BD FEV1, E-RS:COPD, or SGRQ at Week 52). Note, if the former smoker sample size is not increased as per Section 9.2 (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. There will be a safety population for the former smoker cohort, as well as for the current smoker cohort. In case of comparable outcomes in both cohorts, a combined analysis is planned as well. Details will be described in the SAP. Pharmacodynamics analyses will be performed in safety populations as well.

Population	Description
Pharmacokinetic (PK)	The PK population includes all participants in the safety population with at least 1 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. There will be a PK population for the former smoker cohort, as well as for the current smoker cohort. In case of comparable outcomes in both cohorts, a combined analysis is planned as well. Details will be described in the SAP.
Antidrug antibody (ADA)	ADA population includes all participants in the safety population who have at least 1 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. There will be an ADA population for the former smoker cohort, as well as for the current smoker cohort. In case of comparable outcomes in both cohorts, a combined analysis will be performed as well. Details will be described in the SAP.

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.

9.4 STATISTICAL ANALYSES

The SAP will be developed and finalized prior to database lock or prior to any administrative IA. The SAP will include more technical and detailed descriptions of the statistical analyses, including methods to assess the impact of missing data, subgroup analyses, etc. The following subsections present summaries of the planned statistical analyses of the most important endpoints including primary and key secondary.

9.4.1 General considerations

The baseline value of efficacy parameters is defined as the last available value up to randomization but prior to the first dose of study treatment unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of IMP. The baseline value of the other parameters is defined as the last available value prior to the first dose of IMP if the participant is treated, or the last available value up to randomization if the participant is not exposed to IMP.

Countries will be pooled into regions for analysis.

All efficacy analyses will be performed on the ITT/efficacy population of former smokers defined above unless otherwise specified (see [Table 13](#) for definitions of analysis populations). For estimation purposes, similar efficacy analyses will also be performed on the secondary population of current smokers.

The database lock for final analysis will be planned 52 weeks after the last participant is randomized, or alternatively 24 weeks after the last additional former smoker randomized participants, if the sample size is increased as per Section 9.2, 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. Additional data between this database lock and the last participant completing the last visit will be summarized in a CSR addendum.

9.4.2 Primary estimand

The primary estimand will be a treatment policy estimand for both the primary endpoint (annualized rate of moderate-or-severe AECOPD over the placebo-controlled treatment period) and the key secondary endpoint (change from baseline in pre-BD FEV1 at Week 24). This estimand compares the treatment effect on efficacy for the participants randomized to an itepekimab regimen versus placebo, regardless of what treatment participants actually received or treatment adherence status. It assesses the benefits of the treatment policy relative to placebo (6).

The supportive estimand for both primary and key secondary endpoints will be a while-on-treatment estimand. This estimand evaluates the efficacy of itepekimab while on treatment (6).

The primary and supportive estimands for both primary and key secondary endpoints are provided in detail in Appendix 20 (Section 10.20). Estimands for other endpoints will be defined in detail in the SAP.

9.4.3 Primary endpoint

Table 14 - Statistical analysis methods for primary endpoint in former smoker cohort (primary population)

Endpoint	Statistical analysis methods
Primary	
Annualized rate of AECOPD over the placebo-controlled treatment period (Analysis population: ITT)	The primary analysis of the annualized rate of moderate-or-severe AECOPD during the placebo-controlled treatment period will be performed following the ITT principle. The primary estimand is a treatment policy estimand. All moderate-or-severe AECOPD events during the placebo-controlled treatment period in former smokers will be included 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, 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. No imputation will be performed for the unobserved AECOPD events that may happen after study discontinuation and up to up to the end of the planned treatment period. 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 (placebo, itepekimab 300 mg SC Q2W, itepekimab 300 mg SC Q4W), region (pooled country), screening eosinophil strata (<30 cells/mm³, ≥300 cells/mm³), controller

Endpoint	Statistical analysis methods
	therapy (double, triple) 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. The treatment comparison with placebo will be performed using a step-down procedure to compare itepekimab 300 mg SC Q2W versus placebo first; only if this is statistically significant, will the comparisons of itepekimab 300 mg SC Q4W versus placebo be performed. 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 RR of each itepekimab regimen versus placebo, and the corresponding 2-sided 95% CI and p-value will also be provided. An on-treatment estimand will be used for all participants in a supportive analysis to assess the efficacy of itepekimab excluding data measured when participants do not adhere to the treatment regimen will also be performed and be used to estimate the benefit when adhering to itepekimab treatment. In this analysis, only the AECOPD events observed during the on-treatment period (from first administration of IMP to last administration of IMP +14 days) will be included. 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. This approach defines the estimand to evaluate the efficacy of itepekimab while on treatment (6). Sensitivity analyses The reason and pattern of missing data will be carefully examined. Sensitivity analyses to assess the robustness of the conclusion of the primary analysis will be performed using a pattern mixture model by multiple imputation for missing data and/or tipping point analysis. The impact of nonadherence to smoking abstinence on the primary analysis will also be evaluated. Details will be included in the SAP The impact of the regional or national emergency declared by a governmental agency on-study conduct (if applicable) will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP. Subgroup analyses To assess the consistency of treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoints with respect to age, gender, region (pooled countries), race, ethnicity, weight, BMI, smoking resumption status, controller therapy (ICS + LABA and LABA + LAMA and ICA + LABA + LAMA), background ICS dose at randomization (high and low), baseline median CAT score, baseline % predicted post-BD FEV1, screening/baseline blood eosinophil levels ($<150/\text{mm}^3$, ≥ 150-<300 cells/mm^3, ≥ 300 cells/mm^3) and other factors. Details will be specified in the SAP that will be finalized prior to study database lock. In addition to the analysis in the current study, statistical analysis for subgroups with triple controller therapy only will be further conducted using the pooled data of Study EFC16750 and Study EFC16819; the details will be provided in the SAP.

9.4.4 Secondary endpoint(s)

Key secondary endpoints

Table 15 - Statistical analysis methods for key secondary endpoints in former smoker cohort (primary population)

Key secondary endpoint	Statistical analysis methods
- Change from baseline in pre-BD FEV1 at Week 24 (Analysis population: ITT)	The main analysis of change from baseline in pre-BD FEV1 at Week 24 is to assess the efficacy of itepekimab on pulmonary function. The change from baseline in pre-BD FEV1 at Week 52 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 in former smokers up through Week 24 as response variables, and treatment, age (continuous variable), sex, baseline height (continuous variable), region (pooled country), screening eosinophil strata, controller therapy strata (double or triple), visit, treatment by-visit interaction, and baseline pre-BD FEV1 value (continuous variable) and baseline-by-visit interaction as covariates. Participants who discontinue IMP before Week 24 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 up through Week 24 will be included in the analysis. For participants who withdraw from the study before Week 24, pre-BD FEV1 values will be missing after study discontinuation or last contact. No imputation will be performed for missing values in this analysis. An unstructured correlation matrix will be used to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on-treatment comparisons for the change from baseline 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. To assess the treatment effect when the participants adhere to the study treatment as directed, an on-treatment estimand will be used for all participants in a supportive analysis where 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 through Week 24 as response variables. A pre-BD FEV1 value is considered as on-treatment if it is measured on or before the last dose date +14 days. Additionally, sensitivity analyses to assess the robustness of the conclusion of the main model will be performed using pattern mixture model by multiple imputation for missing data and/or tipping point analysis. Details will be included in the SAP. Subgroup analyses will be performed similar as described in Section 9.4.3.

Other secondary endpoints

Table 16 - Statistical analysis methods for other secondary endpoints

Other secondary endpoints	Statistical analysis methods
Primary population (former smoker cohort)	
Change from baseline in pre-BD FEV1 at Week 52 (Analysis population: ITT-Week 52)	This analysis will be performed in the same way as for the key secondary endpoint and the response variable will include change from baseline in pre-BD FEV1 values up through to Week 52.
Change from baseline in post-BD FEV1 at Week 24 (Analysis population: ITT) and at Week 52 (Analysis population: ITT-Week 52)	The change from baseline at Week 24 and at Week 52 in post-BD FEV1 will be analyzed in the same way as the key secondary efficacy endpoint of the change from baseline in pre-BD FEV1 at Week 24 and at Week 52.
Time to first moderate-or-severe AECOPD over the placebo-controlled treatment period (Analysis population: ITT)	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 (pooled country), 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 (Analysis population: ITT)	This will be analyzed similar to the primary endpoint of "Annualized rate of moderate-or-severe AECOPD over the placebo-controlled treatment period", but only severe AECOPD events will be taken into consideration.
Time to first severe AECOPD over the placebo-controlled treatment period (Analysis population: ITT)	This will be analyzed similar to the secondary endpoint of "Time to first moderate-or-severe AECOPD during the placebo-controlled treatment period and other time to event endpoints", but only severe AECOPD events will be taken into consideration.
Annualized rate of corticosteroid-treated AECOPD over the placebo-controlled treatment period (Analysis population: ITT)	This will be analyzed similar to the primary endpoint of "Annualized rate of moderate-or severe AECOPD over treatment period", but only 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.
Change from baseline in E-RS:COPD total score at Week 24 (Analysis population: ITT) and at Week 52 (Analysis population: ITT-Week 52)	The baseline, Week 24 and Week 52 E-RS:COPD total score 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. Change from baseline in E-RS:COPD total score at Week 24 and at Week 52 will be analyzed using the MMRM approach described for the analysis of pre-BD FEV1. Here the model will include all E-RS:COPD total scores up through Week 24 or Week 52, regardless if the participant is on treatment or not when the endpoint is measured. The model covariates will be treatment, screening eosinophil strata, region (pooled country), 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.

Other secondary endpoints	Statistical analysis methods
Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4-12 weeks (Analysis population: ITT)	Rate of change in post-BD FEV1 (L) (post-BD FEV1 slope) after a period of initial bronchodilator effect during which a rapid increase in post-BD FEV1 is expected for all active treatment arms will be analyzed. The specific length of this period or the number of weeks will be provided in the SAP. Descriptive summary statistics will be provided based on the individual post-BD FEV1 slope, which 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 Week 52) as the response variable and the time (continuous variable) as the independent variable for each participant. Formal statistical inferences including estimated post-BD FEV1 slopes for each treatment group, 95% CIs and p-values on the slope differences between active treatment groups and placebo will be derived from a mixed-effects model with repeated post-BD FEV1 measured during the treatment period after the initial bronchodilator effect period (up to Week 52) 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 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 2 COPD Phase 3 studies, ie, this study, and the EFC16819 study. Details will be provided in the SAP. - In addition, 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. Details will be provided in the SAP.
Change from baseline in SGRQ total score at Week 24 (Analysis population: ITT) and at Week 52 (Analysis population: ITT-Week 52)	Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 and at Week 52 will be analyzed using the MMRM approach described for the analysis of pre-BD FEV1. Here the model will include all SGRQ scores up through Week 52, regardless if the participant is on treatment or not when the endpoint is measured. Again, participants who discontinue IMP prior to 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 (pooled country), controller therapy strata, visit, treatment-by-visit interaction, baseline 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.
Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24 (Analysis population: ITT) and at Week 52 (Analysis population: ITT-Week 52)	The proportion of participants with SGRQ improvement ≥ 4 points at Week 24 and at Week 52, regardless if 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 (pooled country), controller therapy strata, and baseline SGRQ total score as covariates. Participants with SGRQ improvement < 4 points or missing SGRQ total score at Week 24 and at Week 52 will be considered as non-responders. The odds ratio of being a responder comparing each itepekimab regimen to placebo will be provided along with the corresponding 95% CI and p-value. 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 completing the planned placebo-controlled treatment period on treatment.

Other secondary endpoints	Statistical analysis methods
Secondary population (current smoker cohort)	
- Annualized rate of moderate-to-severe acute exacerbation of COPD (AECOPD) over the placebo-controlled treatment period - Change from baseline in pre-bronchodilator FEV1 at Week 24 and at Week 52	This will be analyzed similarly to the primary endpoint of “Annualized rate of moderate-or-severe AECOPD over the planned treatment period”, but only in the current smoker secondary population. The impact of smoking cessation in current smoker secondary population on the analysis will also be evaluated. This analysis will be performed in the same way as for the key secondary endpoint (see Section 9.4.4, Key Secondary Endpoint), but only participants in the current smoker secondary population.
Primary population (former smoker cohort) and secondary population (current smoker cohort)	
- Pharmacokinetics (PK) - Antidrug antibody (ADA)	Drug concentrations of functional itepekimab in the serum will be summarized using arithmetic and geometric means, standard deviation, standard error of the mean (SEM), coefficient of variation (CV), minimum, median, and maximum by treatment per visit. The PK analysis will be detailed in the SAP. The incidence of positive ADA response for itepekimab will be assessed as absolute occurrence (n) and percent of participants (%), presented by treatment groups. Listing of ADA titer levels will be provided for participants positive in the ADA assay. The ADA analysis will be detailed in the SAP.

9.4.5 Tertiary/exploratory endpoint(s)

Pharmacodynamic and biomarker exploratory analyses are briefly described in [Table 17](#). More details on these analyses, and other tertiary/exploratory endpoints analyses will be provided in the SAP, which will be finalized before database lock.

The population PK analysis and pharmacodynamic analyses may be presented separately from the main clinical study report (CSR).

Table 17 - Tertiary/exploratory endpoints

Endpoint	Statistical analysis methods
Pharmacodynamics	For all parameters, raw data, changes from baseline, and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point. Summary plots (mean $\pm$SEM) on raw data, changes from baseline and percent changes from baseline will be provided by treatment group.

9.4.6 Multiplicity considerations

Multiplicity is considered for the significance testing of multiple efficacy endpoints within the former smokers population. The overall Type-I error rate will be controlled at the 2-sided 0.05 level. A testing hierarchy across the efficacy endpoints will be developed and described in the SAP.

As a nonbinding futility IA is planned for the study ([Section 9.5](#)), an administrative penalty of $\alpha=0.001$ will be taken from the significance level used at 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 performed for the IA.

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 and the key secondary endpoint and a selective set of secondary endpoints for both doses will be tested using a prespecified multiplicity testing procedure with the overall Type I error rate being controlled at 0.049 level among the multiple endpoints and the comparisons between each dose (300 mg Q2W or 300 mg Q4W) and placebo. The complete list of the endpoints and the multiplicity testing procedure will be specified in the SAP.

Statistical analysis on the current smoker population is descriptive. No multiplicity control will be applied, and all p-values will be nominal.

9.4.7 Safety analyses

Safety analyses will be descriptive, based on the safety population. There will be a safety population for the former smoker cohort, as well as for the current smoker cohort. In case of comparable outcomes in both cohorts, a combined analysis is planned as well. Details will be described in the SAP. The safety analysis will focus on the TEAEs reported during the treatment-emergent period. This period is defined as the time from the first administration of the IMP to the end of 20-week follow-up period or last contact date in this study, whichever is earlier.

Table 18 - Safety analyses

Assessments	Statistical analysis methods
TEAEs, AESIs, SAEs, AEs leading to death, and AEs leading to permanent treatment discontinuation	Adverse event incidence tables will present by system organ class (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of participants experiencing an AE. Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Proportion of participants with at least 1 TEAE, treatment-emergent SAE, TEAE leading to death, and TEAE leading to permanent treatment discontinuation will be tabulated by treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the study drug. AEs that occur outside the treatment-emergent period will be summarized separately.
Major Cardiovascular Adverse Events (MACE)	The number and percentage (%) of participants with any treatment-emergent event selected for adjudication will be summarized by primary system organ class and PT. All events submitted for adjudication will be listed, including the final adjudicated result. The number and percentage (%) of participants experiencing a treatment-emergent adjudicated event will be summarized within each treatment group.
Death	The following deaths summaries will be generated: • Number (%) of participants who died by study period (TEAE, on-study) summarized on the safety population by treatment received. • Death in nonrandomized participants or randomized and not treated participants. • Treatment-emergent AE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary system organ class, HLGT, HLT, and PT showing number (%) of participants sorted by internationally agreed order of system organ class and alphabetic order of HLGT, HLT, and PT. • All-cause mortality and mortality related to respiratory events including COPD plus mortality related to MACE.

Assessments	Statistical analysis methods
AESI and other AE groupings	Incidence of each type of AESI and other AE groupings will be tabulated by treatment group. An overview summary of the number (%) of participants with any AESI will be provided by following: - Any TEAE. - Any SAE (regardless of treatment-emergent status). - Any treatment-emergent SAE. - Any AE leading to death. - Any TEAE leading to death. - Any TEAE leading permanent treatment discontinuation. - Any TEAE related to IMP reported by the Investigator. - Number of participants with the TEAE per 100 person-years. - Any TEAE by maximum intensity, corrective treatment, and final outcome. The method to identify AESIs and other AE groupings will be specified in the SAP.
Potentially clinically significant laboratory test, vital signs and ECG abnormalities	Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point. Summary statistics will include number of participants, mean, standard deviation, median, Q1, Q3, minimum, and maximum. The following definitions will be applied to laboratory parameters: - The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests. - PCSA criteria will determine which participants had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such participants will be the numerator for the TEAE PCSA percentage. The proportion of participants who had at least 1 incidence of PCSA at any time during the TEAE period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

9.4.8 Other analyses

The impact of exceptional emergency situations on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

9.5 INTERIM ANALYSES

A nonbinding futility IA is planned to be performed after a minimum of approximately [REDACTED] of originally planned 1860 randomized former smoker participants have completed at least a minimum of [REDACTED] in both planned Phase 3 studies combined: Study EFC16750 (n=930) and Study EFC16819 (n=930 former smokers only) corresponding to a total of approximately [REDACTED] participants. [REDACTED]

[REDACTED] Any unblinded interim look will be performed by an independent group separated from personnel involved in the trial conduct, data

collection and management, and final statistical analysis. The independent DMC will review the unblinded IA results and recommend action based upon criteria that will be specified in the DMC Charter and SAP. Unblinded results can only be viewed by a small group of senior sponsor individuals, who are separate from sponsor personnel involved in the conduct of the study. A detailed IA plan will be finalized, including 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, prior to any interim administrative look. Anyone involved in the conduct of the study (participants, Investigators, and study team) 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, if applicable.

The SAP will describe the planned IA in greater detail.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
 - Applicable ICH Good Clinical Practice (GCP) Guidelines.
 - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR]).
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted, as required by local regulations, to the relevant health authority and an IRB/IEC by the Investigator or Sponsor and, where further required by regulations, reviewed and approved by the health authority and the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and healthy authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the health authority (as applicable) and IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
 - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and,
 - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
 - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. In addition to a hard copy informed consent form, alternately, potential participants may be consented [or re-consented] electronically, if allowed by local regulation, via a third-party platform accessed through a computer or mobile phone.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In addition to “main” protocol ICF required for study participation, the participant can consent to the following optional assessments:
 - Pharmacogenetic RNA/DNA assessments.
 - Future use of samples.
 - Home nursing visits.

- Prior to any additional optional assessment, such as collection of blood for pharmacogenetics, the optional section of ICF (written) should be completed by the participant, and by the person who conducted the informed consent discussion.
- The screening period starts on the day of ICF signature. The registration of Visit 1A in the IRT system should also be performed on the day of ICF signature.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF. More information related to rescreening is included in [Section 5.4](#).

The ICF contains 2 separate sections that address the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, and ethics committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data are intended to be used for the whole drug development program from collection to reimbursement.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation[s] details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or precontractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at [Sanofi.com](https://www.sanofi.com)).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
 - Personnel within Sanofi or partners or service providers involved in the study.
 - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
 - The standard contractual clauses of the European Commission for transfers towards our partners and service providers.
 - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (<https://transceleratebiopharmainc.com/initiatives/investigator-registry/>). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit <https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact>).

10.1.5 Committees structure

Independent Data Monitoring Committee

A DMC, independent from the Sponsor, will be established for this study. This committee is governed by a DMC Charter. The DMC will comprise externally based individuals with expertise in the diseases under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review safety data, and efficacy where needed, during the course of the trial for evaluation of benefit/risk, review results (eg, IA), and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor. In the above-mentioned capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.

Adjudication Committee

Adjudication will be performed by experts independent of the Sponsor for the evaluation of whether deaths and (potential) cardiovascular SAEs meet criteria for certain safety endpoints.

A separate confirmatory adjudication will occur for AECOPD exacerbations. Adjudicators will adjudicate these events in a consistent and unbiased manner throughout the study.

More details are provided in [Section 8.3.6](#).

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available, privacy of participants in the clinical trial continues to remain protected. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the “European Federation of Pharmaceutical Associations and Industries (EFPIA) Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations”

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
 - Information on the product leads to doubt as to the benefit/risk ratio.
 - Discontinuation of further study intervention development.
- For site termination:
 - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
 - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
 - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in [Table 19](#) will be performed by the central laboratory.
- Local laboratory results are only required in the event that:
 - a) the central laboratory results are not available in time for either study intervention administration and/or response evaluation, or
 - b) in case the participant cannot come to the clinic due to travel restrictions related to a pandemic and the blood sample cannot be obtained at the participant's home using the central laboratory kit supplied by the vendor (after Sponsor approval).

- c) Local regulation does not allow the transportation of (specific) samples outside of the country of origin (after Sponsor approval).
 - d) If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
 - e) If screening (Visit 1; Week 0) blood eosinophil count cannot be analyzed in a timely manner at the central laboratory, a local certified laboratory can be used only after Sponsor approval.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 5](#) of the protocol.
 - Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
 - TB testing must be done using local laboratory according to local guidelines. In case no local guidelines are available, or local TB testing is not possible, a blood sample can be sent to the central laboratory for a QuantiFERON test.
 - For TB testing, see [E 15](#).
 - In case a TB test result is positive or indeterminate, a repeat test is allowed. In case the repeated test is negative, or in case the first AND the second tests are indeterminate, an Investigator assessment should take place. If the Investigator confirms the participant has no signs of infection, AND the participant is not at high risk of contracting TB AND the participant is not from a TB endemic area, AND specialist consultation has ruled out active disease, the participant can be randomly assigned if eligible.
 - Pregnancy testing will be performed at screening with a blood test using a central laboratory, and at subsequent visits using Sponsor-provided urine tests, or locally provided urine test (China only).

Table 19 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit <u>Total white blood cell (WBC) count with differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils

Laboratory assessments	Parameters
Clinical chemistry ^a	Blood urea nitrogen (BUN) Creatinine C-reactive Protein Glucose [fasting] Potassium Sodium Bicarbonate Creatinine phosphokinase Albumin Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase Uric acid Lactate dehydrogenase Total bilirubin (case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin) Total protein Total Cholesterol
Routine urinalysis	• Specific gravity. • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick. • Microscopic examination (if blood or protein is abnormal).
Other screening tests	• For women of childbearing potential: Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test at Screening (Visit 1A) and urine pregnancy tests during the Treatment (from Visit 2 to visit 28, at least once per month) and the Follow-Up Periods (at Visit 29 and Visit 31) as the plan in SoA. A negative result must be obtained at Visit 1A and at Visit 2 prior to randomization. In case of positive urine test the study treatment will be withheld and a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. Pregnancy urine test at home administration/telephone visits will be performed by the participant herself at home at Week 20, 28, and 44. The result will be recorded. Participant will be instructed to not administer next IMP in case of suspected/confirmed pregnancy and contact the site. • Hepatitis serologic testing at Screening (Visit 1A): hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb IgM and Total), and hepatitis C virus antibodies (HCVAb). In case of results showing HBsAg (negative) and HBcAb Total (positive), HBV DNA testing will be performed prior to randomization to rule out a false positivity to clarify the serological status. In case of results showing HCV Ab (positive), HCV RNA testing will be performed to rule out a false positivity. • HIV serologic testing at Screening (Visit 1A): Human immunodeficiency virus (HIV) screen (anti-HIV-1 and HIV-2 antibodies). • Routine urine cotinine test. • High-sensitivity urine cotinine/anabasine test. • Tuberculosis testing according to local guidelines (local laboratory) or if not available, in central laboratory (Quantiferon test) at Screening (Visit 1A).

Laboratory assessments	Parameters
------------------------	------------

- | | |
|--|--|
| | <ul style="list-style-type: none"> Nasopharyngeal/oropharyngeal swabs and a quantitative polymerase- chain- reaction tests (or polymerase- chain- reaction / antigen test in local laboratory if needed) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes coronavirus disease 2019 [COVID-19]) at Screening (Visit 1A). |
|--|--|

NOTES :

- a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 6 ([Section 10.6](#)).
Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
 - Symptomatic and/or,
 - Requiring either corrective treatment or consultation, and/or,
 - Leading to IMP discontinuation or modification of dosing, and/or,
 - Fulfilling a seriousness criterion, and/or,
 - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. For COPD events, different rules apply (see [Section 8.1.1.1](#)).

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition. For COPD events, different rules apply (see [Section 8.1.1.1](#)).
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease). An exemption is an exacerbation of COPD; these events do not need to be reported as AEs. Only exacerbation of COPD events that meet seriousness criteria should be reported as SAEs (see [Section 8.1.1.1](#)).

A SAE is defined as any untoward medical occurrence that, at any dose:

- a) Results in death**
- b) Is life-threatening**

The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an ER or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor representative in lieu of completion of the SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor representative. In this case, all participant identifiers, with the exception of the

participant number, will be redacted on the copies of the medical records before submission to the Sponsor representative.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor representative via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor or Sponsor representative(s) by telephone.
- Contacts for SAE reporting can be found in the contact list in the Investigator Study File.

SAE reporting to the Sponsor representative via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor or Sponsor representative(s).
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts for SAE reporting can be found in the contact list in the Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal.
2. Pre-menopausal female with 1 of the following:
 - Documented hysterectomy.
 - Documented bilateral salpingectomy.
 - Documented bilateral oophorectomy.
 - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Post-menopausal female
 - A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.
4. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
5. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

CONTRACEPTION GUIDANCE:

Female participants of childbearing potential are eligible to participate if they agree to use a method of contraception consistently and correctly as described below.

CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods^b That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation^c.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS)^c.
- Bilateral tubal occlusion.
- Vasectomized partner.

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)

Highly Effective Methods^b That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^c
 - Oral
 - Intravaginal
 - Transdermal
 - Injectable.
- Progestogen-only hormone contraception associated with inhibition of ovulation^c
 - Oral
 - Injectable.
- Sexual abstinence

(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

COLLECTION OF PREGNANCY INFORMATION:**Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.

Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in [Section 8.3.4](#). While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA or RNA

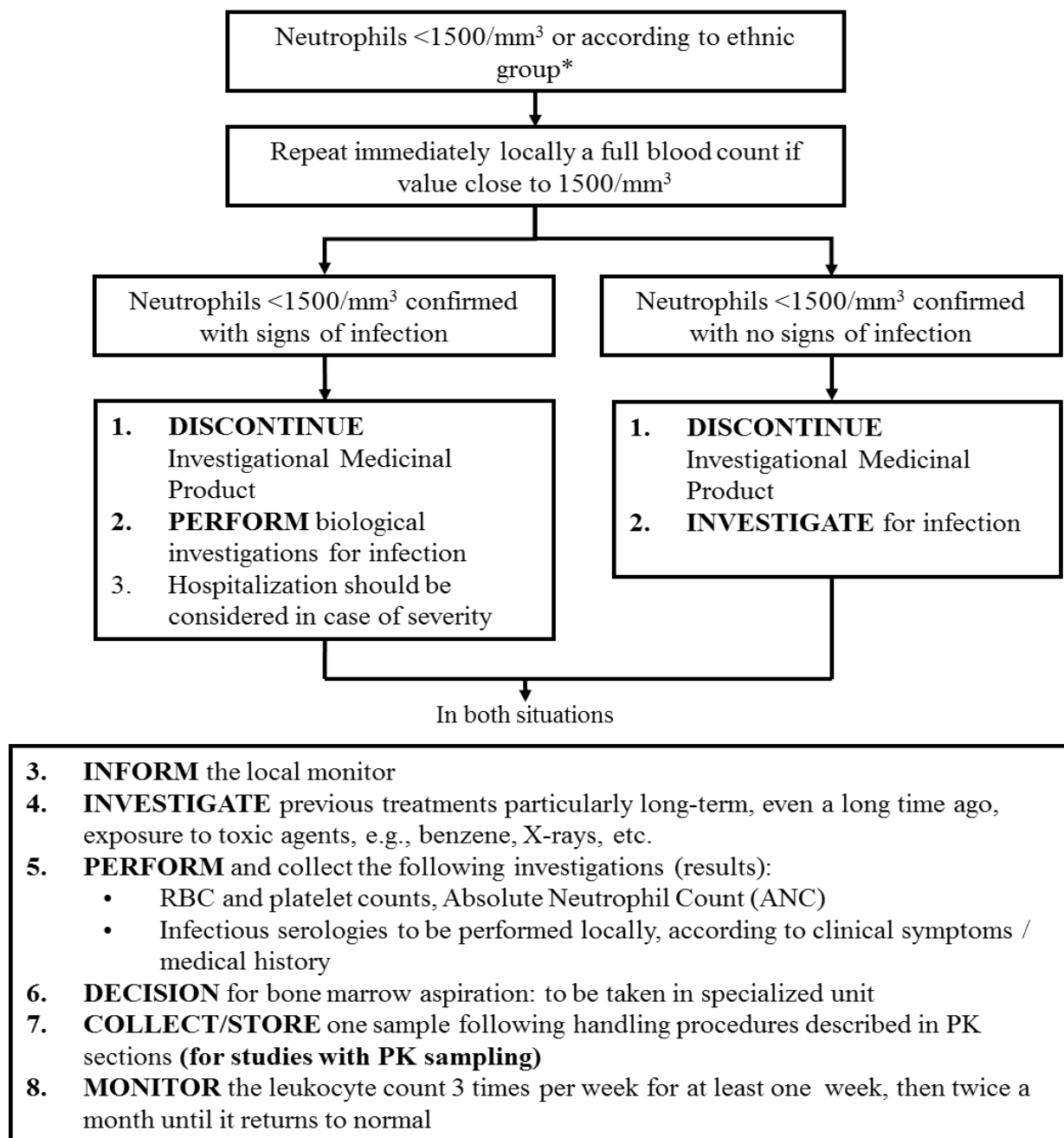
- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA or RNA analysis from consenting participants.
- DNA or RNA samples will be used for research related to itepekimab or COPD and related diseases. They may also be used to develop tests/assays including diagnostic tests related to itepekimab or related drugs and other pulmonary diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome including whole-exome sequencing, whole-genome sequencing

and DNA copy number variation. Transcriptome sequencing (or other methods for quantifying RNA expression) may be performed (as appropriate).

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to itepekimab or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA and RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on itepekimab or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

NEUTROPENIA

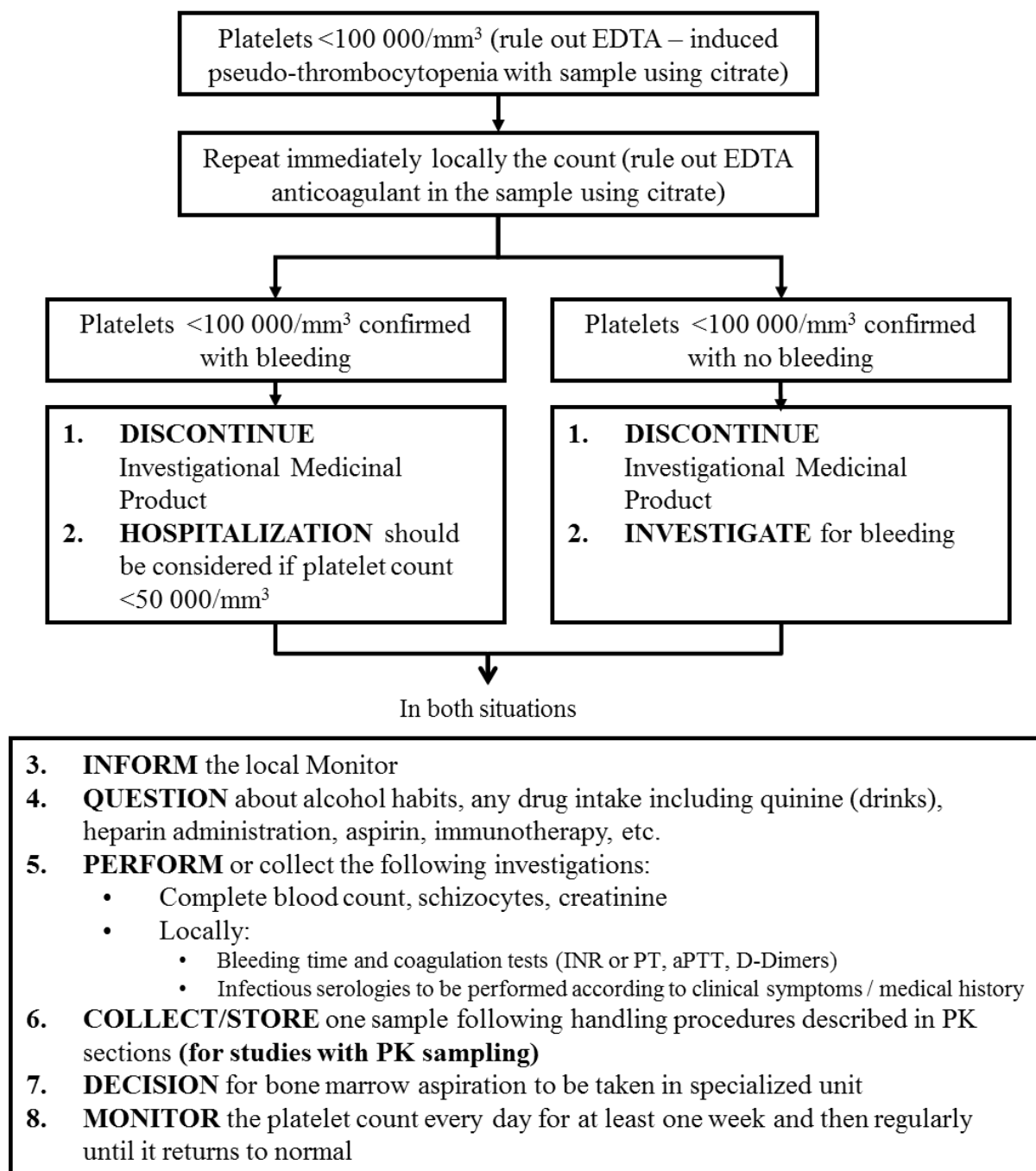


* For individuals of African descent, the relevant value of concern is $<1000/\text{mm}^3$

PK = pharmacokinetic(s).

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 ([Section 10.3](#)) is met.

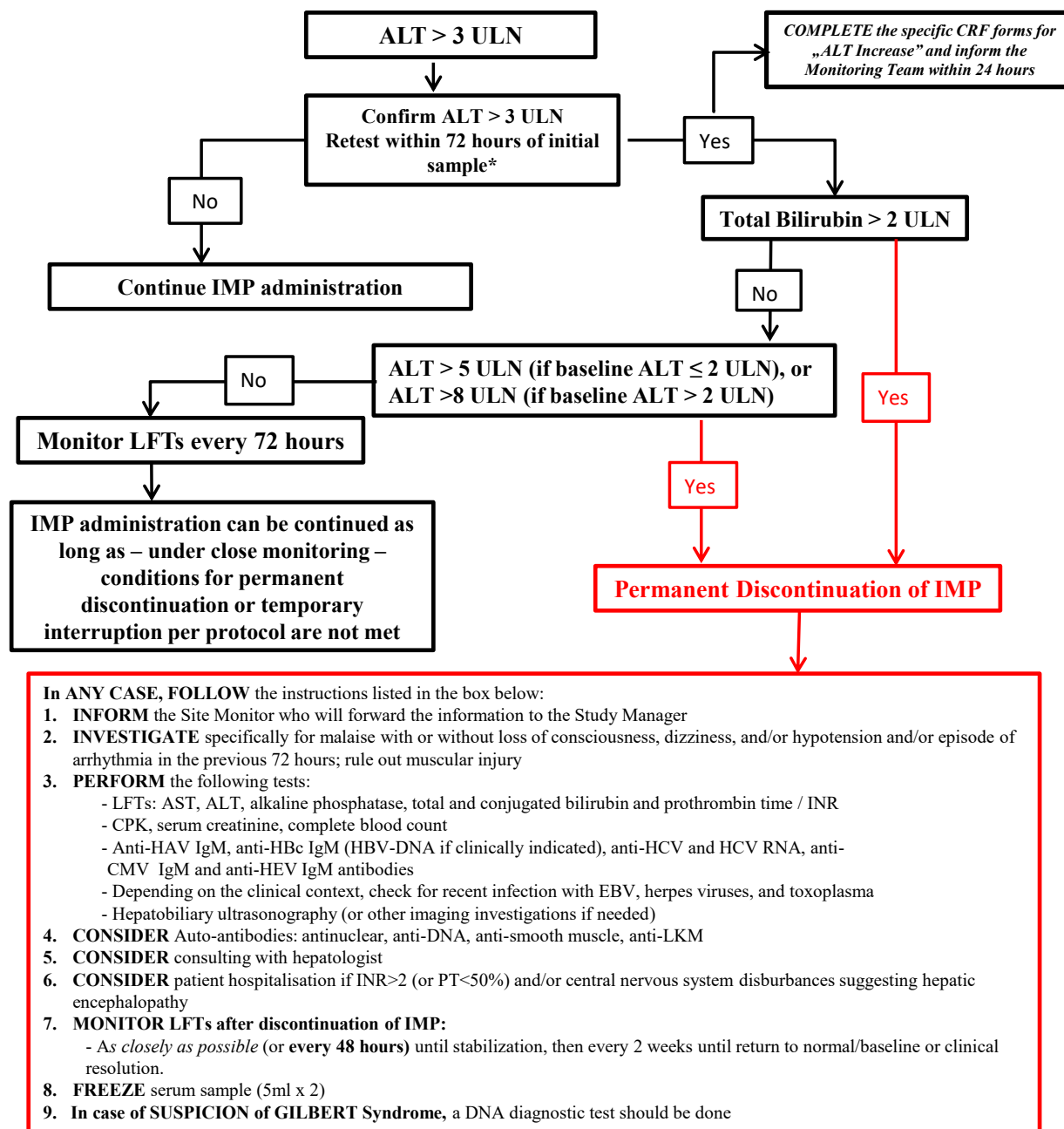
THROMBOCYTOPENIA



aPTT = activated partial thromboplastin time; EDTA = ethylenediaminetetraacetic acid; INR = international normalized ratio; PK = pharmacokinetic(s); PT = prothrombin time.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 ([Section 10.3](#)) is met.

INCREASE IN ALT



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; CRF = case report form; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; HAV = hepatitis A virus; HBc = hepatitis B core; HBV = hepatitis B virus; Ig = immunoglobulin; IMP = investigational medicinal product; INR = international normalized ratio; LFT = liver function test; LKM = liver kidney microsomal; PT = prothrombin time; ULN = upper limit of normal.

*If unable to retest in 72 hours, use original laboratory test results to decide on further reporting/monitoring/discontinuation.

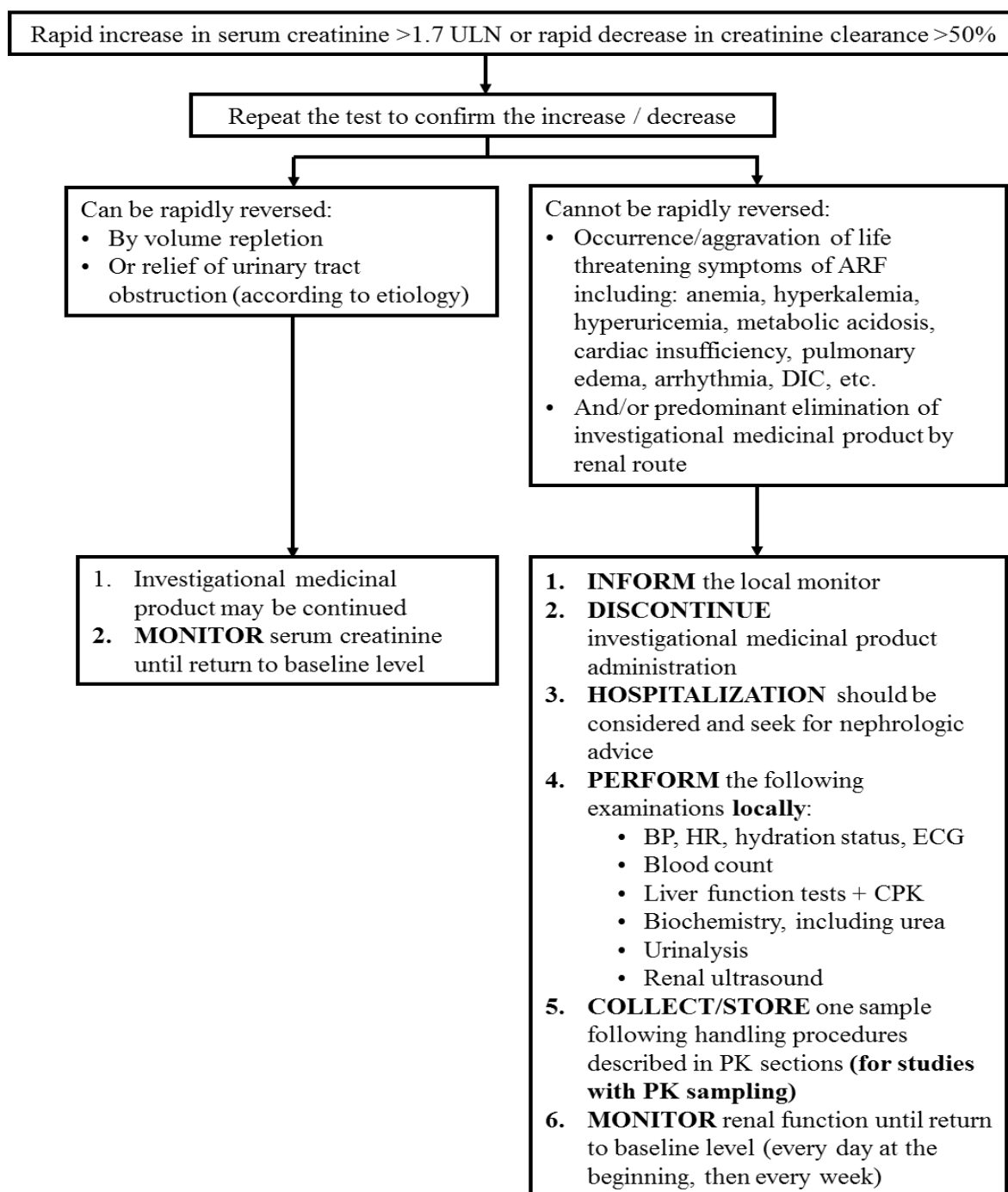
Note:

“Baseline” refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Appendix 3 (Section 10.3) for guidance on safety reporting.

Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

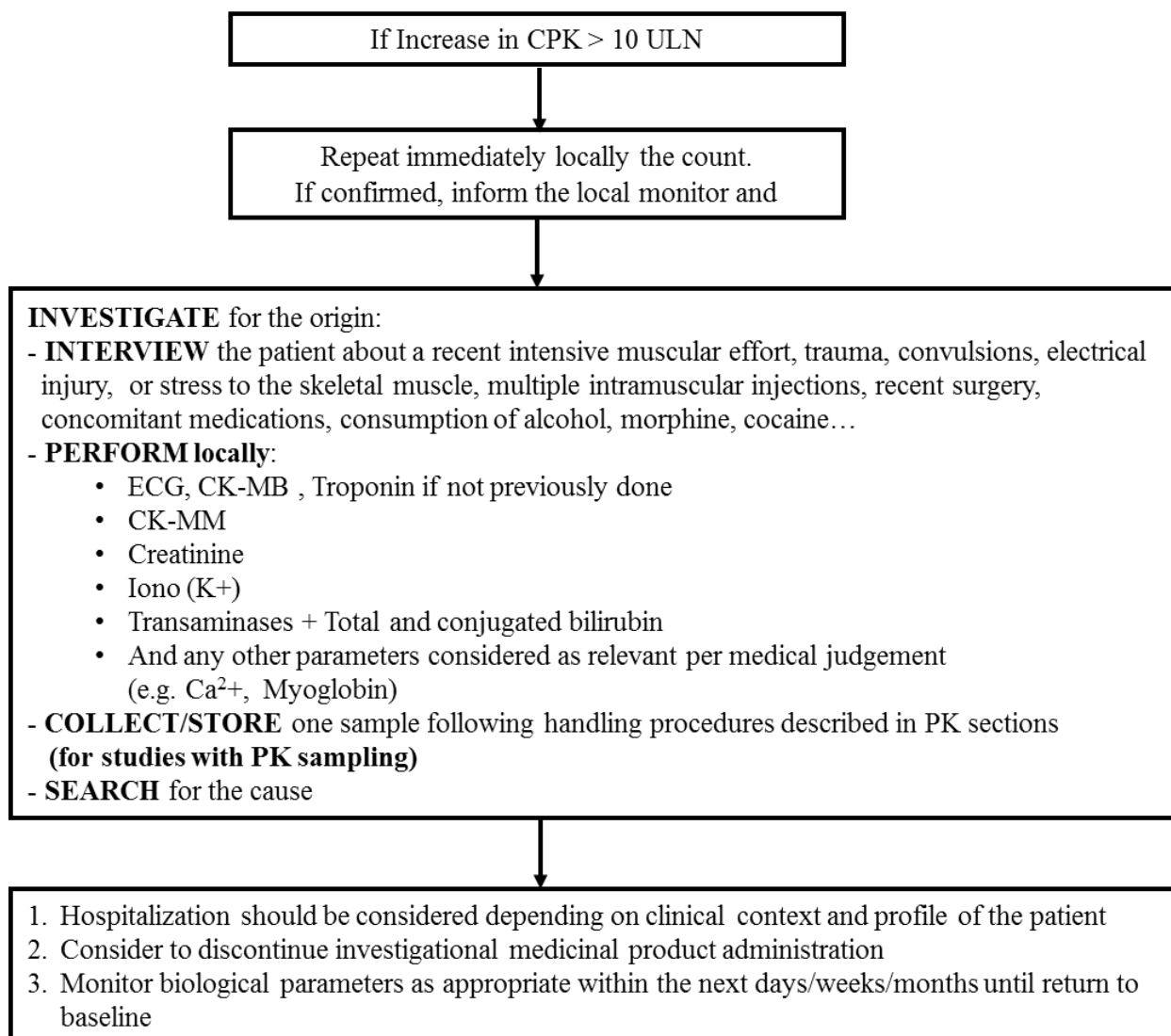
**INCREASE IN SERUM CREATININE in patients with normal baseline
(creatininemia between 45 µmol/L and 84 µmol/L)**



ARF = acute renal failure; BP = blood pressure; CPK = creatine phosphokinase; DIC = disseminated intravascular coagulation; ECG = electrocardiogram; HR = heart rate; PK = pharmacokinetic(s); ULN = upper limit of normal.

Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 ([Section 10.3](#)) is met.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



CK-MB = creatine kinase MB; CK-MM = creatine kinase MM; CPK = creatine phosphokinase; ECG = electrocardiogram; ULN = upper limit of normal.

Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Appendix 3 ([Section 10.3](#)) is met.

10.7 APPENDIX 7: MEDICAL DEVICE INCIDENTS: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

This section is not applicable as devices will not be supplied for this study.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Informed consent process: All references to “legally authorized representative” are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to “legally authorized representative” are found in [Section 7.1.1](#), [Section 8.3](#), [Section 10.1.3](#) and [Section 10.19](#).

10.9 APPENDIX 9: LIST OF PROHIBITED LIVE-ATTENUATED VACCINES

- BCG anti-TB vaccine.
- Chickenpox (Varicella).
- Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted.
- Measles (Rubeola).
- Measles-mumps-rubella (MMR) combination.
- Measles-mumps-rubella-varicella (MMRV) combination.
- Mumps.
- Oral polio (Sabin).
- Oral typhoid.
- Rotavirus.
- Rubella.
- Smallpox (Vaccinia).
- Varicella zoster (shingles).
- Yellow fever.

This list is indicative and not exhaustive.

10.10 APPENDIX 10: DEFINITION OF ANAPHYLAXIS

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (42).

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.

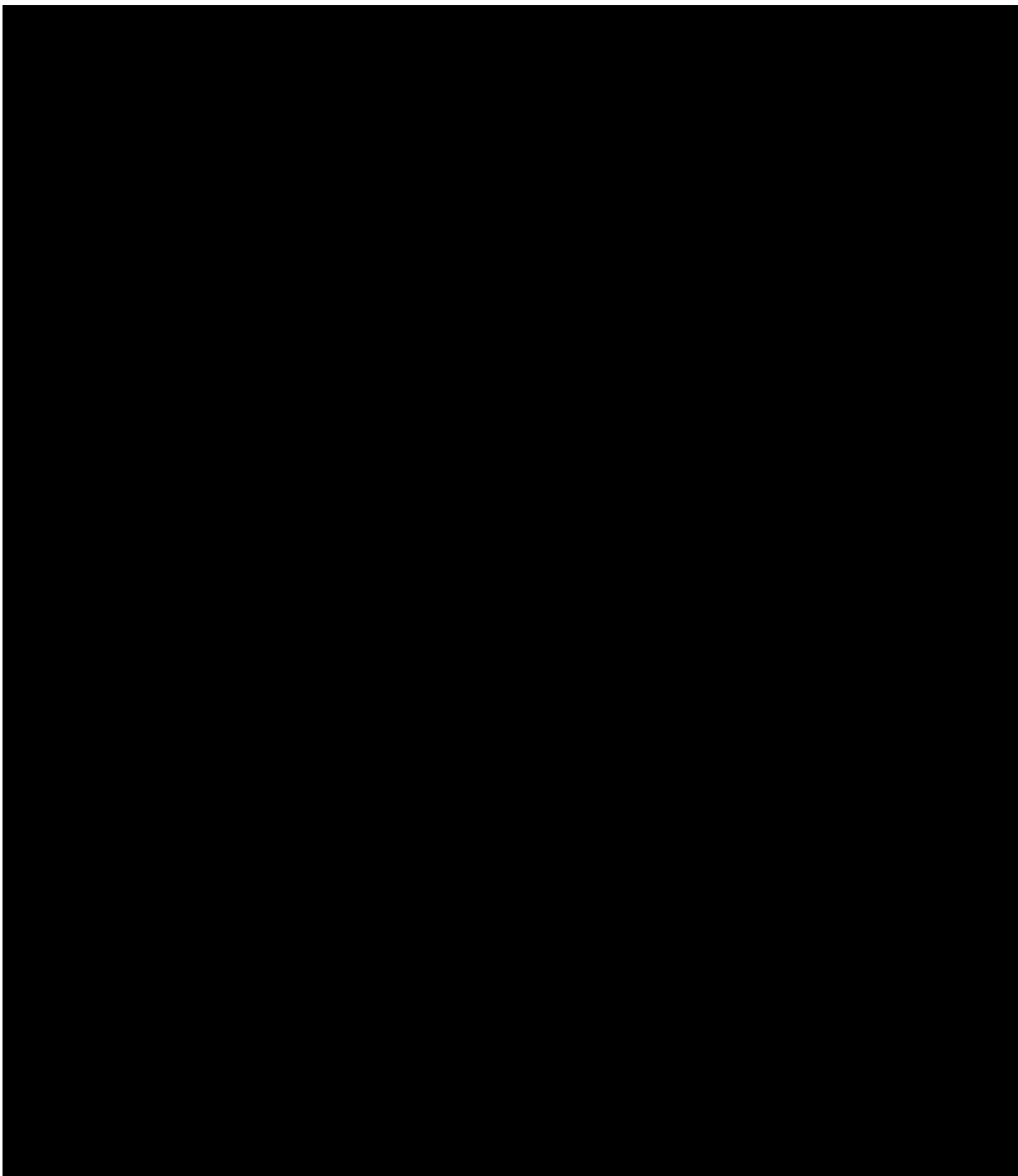
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.11 APPENDIX 11: LIST OF OPPORTUNISTIC INFECTIONS

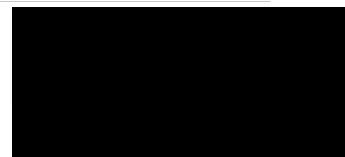
- Aspergillosis.
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along the Mississippi and Ohio Rivers).
- Candidiasis - only systemic, extensive mucosal or cutaneous candidiasis.
- Coccidioides immitis (endemic south-western US and Central and South America).
-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

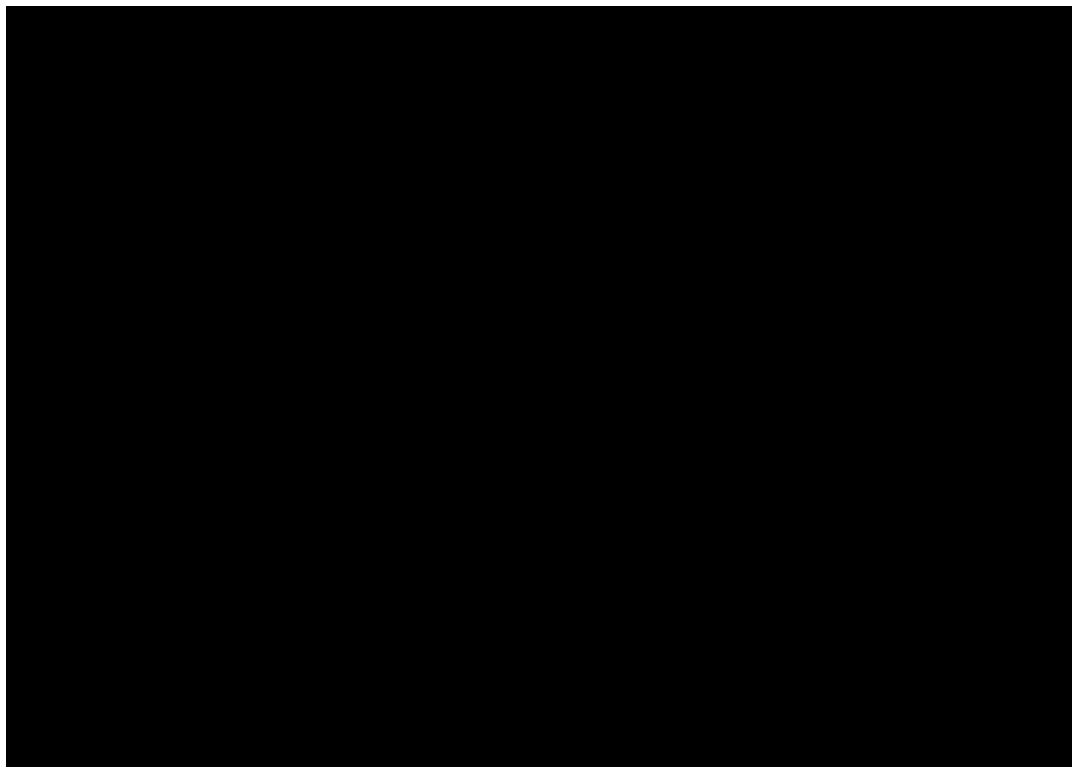
10.12 APPENDIX 12: COPD ASSESSMENT TEST



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



10.13 APPENDIX 13: ST. GEORGES'S RESPIRATORY QUESTIONNAIRE

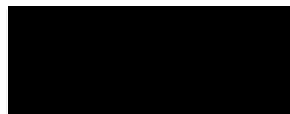


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P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 0RE, UK.

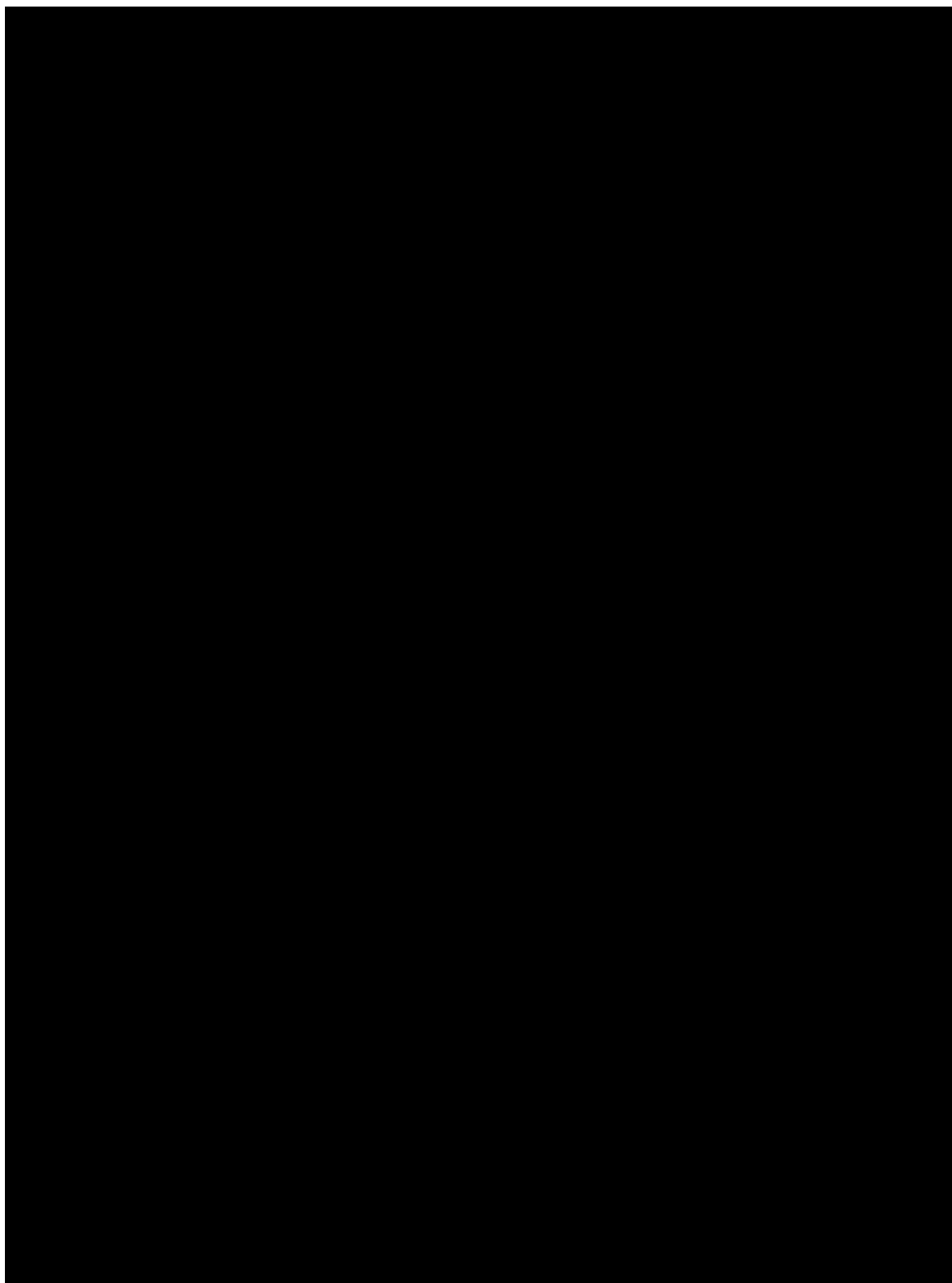
UK/ English (original) version

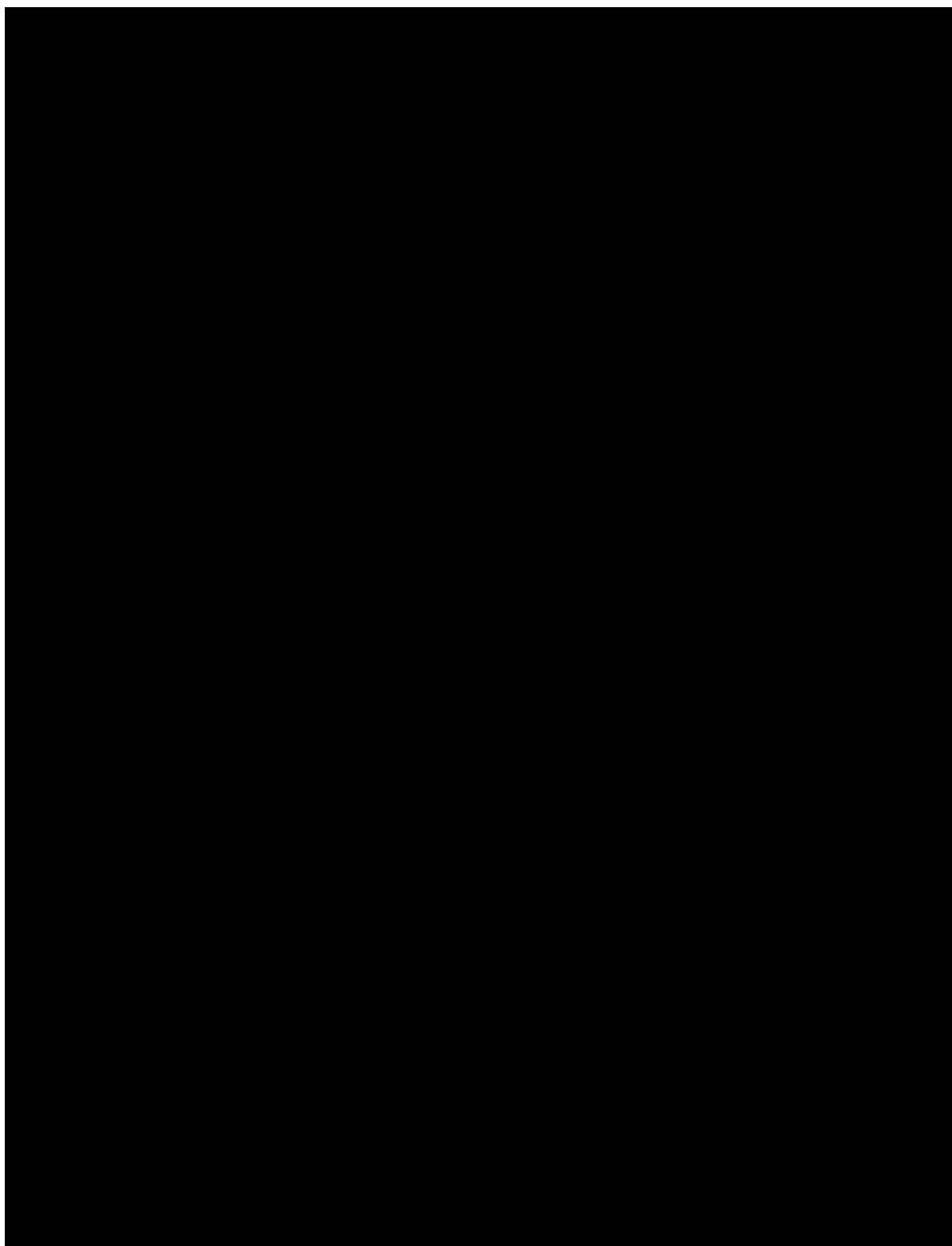
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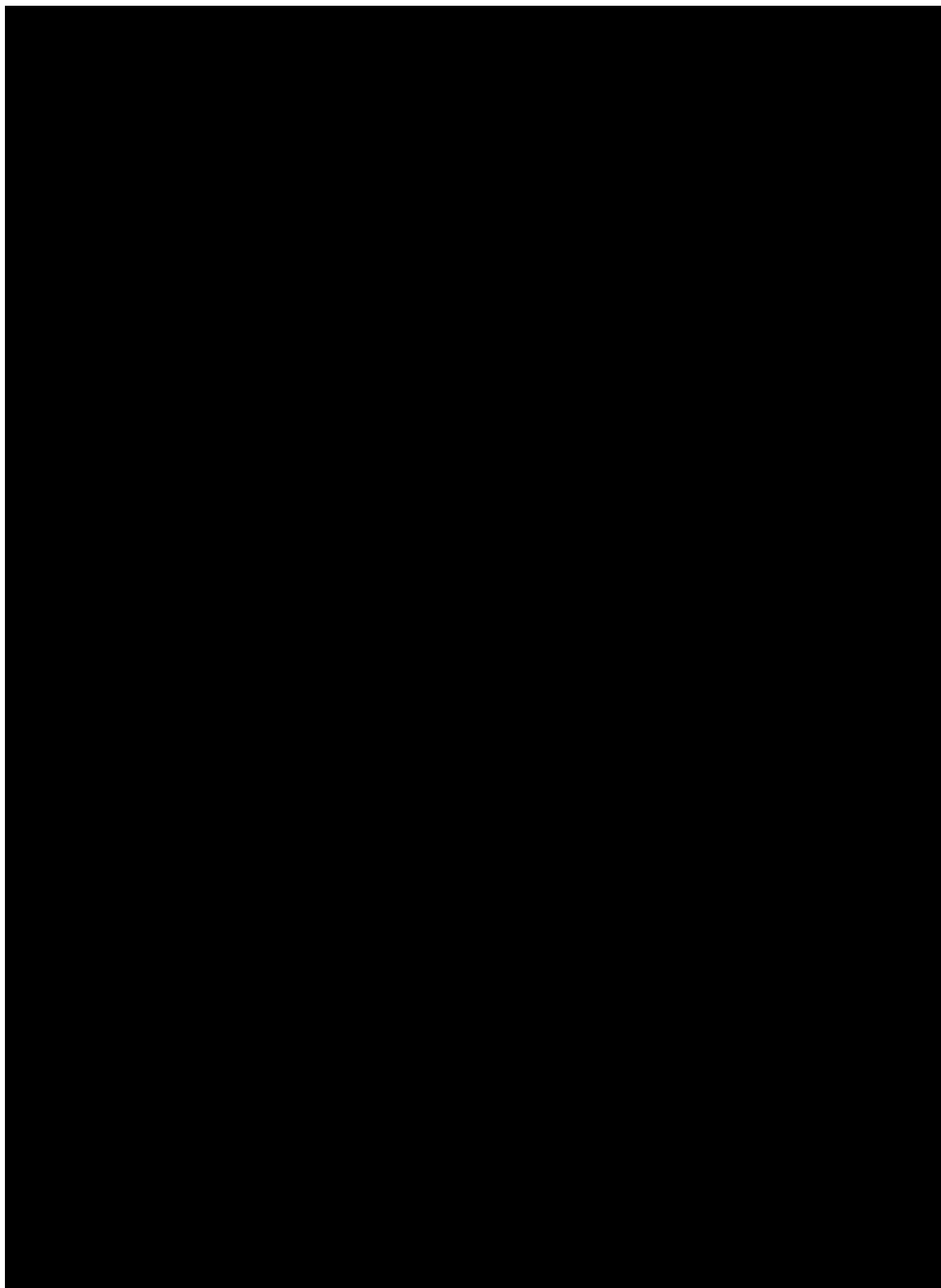
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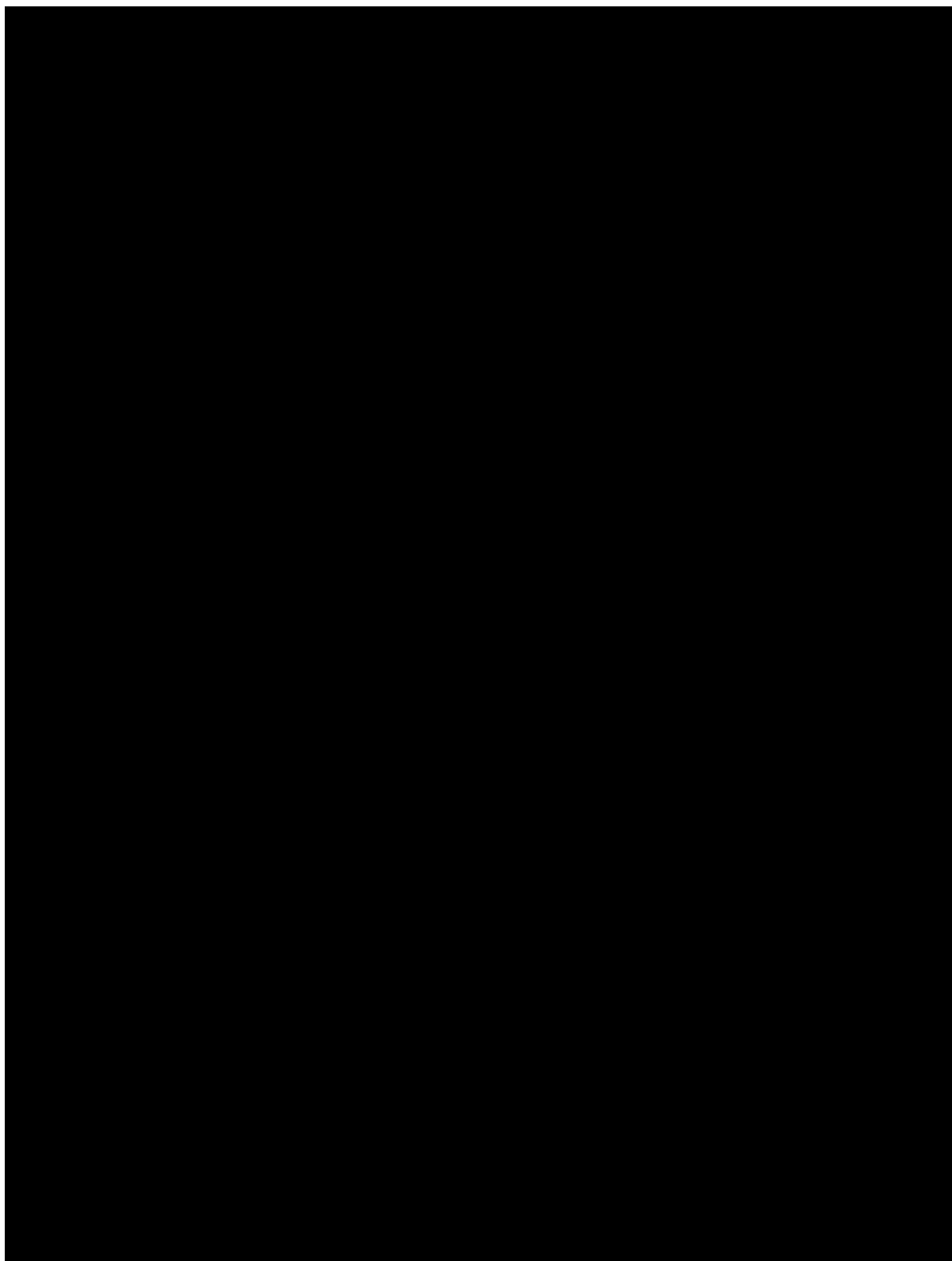


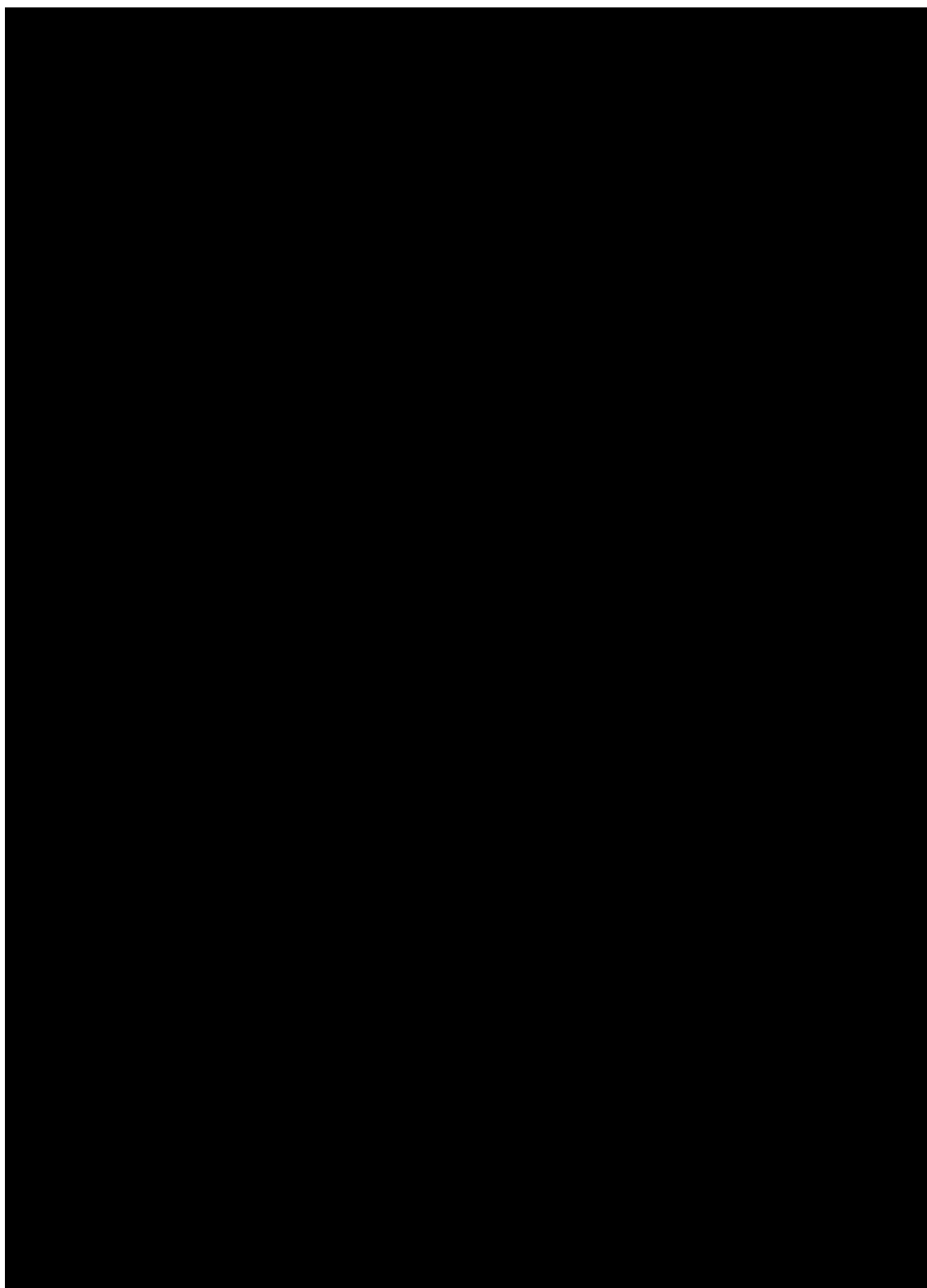
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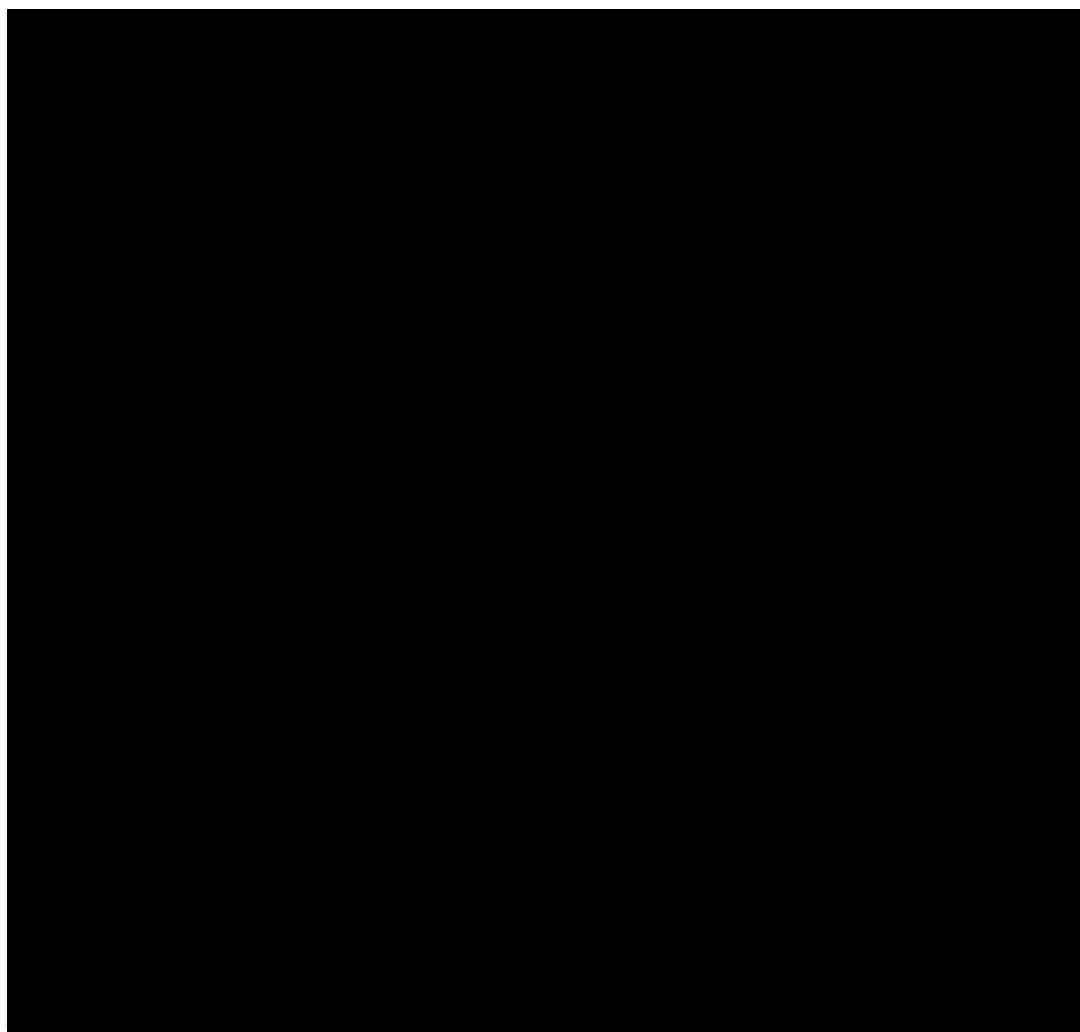


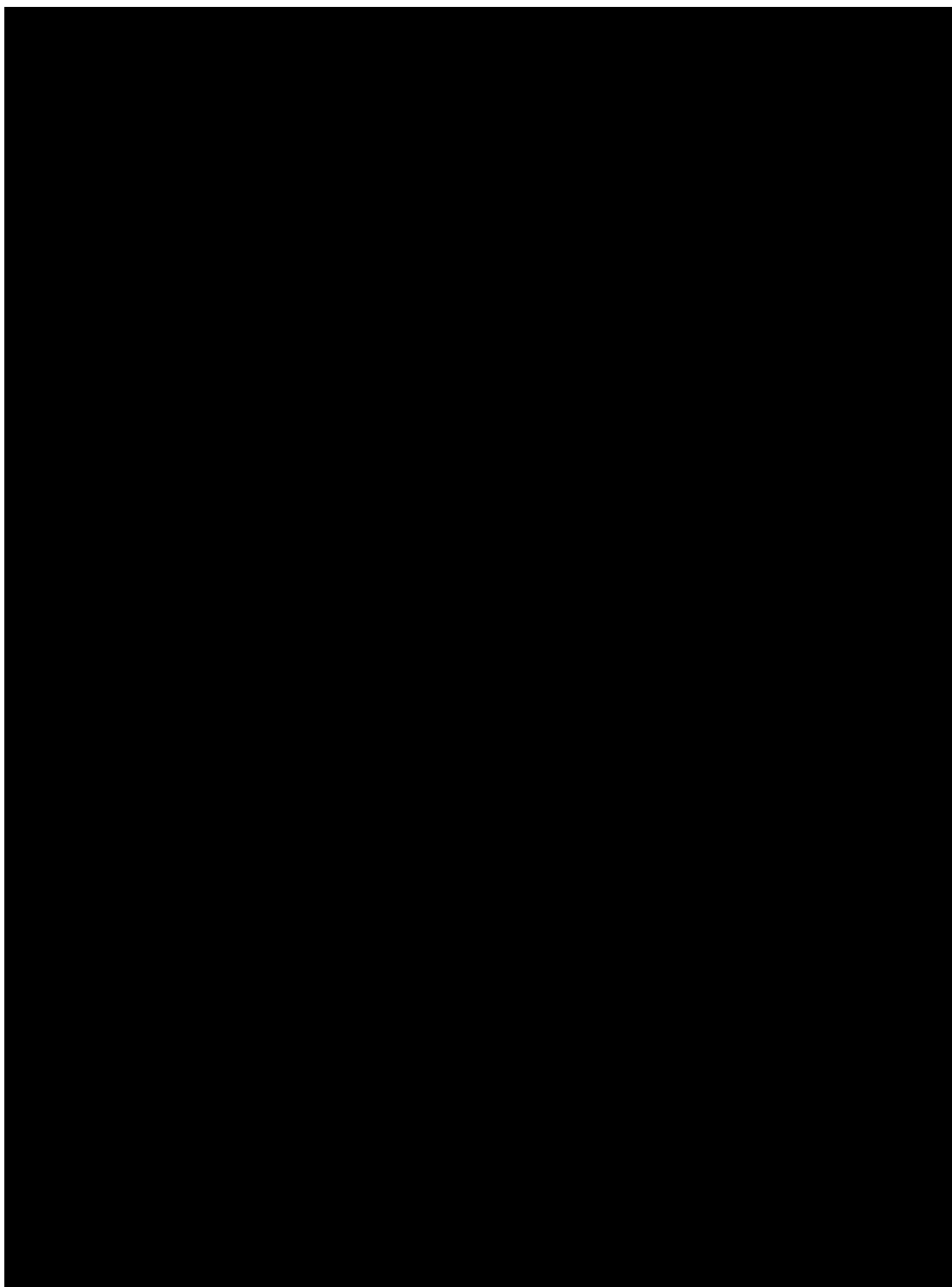


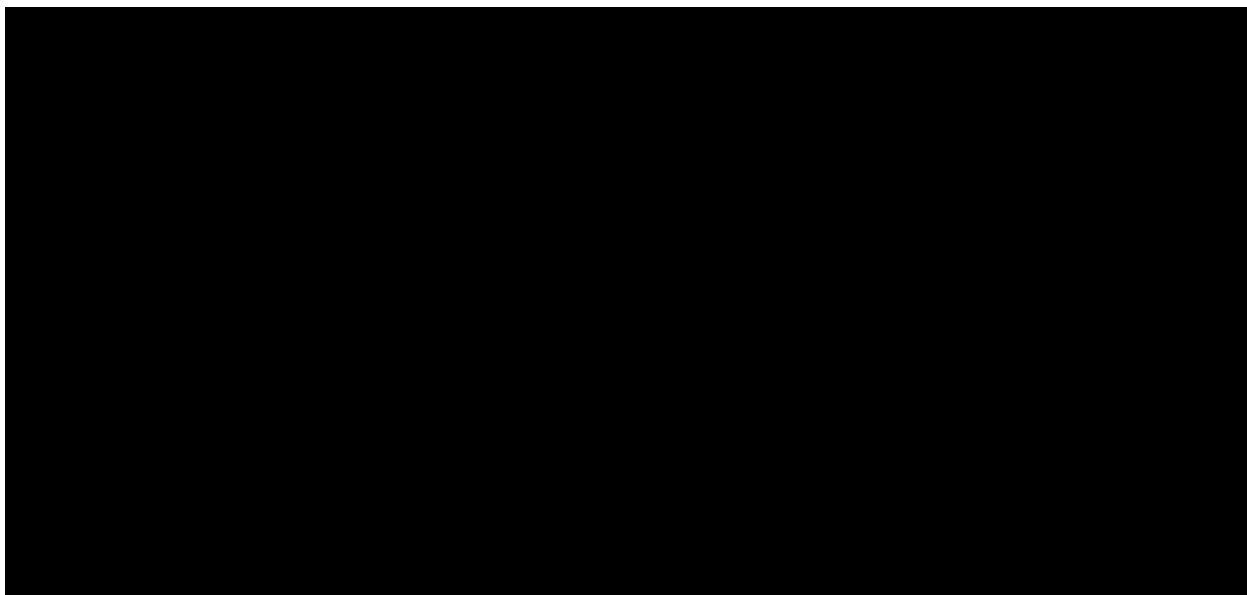




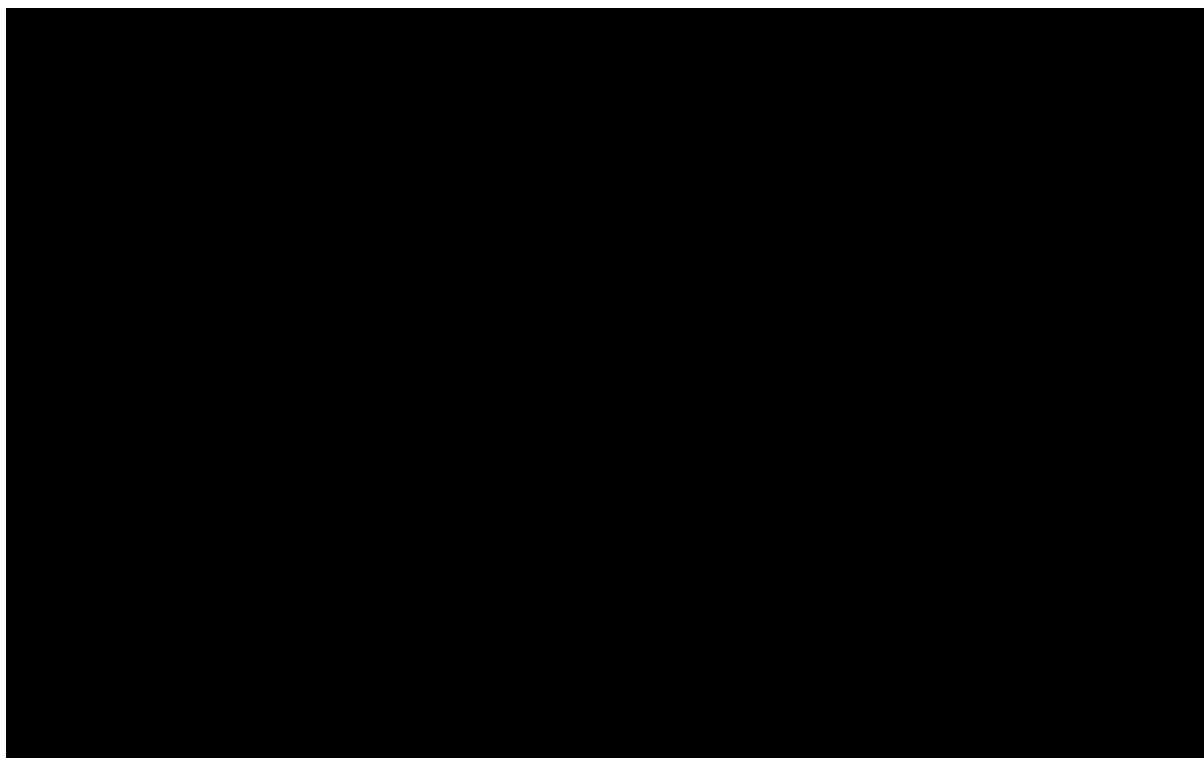
10.14 APPENDIX 14: THE EXACT AS FORMATTED FOR PERSONAL DIGITAL ASSISTANT (PDA)

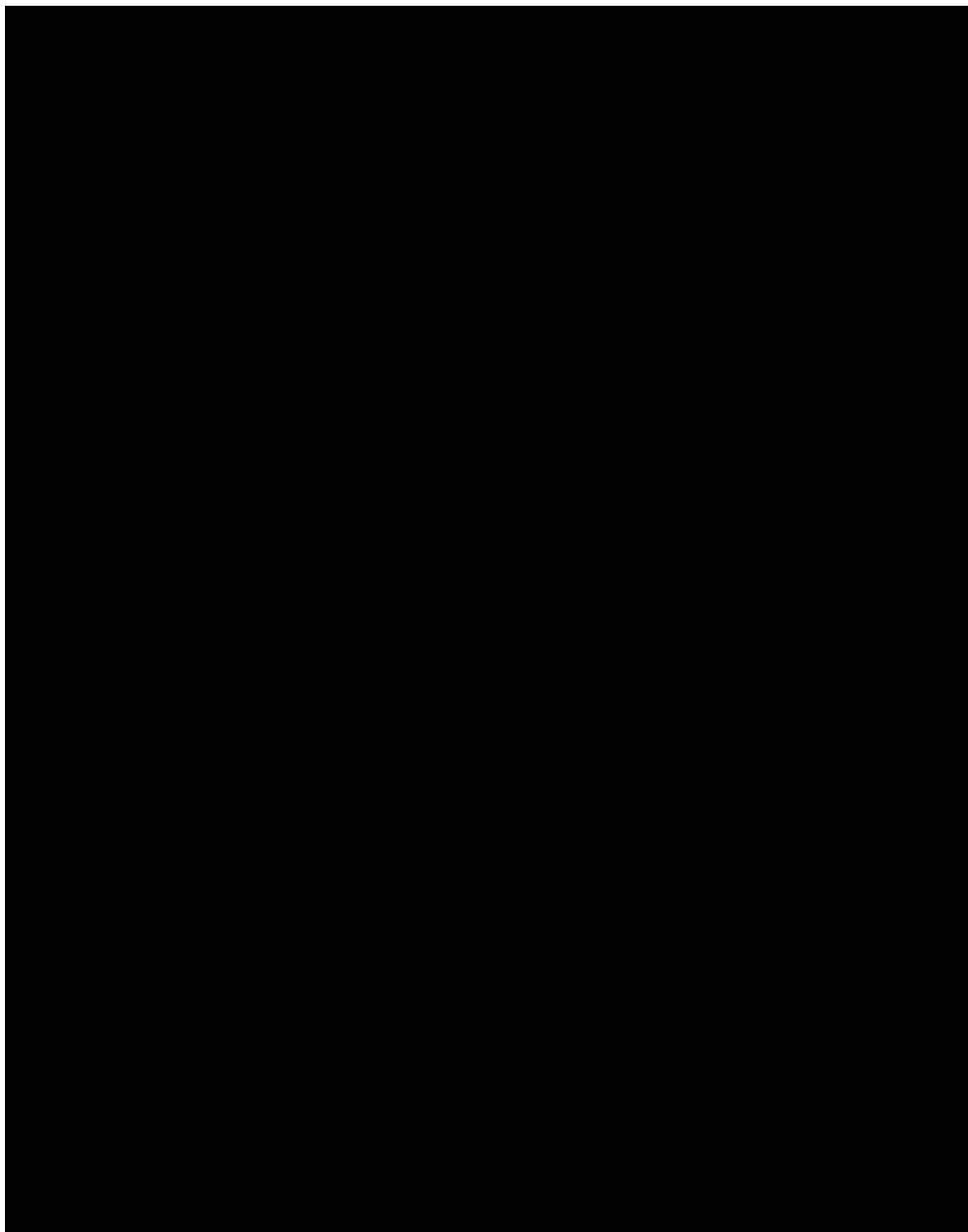


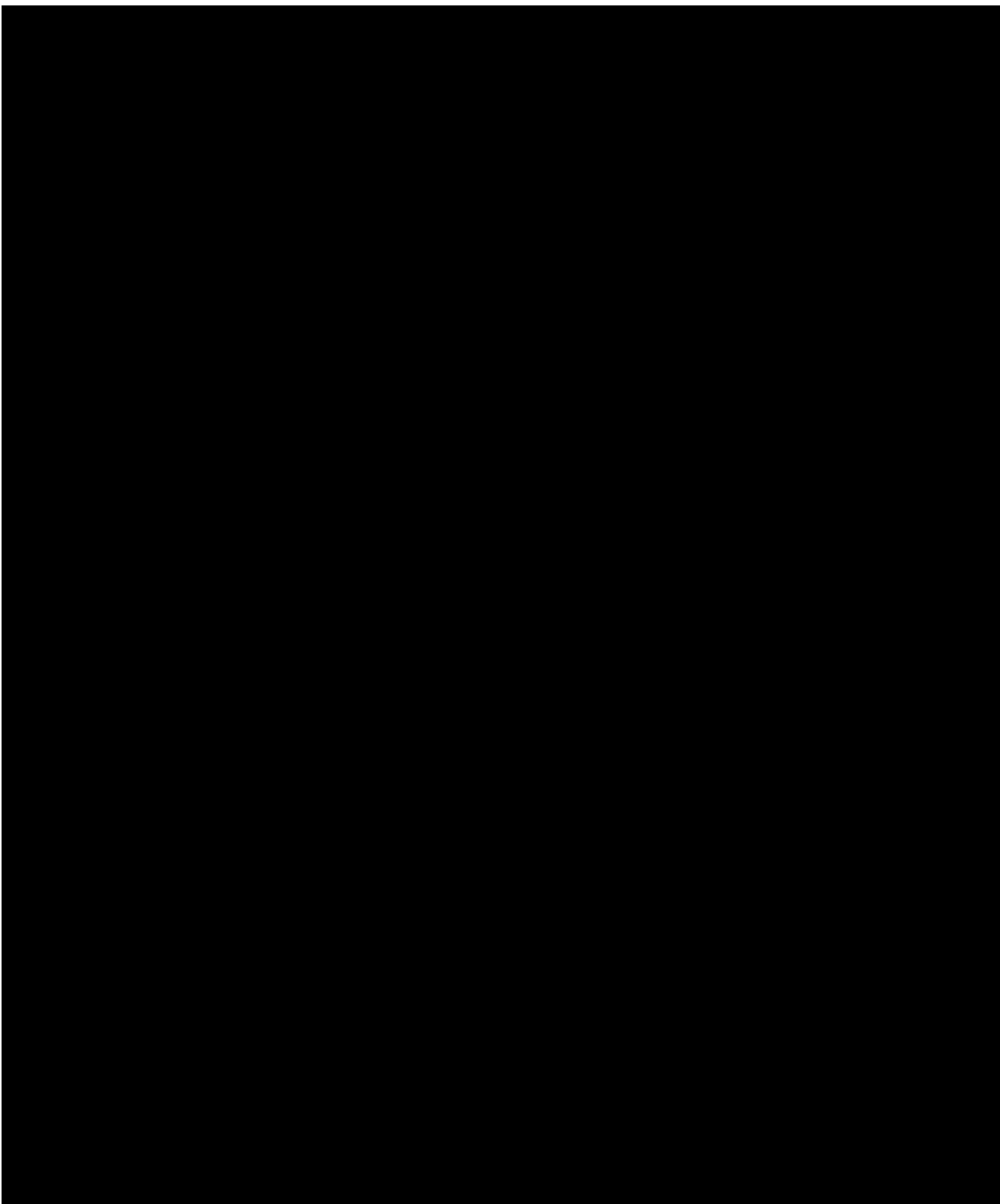


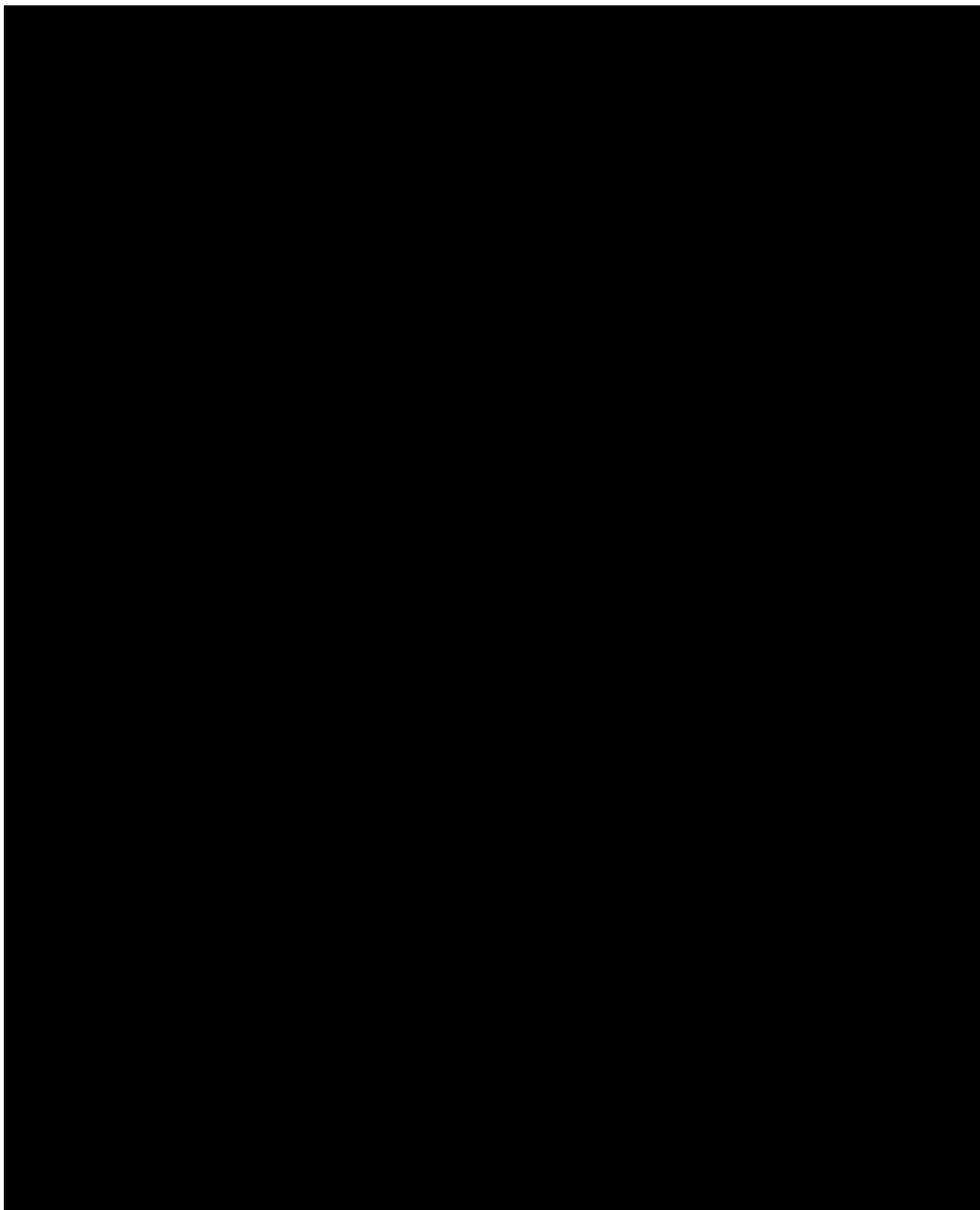


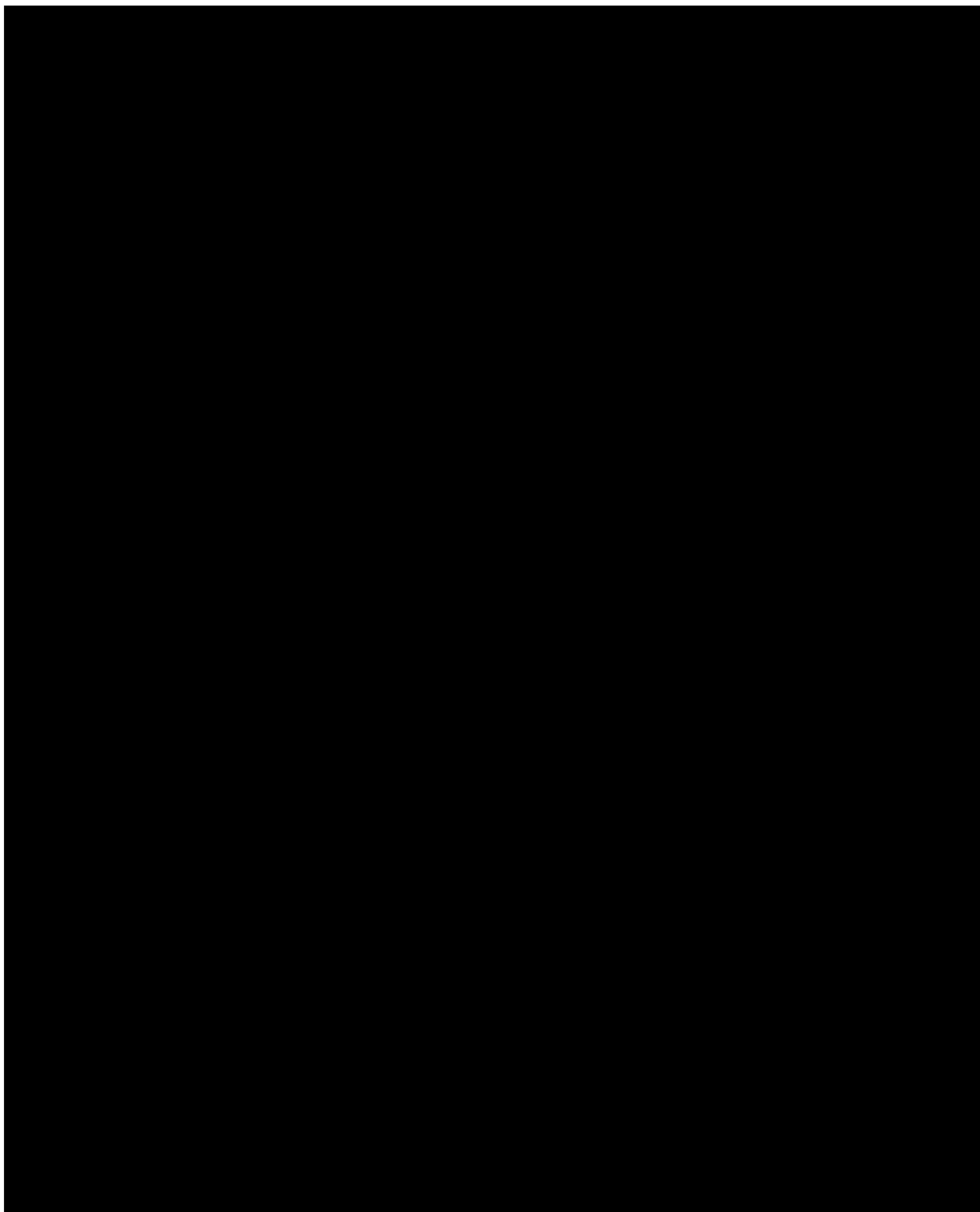
10.15 APPENDIX 15: EXACT INSTRUMENT

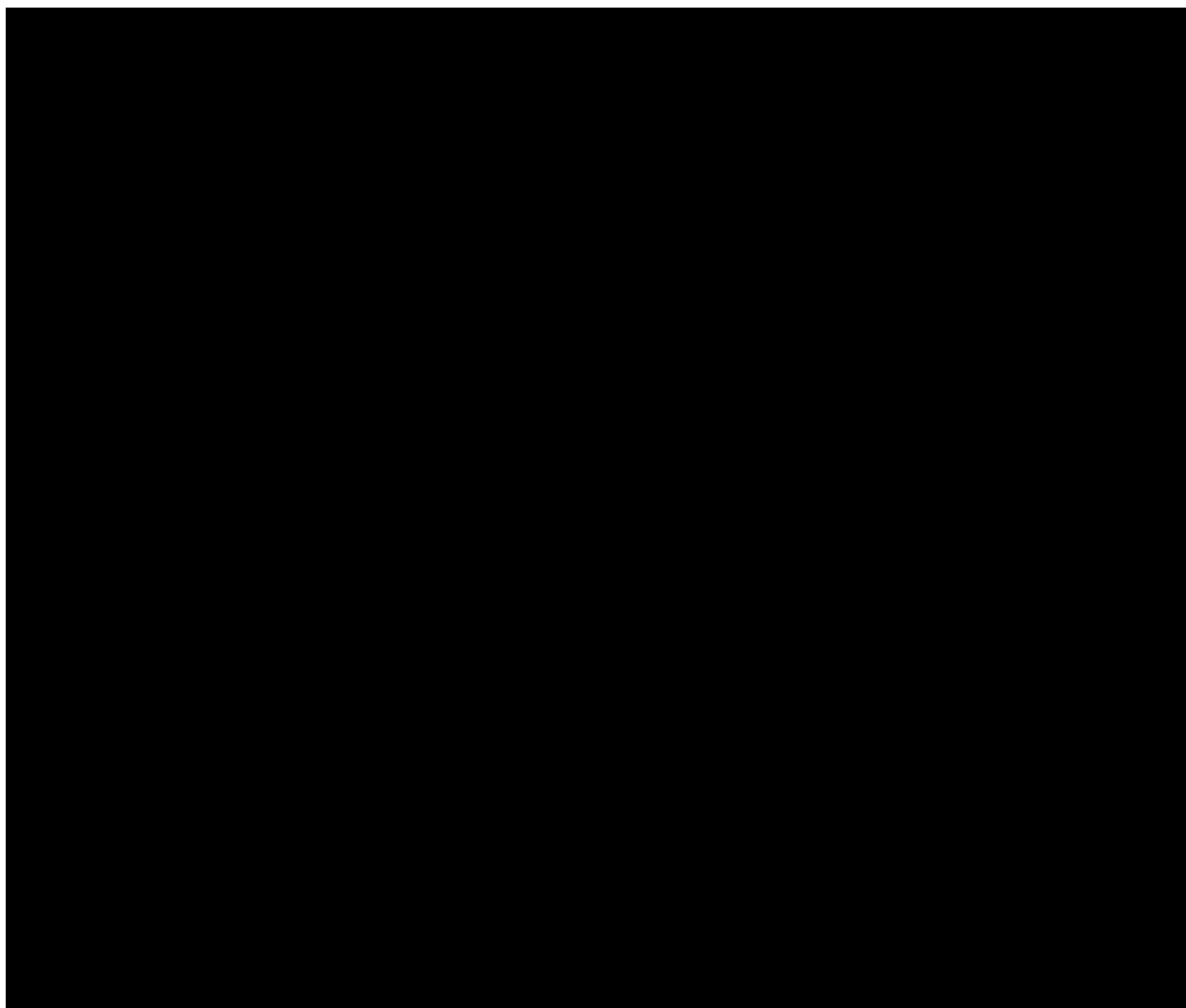




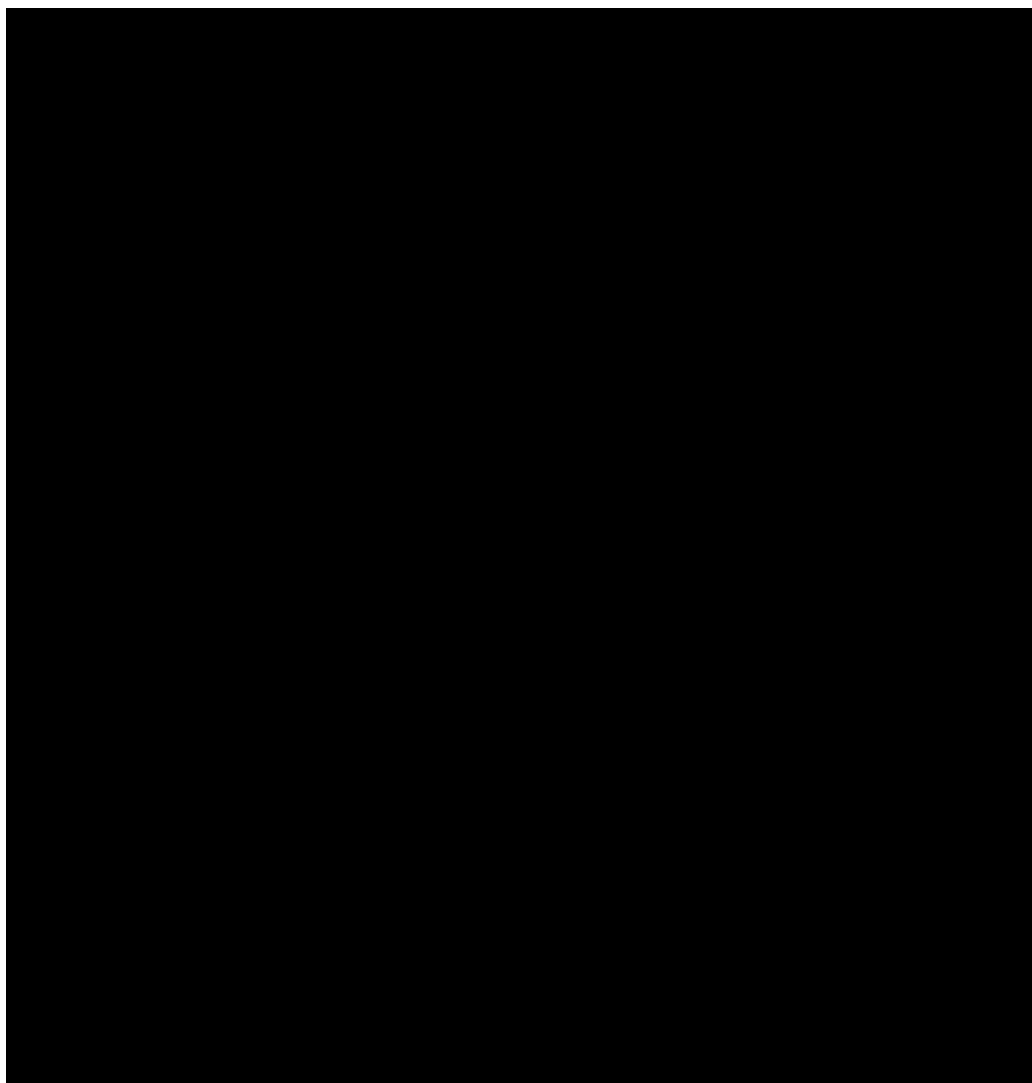




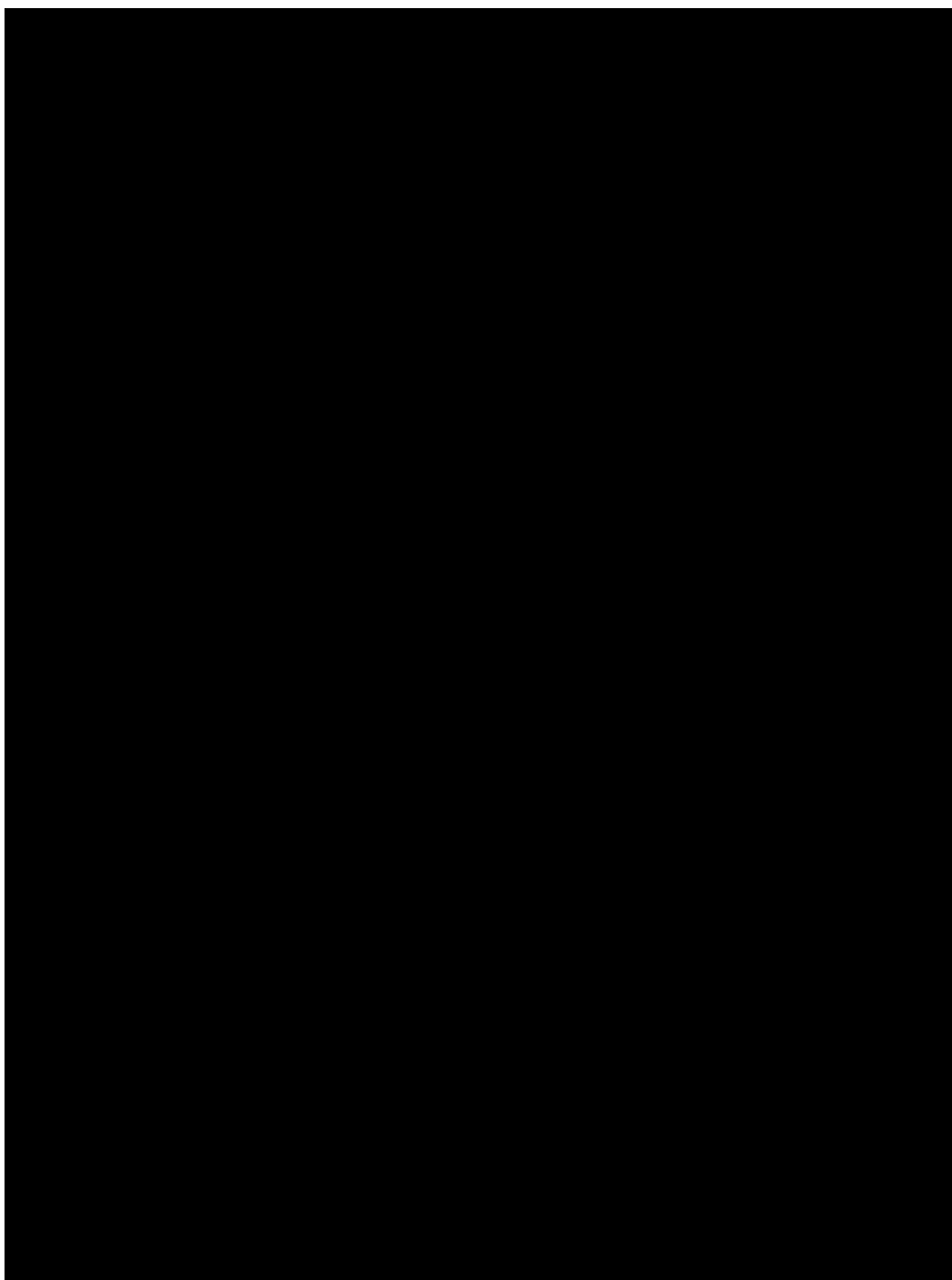


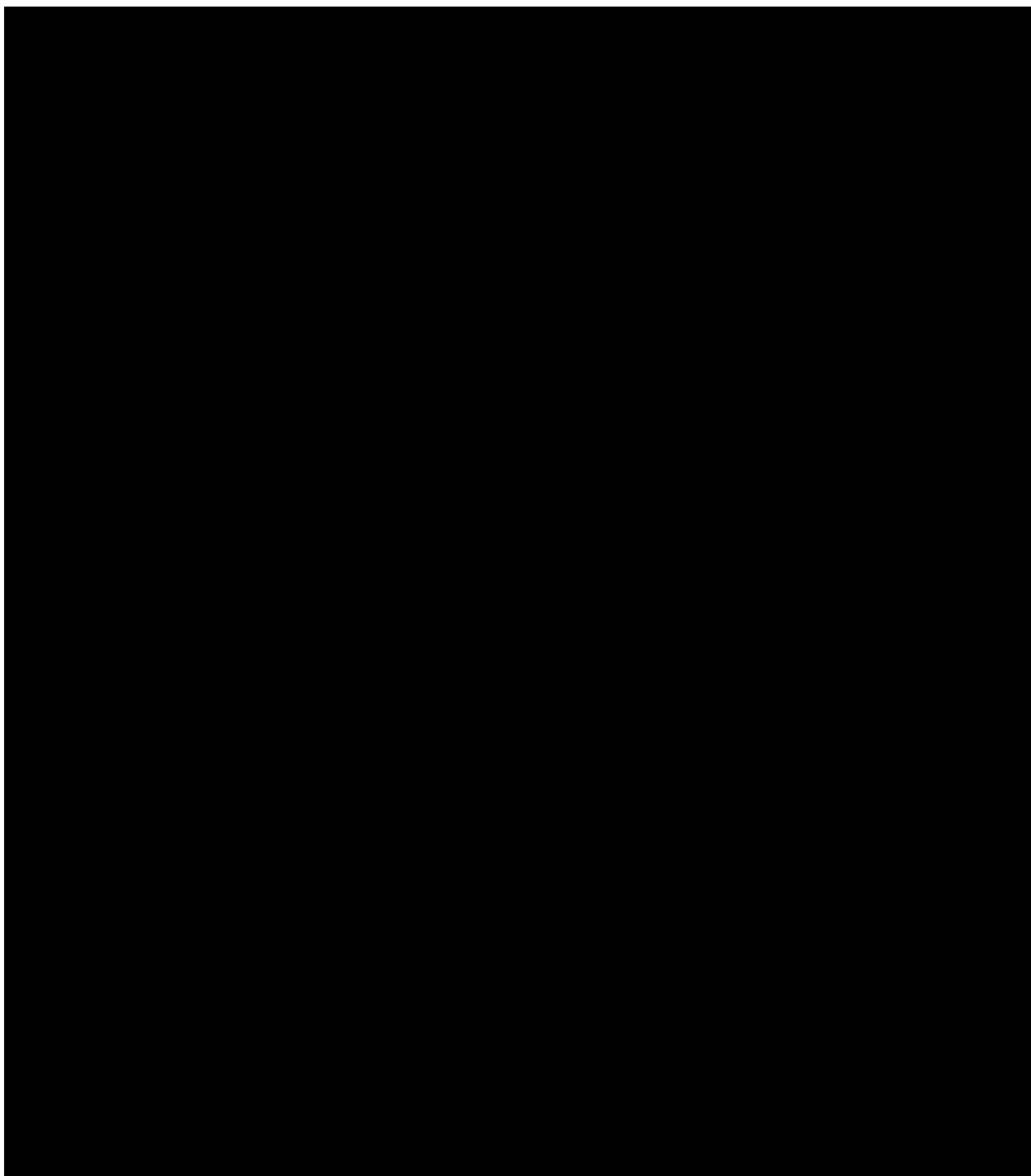


10.16 APPENDIX 16: EQ-5D-5L

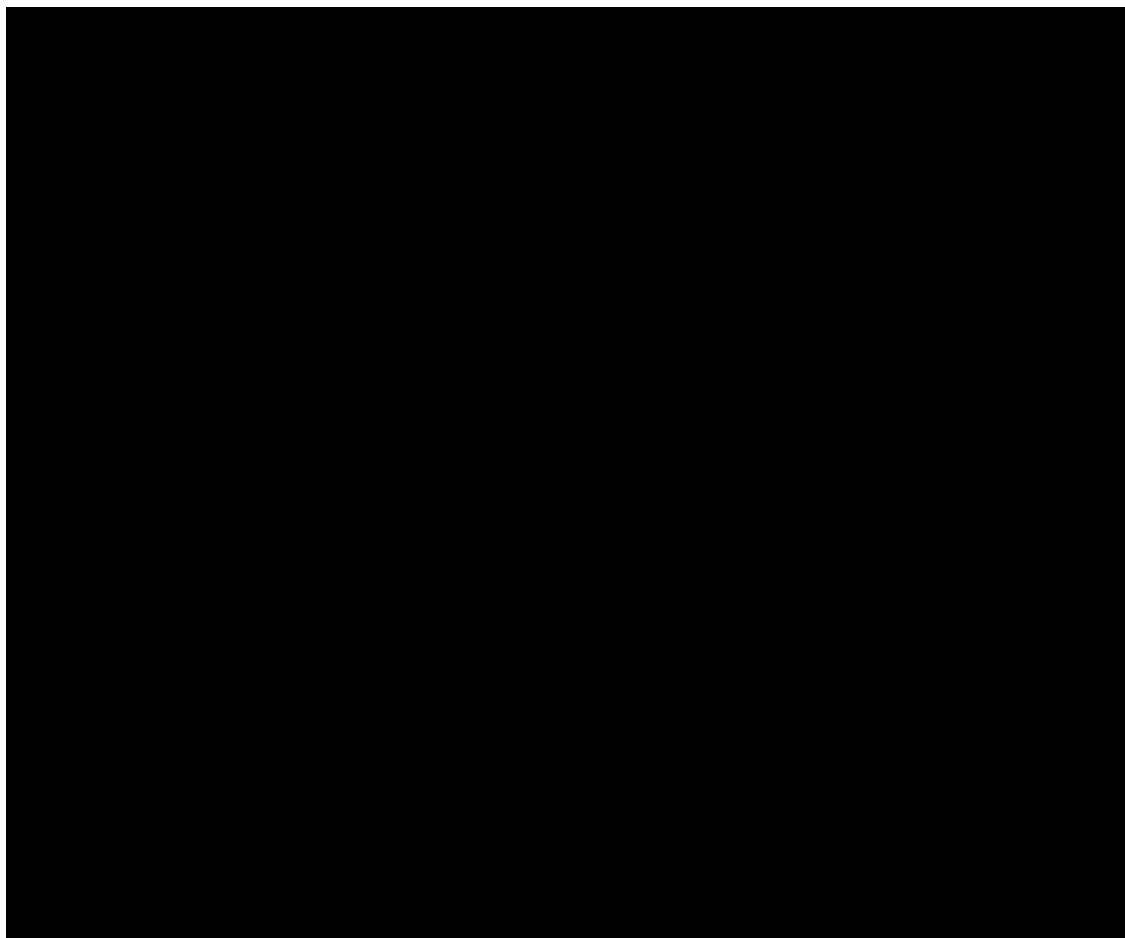


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10.17 APPENDIX 17: BODE INDEX



10.18 APPENDIX 18: 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

10.19 APPENDIX 19: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EXCEPTIONAL EMERGENCY SITUATIONS

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

- A regional or national exceptional emergency situation (such as public health emergency, natural disaster, pandemic, terrorist attack, military conflict, humanitarian crisis) may prevent access to the clinical trial site.
- Contingency procedures are suggested in this appendix and in [Section 6.1](#), and [Section 8](#), for an exceptional emergency situation that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the exceptional emergency situation.
- During the period of exceptional emergency situation, if the site will be unable to adequately follow protocol-mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/randomization, and administration of study intervention may be temporarily delayed/halted.
- For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the exceptional emergency situation (eg, study visit delays/treatment extension, use of local laboratories, remote spirometry).

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by a regional or national exceptional emergency situation, focus should be given to assessments necessary to ensure the safety of participants and those assessments important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national exceptional emergency situation for the duration of the situation (after Sponsor agreement is obtained):

- The DTP supply of itepekimab/placebo from the Sponsor where allowed by local regulations and agreed upon by the participant
- If on-site visits are not possible, remote visits (eg, with home nurses, home health vendor) may be planned for the collection of possible safety and/or efficacy data. Vital signs, hematology and clinical chemistry, routine urine analysis plus dipstick test (pregnancy/cotinine) and AE reporting should have priority from a safety perspective. The COPD exacerbation reporting, spirometry (if remote spirometry is available/possible), and PROs (SGRQ, E-RS:COPD, PGIC, PGIS, EQ-5D-5L) should have priority from an efficacy perspective.

- If on-site visits are not possible visit, windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely (eg, spirometry visit window ± 2 weeks for the randomized IMP treatment period, and ± 2 weeks for the visits during the post-IMP treatment follow-up period for participants transitioning to the LTS18133 study).
- Use of local clinic or laboratory locations may be allowed for hematology and clinical chemistry samples.

Contingencies implemented due to an exceptional emergency situation will be documented.

- If in case of unforeseen circumstances, a decision for each individual participant to remain and/or start in the study has to be made; this should be done on a case-by-case basis by the Investigator based on his/her best medical judgment. Clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment. All applicable local laws, institutional and IEC/IRB regulations regarding study visits should be followed. Local guidelines related to Personal Protective Equipment use should also be followed. As previously mentioned, attempts should be made to perform all assessments in accordance with the protocol, but only if and when possible. Investigators should closely monitor and document all deviations to the study protocol and share them with the Sponsor contact on a real-time basis.

10.20 APPENDIX 20: SUMMARY OF PRIMARY AND SUPPORTIVE ESTIMANDS FOR THE PRIMARY AND KEY SECONDARY ENDPOINTS

Endpoint category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) 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.				
Primary endpoint Primary estimand (Treatment policy/while-on-treatment estimand)	The annualized rate of moderate-or-severe AECOPD over the placebo-controlled treatment period	- Former smoker cohort (primary population for efficacy and safety analyses) - ITT/efficacy	The following ICEs may occur: - Early discontinuation of study treatment for any reason which includes the mandatory permanent discontinuation of study intervention as prescribed in Section 7.1 and the participant voluntary premature discontinuation. - Taking prohibited medications post randomization. - Taking study treatment not as randomized (eg, dispensing error). - Change in background therapy during the treatment period. 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) will be from randomization to the last contact date for participants within the planned treatment duration; - For participants taking prohibited medications, all the data observed during the 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 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 treatment period as the response variable, with treatment group, region (pooled country), screening eosinophil strata (<300 cells/mm³ or ≥300 cells/mm³), controller therapy (double, triple) 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(s) (ICEs) strategy and missing data handling	Population-level summary
			4. For participants with change in background therapy, all the data observed during the planned treatment period (as defined above) will be included in the analyses. 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 possibility of additional AECOPD events. Missing data handling: Missing data assumption for the primary estimator: Although using the treatment policy strategy for all types of ICEs 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 will be provided in the SAP.	
Primary endpoint Supportive estimand (While-on-treatment estimand)	Number of moderate-or-severe AECOPD during the placebo-controlled treatment period	Former smoker cohort (primary population for efficacy and safety analyses)	The ICEs will be handled in the same way as specified for the primary estimand except that: 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.	The same as for the Primary endpoint/Primary estimand above.

Endpoint category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) (ICEs) strategy and missing data handling	Population-level summary
		ITT/efficacy	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.	
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in former smokers with moderate-to-severe COPD.				
Key secondary endpoint Primary estimand (Treatment policy / while-on-treatment estimand)	Change from baseline in pre-BD FEV1 at Week- 24	- Former smoker cohort (primary population for efficacy and safety analyses) - ITT/efficacy	The ICEs will be handled using treatment policy strategy as follows: - Early discontinuation of study treatment for any reason before Week 24: All pre-BD FEV1 data up to Week 24 will be included in the analysis irrespective of treatment adherence. - Taking prohibited medications prior to Week 24: All pre-BD FEV1 data up to Week 24 will be included in the analysis irrespective of use of prohibited medications. - 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). - For participants with change in background therapy, all the data observed during the 24-Week treatment period (as defined above) will be included in the analyses. Missing data handling: Missing data assumption for the primary estimator : Participants 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 Week 24 as response variables, and treatment, age (continuous variable), sex, baseline height (continuous variable), region (pooled country), screening eosinophil strata (<300/mm ³ or ≥300/mm ³), controller therapy strata (double or triple), visit, treatment-by-visit interaction, baseline and 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 and/or tipping point analysis. Details will be provided in the SAP.	
Key secondary endpoint: Supportive estimand (Treatment policy/While-on-treatment estimand)	Change from baseline in pre-BD FEV1 at Week 24	- Former smoker cohort (primary population for efficacy and safety analyses) - ITT/efficacy	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.	- 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 a MMRM approach. The model will include change from baseline in on-treatment pre-BD FEV1 values as response variables, and treatment, age (continuous variable [years]), sex, baseline height (continuous variable), region (pooled country), screening eosinophil strata (<300/mm³ or ≥300/mm³), controller therapy strata (double or triple), visit, treatment-by-visit interaction, baseline pre-BD FEV1 value used as a continuous variable and baseline-by-visit interaction as a covariate.

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; SAP = statistical analysis plan; SC = subcutaneous(ly).

10.21 APPENDIX 21: ABBREVIATIONS

6MWD:	6-Minute Walking Distance
ACOS:	asthma-COPD overlap syndrome
ADA:	antidrug antibody
AECOPD:	acute exacerbation of COPD
AEs:	adverse events
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
BCG:	Bacillus Calmette-Guérin
BD:	bronchodilator(y)
BMI:	body mass index
BODE Index:	Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index
BP:	blood pressure
CAT:	COPD assessment test
CFR:	Code of Federal Regulations
CIs:	confidence intervals
COPD:	chronic obstructive pulmonary disease
COVID-19:	coronavirus disease 2019
CRF:	case report form
CRP:	C-reactive protein
CSICF:	core study informed consent form
CSR:	clinical study report
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
DPI:	dry powder inhaler
DTP:	direct to patient
ECG:	electrocardiogram
eCRF:	electronic case report form
eDiary:	electronic diary
EQ:	EuroQol
EQ-5D-5L:	EuroQol 5-Dimension 5-Level Quality-of-Life Questionnaire
ER:	emergency room
E-RS: COPD:	evaluating respiratory symptoms in COPD
ERS/ATS:	European Respiratory Society/American Thoracic Society
ETD:	early treatment discontinuation
EU:	European Union
EXACT:	EXAcerbations of Chronic Pulmonary Disease Tool
FDA:	US Food and Drug Administration
FEV1:	forced expiratory volume in 1 second
FSH:	follicle stimulating hormone
FVC:	forced vital capacity
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation

GINA:	Global Initiative for Asthma
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
HBcAb:	hepatitis B core antibody
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus total antibody
HDMs:	house dust mites
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
HRT:	hormone replacement therapy
IA:	interim analysis
IB:	investigator's brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
ICS:	inhaled corticosteroid
IEC:	Independent Ethics Committee
Ig:	immunoglobulin
IL:	interleukin
IM:	intramuscular
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
ISRs:	injection site reactions
ITT:	intent-to-treat
IV:	intravenous
IVRS:	Interactive Voice Response System
IWRS:	Interactive Web Response System
JAK:	janus kinase
LABA:	long-acting beta-agonist
LAMA:	long-acting muscarinic antagonist
LOAC:	loss of asthma control
LS:	least squares
LTRA:	leukotriene receptor antagonists
mAb:	monoclonal antibody
MDI:	metered dose inhaler
MMRM:	mixed-effect model with repeated measures
NIMP:	noninvestigational medicinal product
NRT:	nicotine replacement therapy
PCSA:	potentially clinically significant abnormality
PDE-4:	phosphodiesterase type 4
PGIC:	patient global impression of change
PGIS:	patient global impression of severity
PoC:	proof-of-concept

PROs:	patient-reported outcomes
PT:	preferred term
Q2W:	every 2 weeks
Q4W:	every 4 weeks
RNA:	ribonucleic acid
RR:	rate ratio
RRR:	relative risk reduction
SABA:	short-acting β agonist
SAEs:	serious adverse events
SAP:	statistical analysis plan
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
SC:	subcutaneous(ly)
SEM:	standard error of the mean
SGRQ:	St. George's Respiratory Questionnaire
SOA:	schedule of activities
SoC:	standard of care
TB:	tuberculosis
TBI:	TB infection
TEAE:	treatment-emergent adverse event
TNF:	tumor necrosis factor
ULN:	upper limit of normal
VAS:	visual analog scale
WOCBP:	women of childbearing potential

10.22 APPENDIX 22: PROTOCOL AMENDMENT HISTORY

Amended protocol 01 (20 September 2022)

This amended protocol 01 is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Due to a lower-than-expected rate of acute exacerbations of COPD during the COVID-19 pandemic, an adaptive sample size increase based on blinded data is planned to ensure the study is adequately powered for the primary endpoint of the annualized rate of moderate or severe acute exacerbation of COPD. Secondly, changes are made in the timepoints of several secondary endpoints, and a variable treatment duration is introduced for study participants enrolled as part of the adaptive sample size increase. In addition, discrepancies are also being addressed in this amendment, as well as minor corrections and clarification.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
THROUGHOUT PROTOCOL	Made textual changes to reflect recruitment of potential additional former smoker participants enrolled as part of an adaptive sample size increase, for whom a variable treatment duration will be applied (maximal 52 weeks, minimal 24 weeks). Changed treatment duration from '52 weeks' to 'the planned treatment duration' throughout the protocol	A variable treatment duration (maximal 52 weeks, minimal 24 weeks) was introduced for potential additional randomized former smoker 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.
1.1 SYNOPSIS 4.1 STUDY DESIGN	The following sentence was added: 'Former smoker participants enrolled into the potential variable 24-to-52-week treatment period will remain in the treatment period for a maximum of 52 weeks or until the last participant randomized completes a minimum treatment period of 24 weeks.'	
1.3 SCHEDULE OF ACTIVITIES	Changed 'Week 58', 'Week 66; and 'Week 72' to 'EOT+6 weeks', 'EOT+14 weeks' and 'EOT+20 weeks', respectively	In participants with a planned treatment duration between 24-52 weeks, follow up visits will not occur at Week 58, 66 and Week 72, but will be scheduled after the EOT visit ranging in between Week 24 and Week 52.
THROUGHOUT PROTOCOL	Changed 'at Week 52' to 'at Week 24 and Week 52' for secondary endpoints related to post-BD FEV1, E-RS-COPD total score, SGRQ total score and SGRQ decrease of at least 4 points in SGRQ total score. Changed 'at Week 24' to at Week 52' for secondary endpoint related to preBD FEV1 Changed 'at Week 52' to 'at Week 24' for key secondary endpoint related to preBD FEV1	The PK concentration steady state is expected to be reached by Week 24 and to minimize missing data due to participants with a planned treatment duration less than 52 weeks or early dropouts. Key secondary endpoint will be assessed at Week 24 instead of Week 52 Related secondary endpoint will now be assessed at Week 52 instead of Week 24
THROUGHOUT PROTOCOL + APPENDIX 19	The following text: 'a regional or national emergency declared by a governmental agency' was replaced by: 'For exceptional emergency situations'	To broaden the 'emergency' definition. Examples of this definition are provided in Appendix 19.
1.1 SYNOPSIS OBJECTIVES AND ENDPOINTS 3. OBJECTIVES AND ENDPOINTS	The following sentence was changed from: 'The primary estimand will be a treatment policy estimand.' Into: 'The primary estimand will be a treatment policy/while-on-treatment policy estimand (see Section 9.4.2).'	Clarification
1.1 SYNOPSIS OVERALL DESIGN 6.1 STUDY INTERVENTION(S) ADMINISTERED	Added: '(not to be provided by Sponsor)' to non-investigational medicinal product(s) (controller and reliever medication).	To be more explicit that non-investigational medicinal products are not provided by the sponsor.

Section # and Name	Description of Change	Brief Rationale
1.2 SCHEMA FIGURE 1 - GRAPHICAL STUDY DESIGN - Initial 930 former smokers	Replaced 'Week 52 days' and 'Week 72 days' with 'Week 52' and 'Week 72' in Figure 1 for the beginning and end of post-treatment period'.	Correction
	Inserted changes to reflect variable treatment duration	Update to reflect variable treatment duration
1.3 SCHEDULE OF ACTIVITIES	The following text was added to footnote m: 'For China: If local regulations restrict use of sponsor provided dipstick, a urine sample can be sent for urinalysis to the central laboratory.'	To comply with Chinese local regulations.
8.2.5 Pregnancy testing	The following sentence was modified: 'Pregnancy testing will be performed in all WOCBP at screening with a blood test using a central laboratory, and at all subsequent clinic visits using Sponsor provided urine tests, or locally provided urine test (China only).'	
10.2 APPENDIX 2 CLINICAL LABORATORY TESTS	The following sentence was modified: ' •Pregnancy testing will be performed at screening with a blood test using a central laboratory, and at subsequent visits using Sponsor provided urine tests, or locally-provided urine test (China only).'	
1.3 SCHEDULE OF ACTIVITIES TABLE 19- PROTOCOL- REQUIRED LABORATORY ASSESSMENTS	Footnote q text: 'Nasopharyngeal swabs and a quantitative polymerase chain reaction test will be performed to detect SARS-CoV-2 infection.' was replaced by: 'Nasopharyngeal/oropharyngeal swabs and a quantitative polymerase chain reaction test or antigen test will be performed to detect SARS-CoV-2 infection at either local or central laboratory. Added following text to Table 19: '(or polymerase-chain- reaction / antigen test in local laboratory if needed)'	To adapt to different sampling methods in different country To allow participants who test negative for SARS-CoV-2 (COVID-19) locally to be enrolled
TABLE 19- PROTOCOL- REQUIRED LABORATORY ASSESSMENTS	Modified the text related to urine pregnancy tests during the treatment period and follow up period.	Provided further clarity for urine pregnancy testing.
2.3.1 RISK ASSESSMENT TABLE 1	Content related to section: 'severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection' was moved to section 'Serious infections, including opportunistic infections' The following text in 'mitigation strategy': 'Participants should be monitored for any signs or symptoms of a SARS-CoV-2 infection and tested/treated as per local/international guidelines. Itepekimab/placebo should temporarily be withheld after a confirmed SARS-CoV-2 infection, and guidelines for resumption	To align with Investigator Brochure reported 'important potential risks of itepekimab' but keeping information on SARS-CoV-2 infections. Updated in response to proceeding insight and correction related to reference to another paragraph.

Section # and Name	Description of Change	Brief Rationale
	of therapy must be followed as per clinical protocol (Section 7.2). Participants must fully clinically recover from SARS-CoV-2 infection prior to resumption of itepekimab' was replaced by: 'Participants should be monitored for any signs or symptoms of a SARS-CoV-2 infection and tested/treated as per local/international guidelines. Itepekimab/placebo can temporarily be withheld after a confirmed symptomatic SARS-CoV-2 infection based upon clinical judgement, and guidelines for resumption of therapy must be followed as per clinical protocol (Section 7.2).'	
	The following sentence in section ' Systemic hypersensitivity reactions, including events associated with immunogenicity': "No ADA data are available for Studies R3500-AS-1633, R3500-AD-1798, and R3500-AD-1805. In Studies R3500-HV-1551, R3500-AS-1619, ACT15102, and ACT15104 studies all subjects/participants tested negative in the itepekimab ADA assay.' was replaced by: ' No ADA data are available for Studies R3500-AS-1633, R3500-AD-1798, and R3500-AD-1805. In Studies R3500-HV-1551, R3500-AS-1619, ACT15102, ACT15104, R3500-AD-1798, R3500 AD 1805, and PKM16966, no treatment emergent ADA were detected'.	Text was updated with latest information
5.1 INCLUSION CRITERIA	Changed 'post-BD FEV1/FVC ratio ≤ 0.70' to 'post-BD FEV1/FVC ratio < 0.70' in inclusion criteria 04 The following text was added to inclusion criterion 09: 'or BMI ≥ 16.0 kg/m² for participants enrolled in East-Asian countries (Japan, South Korea, Singapore, China including Taiwan and Hong-Kong)'	Correction to align with the GOLD guideline definition of COPD In the population of participants with COPD, the mean BMI of participants of East-Asian descent is lower than that of participants from other world regions.
5.2 EXCLUSION CRITERIA	The following text was added to exclusion criterion 01: 'unless asthma resolved ≤ 18 years of age and has not recurred.'	To ensure the enrolled participant population includes participants with childhood asthma, a known risk factor for COPD.
5.4 SCREEN FAILURES	The following sentence was added: Retesting of blood eosinophil values is allowed up to three times during the screening period to meet inclusion criteria for showing blood eosinophil count < 300 or ≥ 300 cells/mm³ before randomization, ie, in case of premature stratum closure.'	To provide guidance for retesting in case of premature stratum closure related to eosinophil count.
6.1 STUDY INTERVENTION(S) ADMINISTERED	Updated the text related to who can perform IMP injection at different injection sites. Updated the text related to the locations of injection applied by caregiver.	To provide further clarity about administration of IMP

Section # and Name	Description of Change	Brief Rationale
	The DTP supply of itepekimab/placebo from the Sponsor to the participant can be used, where allowed by local regulations and agreed upon by the participant.	To also allow DTP supply outside of the context of an exceptional emergency situation
6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING	The following sentence was deleted: "To maintain blinding, the personnel involved with dose preparation will be required to agree not to reveal to other study personnel the type of IMP solution (itepekimab versus placebo) in the syringes."	Was left by mistake. Is not applicable as blinding is ensured by identical aspect of IMP and placebo.
6.5 CONCOMITANT THERAPY	The following text: 'Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the following details' was replaced with: 'Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, if medically relevant) that the participant had received within 1-year prior to the time of enrollment or receives during the study must be recorded along with the following details:'	Prevent non-essential reporting of (old) concomitant medication.
8.1.2.1.1 COPD ASSESSMENT TEST (CAT) 10.12 APPENDIX 12: COPD ASSESSMENT TEST 11 REFERENCE	Text describing the COPD Assessment Test was added Added 2 references related to COPD Assessment Test	To provide a standard tool to all sites for participant recruitment.
8.1.2.1 PARTICIPANT REPORTED OUTCOME QUESTIONNAIRES 8.8 HEALTHCARE RESOURCE UTILIZATION	Replaced 'eDiary' with 'eCRF'	Correction, since healthcare resource utilization data will be collected in the eCRF.
8.1.2.1.5.1 BODY-MASS INDEX, AIRFLOW OBSTRUCTION, DYSPNEA, AND EXERCISE CAPACITY INDEX (BODE INDEX)	The following text was added: 'For degree of pulmonary impairment (FEV1), site should choose the post-bronchodilator FEV1 as a percent of the predicted value'. The following text was changed from '1. Spirometry (pre and post BD portion)' to '1. Spirometry'.	To give a clear instruction about the spirometry result used for the BODE Index calculation. At some visits, only pre-BD spirometry is performed so post-BD is not applicable.

Section # and Name	Description of Change	Brief Rationale
8.8 HEALTHCARE RESOURCE UTILIZATION	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
9.2 SAMPLE SIZE DETERMINATION	The following sentence was added: ‘ During the COVID-19 pandemic, a lower-than-expected rate of exacerbations has been observed in participants with COPD. This is likely the result of social distancing and/or mask wearing leading to fewer respiratory infections, a known trigger for COPD exacerbations (49). The blinded annualized rate of moderate or severe exacerbations in the former smokers at the time of the protocol amendment 01 suggests a lower placebo exacerbation rate compared to the original assumption on an AECOPD rate of [REDACTED] in the placebo group. To preserve the power of the study, an adaptive sample size increase of the former smoker cohort will be based upon the blinded exacerbation rate observed approximately 3 months prior to the last of the planned 930 former smoker participants being randomized as planned. If the observed blinded exacerbation rate is [REDACTED] or higher, the sample size will not be adjusted. If the blinded exacerbation rate is below [REDACTED] a sample size adaptation will be made to the former smoker cohort, based on the blinded rate of moderate or severe investigator-reported exacerbations observed approximately 3 months prior to the randomization of the last of the planned 930 former smoker participants. Details are provided in Table 12. The number of additional former smoker participants will not exceed approximately 207. All additional former smoker participants randomized as part of this sample size adaptation will have a variable treatment duration (minimum of 24 weeks, maximum of 52 weeks). In Section 4.1 the variable treatment duration is described in more detail. More details will be provided in the SAP. Table 12 ‘Summary of sample size adaptation based upon blinded AECOPD rate in former smokers’ has been added.	To ensure the study is adequately powered, despite a lower-than-expected blinded exacerbation rate due to the pandemic era and unexpected loss of treatment exposure in participants impacted by humanitarian crises.

Section # and Name	Description of Change	Brief Rationale
1.1 SYNOPSIS	The following sentence was added in 'number of participants': 'For former smoker cohort, an adaptive sample size increase is planned, based upon the unadjusted, blinded adjudicated exacerbation rate observed in former smokers, approximately 3 months prior to the last participants being enrolled, to compensate for any loss of power induced by the lower than expected rate of AECOPD (see Section 9.2).'	
9.2 SAMPLE SIZE DETERMINATION	The following text was updated: 'In addition to the primary population of former smoker participants, the study will also enroll a secondary population of participants who are current smokers. The targeted enrollment for the current smoker cohort is approximately a total of 280 current smokers (N=140 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, with 280 participants there is an 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 30.0% (95% CI half-width). All current smokers will have a treatment period of 52 weeks.'	The rate of acute exacerbations of COPD for current smokers at the time of protocol amendment 01 is lower than expected. 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% (See SAP for further details).
9.3 POPULATIONS FOR ANALYSES	The following text was added to the description of the ITT/efficacy population: 'The ITT population includes randomized participants from both the 52 weeks treatment duration portion and the variable treatment duration portion. the ITT/efficacy analysis population will be used for the AECOPD related endpoints, and the endpoints assessed at Week 24 (such as change from baseline in pre-BD FEV1, post-BD FEV1, E-RS:COPD, or SGRQ at Week 24). A new row was added to description the ITT-Week 52 population: 'The ITT/Week 52 population includes all the participants who have the opportunity to complete 52 weeks of treatment period based on their randomization date, regardless of whether the participant is enrolled in the 52 weeks treatment duration portion, or in the potential additional variable treatment duration portion. All participants in the ITT-Week 52 population have a planned treatment duration of 52 weeks. The ITT/Week 52 population is the analysis population for the endpoints that assess change from baseline at Week 52 (such as change from baseline in pre-BD	A variable treatment duration (maximal 52 weeks, minimal 24 weeks) was introduced for potential additional randomized participants. This required amending the efficacy populations, since not all participants are now planned to have a 52 week treatment duration.

Section # and Name	Description of Change	Brief Rationale
	FEV1, post-BD FEV1, E-RS: COPD, or SGRQ at Week 52). Note, if the former smoker sample size is not increased as per Section 9.2 (ie, no variable treatment duration portion will be added), then ITT-Week 52 population is identical to the ITT population..'	
9.4.1 GENERAL CONSIDERATION	The following text was added: 'The database lock for final analysis will be planned 52 weeks after the last participants is randomized, or alternatively 24 weeks after the last potential additional randomized former smoker participants, if the sample size is increased as per Section 9.2 , 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. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.'	A variable treatment duration (maximal 52 weeks, minimal 24 weeks) was introduced for potential additional randomized former smoker participants. Text was moved to a more logical place in the protocol (from Section 9.5 to Section 9.4.1).
9.4.4 SECONDARY ENDPOINT(S) TABLE 15 STATISTICAL ANALYSIS METHODS FOR KEY SECONDARY ENDPOINTS IN FORMER SMOKER COHORT (PRIMARY POPULATION)	The following sentence was added to statistical analysis methods related to change from baseline in pre-BD FEV1 at Week 52: ' This analysis will be performed in the same way as for the key secondary endpoint, and the response variable will include change from baseline in pre-BD FEV1 values up through to Week 52.'	To reflect the variable treatment duration in the analysis of this endpoint
TABLE 16 STATISTICAL ANALYSIS METHODS FOR OTHER SECONDARY ENDPOINTS	In the 'other secondary endpoints' column, the analysis population was added (ITT-Week 52 or ITT	To reflect the variable treatment duration in the analysis of this endpoint
9.5 INTERIM ANALYSIS	The following sentence was modified: 'A nonbinding futility IA is planned to be performed after a minimum of approximately [REDACTED] of the originally planned 1860 randomized former smoker participants have completed at least a minimum of [REDACTED] in both planned Phase 3 studies combined: Study EFC16750 (n=930) and Study EFC16819 (n=930) former smokers only), corresponding to a total of approximately [REDACTED] participants.' The following sentence was deleted and moved to Section 9.4.1 GENERAL CONSIDERATIONS:	Improved clarity Text was not located in a logical place in the protocol.

Section # and Name	Description of Change	Brief Rationale
	'The database lock for final analysis will be planned based on the date 52 weeks after the last participant is randomized. Analyses will be based on all data collected up to this database lock and will be considered as the final analysis in the CSR. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.'	
10.1.3 INFORMED CONSENT PROCESS	The following text has been added: "In addition to a hard copy informed consent form, alternately potential participants may be consented [or re-consented] electronically, if allowed by local regulation, via a third-party platform accessed through a computer or mobile phone.	To allow for e-consenting, if accepted by local regulation.
10.1.6 DISSEMINATION OF CLINICAL STUDY DATA	URL of 'Clinicalstudydatarequest.com' was changed in 'vivli.org'	update
10.2 APPENDIX 2 CLINICAL LABORATORY TESTS	The following bullet point was added: " e) If screening (Visit 1; Week 0) blood eosinophil count cannot be analyzed in a timely manner at the central laboratory, a local certified laboratory can be used only after Sponsor approval"	To allow local testing of time critical blood eosinophil count in local laboratory to reduce transit times.
	Added following text to pregnancy testing: 'or locally provided urine test (China only).'	To comply with country specific regulation, a locally approved urine pregnancy test should be used instead of the sponsor-provided urine pregnancy test.
10.12 APPENDIX 12	COPD ASSESSMENT TEST (CAT questionnaire) has been inserted in appendices	Was not included by mistake
10.20 APPENDIX 20 PRIMARY ENDPOINT PRIMARY ESTIMAND AND KEY SECONDARY ENDPOINT PRIMARY ESTIMAND		
PRIMARY ENDPOINT SUPPORTIVE ESTIMAND	Minor textual edits. The following text was added: ' 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.'	

Section # and Name	Description of Change	Brief Rationale
	Column 'Intercurrent event(s) (ICEs) strategy and missing data handling' has been replaced by the following text: "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."	Updated to reduce redundancy and reflect variable treatment duration.
KEY SECONDARY ENDPOINT: SUPPORTIVE ESTIMAND	Minor textual edits Column 'Intercurrent event(s) (ICEs) strategy and missing data handling' has been replaced by the following text: "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."	Updated to reduce redundancy and reflect variable treatment duration

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