AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A randomized, double-blind, placebo-controlled, parallel-group, Proof-of-Concept (PoC) study to assess the efficacy, safety and tolerability of itepekimab, in participants with non-cystic fibrosis bronchiectasis**
Protocol number:	**ACT18018**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR440340/REGN3500 itepekimab**
Brief title:	**A Proof-of-Concept study to assess the efficacy, safety and tolerability of itepekimab (anti-IL-33 mAb) in participants with non-cystic fibrosis bronchiectasis**
Acronym:	**Not applicable**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**82 Avenue Raspail, 94250 Gentilly, France Manufacturer: Same as Sponsor**
Monitoring team's representative name and contact information	

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Pediatric investigational plan number: Not applicable

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	All	20 January 2025, version 1.0 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	15 July 2024, version 1.0 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	25 April 2024, version 1.0 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	02 January 2024, version 1.0 (electronic 1.0)
Original Protocol		25 October 2023, version 1.0 (electronic 1.0)

Amended protocol 04 (20 January 2025)

This amended protocol 04 is considered non-substantial based on the criteria set forth in Article 2(2)(13) of Regulation No 536/2014 of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Amendment 04 addresses multiple textual corrections and clarifications. In addition, the option to submit previously obtained chest CT scans and additional chest CT scans obtained for clinical care during the conduct of the trial for central reading and automated analysis is added to the protocol to allow for further detailed characterization of bronchiectasis in study participants.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall design 9.4 Sample size determination	The following text: A total of 300 participants will be randomized in this study. Was updated to: A total of approximately 300 participants will be randomized in this study.	Textual clarification that approximately 300 participants will be enrolled rather than 300 as an absolute number.
1.1 Synopsis	The following text: Once the last participant in has reached 24 weeks of treatment duration, all participants still on treatment will have an end of treatment visit and transfer into the 20-week safety follow-up period.	The minimum treatment period (ie, 24 weeks) may be extended to achieve the desired amount of total exposure

Section # and Name	Description of Change	Brief Rationale
	Was updated to: Once the last participant in the study has reached the minimum required treatment duration, all participants still on treatment will have an end of treatment visit and transfer into the 20-week safety follow-up period.	
1.3 Schedule of Activities	The following text: Sputum biomarkers (optional) Was updated to: Sputum culture and sputum biomarkers (optional)	Textual correction
1.3 Schedule of Activities (footnote b)	Information added that at the end of the study treatment period, for participants still on treatment, a pre-planned clinic visit will be replaced by an early EOT visit.	Clarification
1.3 Schedule of Activities (footnote f) 8.12 Imaging assessments	Information added on imaging assessments, allowing previously obtained chest CT scans and additional chest CT scans obtained for clinical care during the conduct of the trial to be submitted to the central portal (after having obtained the participant's consent).	To further characterize aspects including but not limited to the severity, location and type of NCFB, and degree of mucus impaction
3 Objectives, Endpoints, and Estimands	The following text: Other exploratory endpoints including the PGIS, PGIC, EQ-5D-5L, SNOT-22 and alternative timepoints for secondary endpoints will be described in the SAP. Was updated to: Other exploratory endpoints including but not limited to the PGIS, PGIC, EQ-5D-5L, SNOT-22 and alternative timepoints for secondary endpoints will be described in the SAP.	Clarification
6.9 Prior and concomitant therapy	List of prohibited medications updated	Clarification of newly available medications, addition to probhibited concomitant medication list
8.2.1 Disease-specific efficacy measures	The following text: For both moderate and severe events to be counted as 2 separate events, they must be separated by at least 14 days between any course of antibiotics, or 14 days between discharge and new admission in case of hospitalization (severe events only). Has been updated to: For both moderate and severe events to be counted as 2 separate events, they must be separated by at least 14 days between any course of antibiotics and/or systemic corticosteroids, or 14 days between discharge and new admission in case of hospitalization (severe events only).	Textual correction for consistency across the document
8.2.3.7 Bronchiectasis Severity Index	The following text: The BSI score will be calculated only at Baseline in order to estimate disease severity.	Textual correction to align with Schedule of Activities and other text in the document

Section # and Name	Description of Change	Brief Rationale
	Was updated to: The BSI score will be calculated during the screening period in order to estimate disease severity.	
8.3.4 Clinical safety laboratory tests	Protocol action for hepatitis serology testing updated	Textual correction
Throughout the document	Minor editorial and typographical error corrections	Textual correction
Cover page and throughout the document	Document updated to "Amended Clinical Protocol 04" including updated summary of changes, protocol amendment history, and formatting (headers, etc.) related to the protocol amendment	As per Sanofi standards

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LIST OF ABBREVIATIONS

ABPA:	allergic bronchopulmonary aspergillosis
ADA:	antidrug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATS:	American Thoracic Society
AxMP:	noninvestigational medicinal product
CF:	cystic fibrosis
CFTR:	cystic fibrosis transmembrane conductance regulator
COPD:	chronic obstructive pulmonary disease
CRP:	c-reactive protein
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
ERS:	European Thoracic Society
HBcAb:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus total antibody
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
IB:	investigator's brochure
ICE:	intercurrent events
ICF:	informed consent form
IgG4P:	human immunoglobulin G4P
IL:	interleukin
IMP:	investigational medicinal product
IV:	intravenous
LABA:	long-acting beta agonist
LAMA:	long-acting muscarinic antagonist
mAb:	monoclonal antibody
NCFB:	non-cystic fibrosis bronchiectasis
NMPA:	National Medical Products Administration
NRT:	Nicotine Replacement Therapy
PA:	Pseudomonas aeruginosa
PE:	pulmonary exacerbation
PK:	pharmacokinetic(s)
PoC:	proof-of-concept
PT:	preferred term
RNA:	ribonucleic acid
SOC:	system organ class

TB:	tuberculosis
TBI:	tuberculosis infection
TSLP:	thymic stromal lymphopoietin
ULN:	upper limit of normal range

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

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

Brief title:

A Proof-of-Concept study to assess the efficacy, safety and tolerability of itepekimab (anti-IL-33 mAb) in patients with non-cystic fibrosis bronchiectasis.

Regulatory agency identifier number(s):

IND:	134401
NCT:	Not applicable
WHO:	U1111-1295-3237
EUDAMED:	Not applicable
EU trial number:	2023-508663-70
Other:	Not applicable

[Pediatric investigational plan number]: Not applicable

Rationale:

Bronchiectasis is a chronic and potentially life-threatening disease with high unmet medical need despite available standard-of-care therapies. The disease is characterized by the permanent abnormal dilation of the bronchi and bronchioles, resulting from a destructive cycle of infection and transmural inflammation. The disease leads to the deterioration of the bronchial walls' epithelial, muscular and elastic components as well as aberrant epithelial remodeling with impaired mucociliary architecture in both large and small airways in patients with refractory NCFB. Common symptoms of bronchiectasis include chronic cough, shortness of breath, sputum production, hemoptysis, chest pain, and wheezing. Lung infections, both viral and bacterial, frequently occur in bronchiectasis patients and can trigger acute exacerbations characterized by a sudden worsening of symptoms. Clinical and etiological similarities exist between bronchiectasis and COPD, as well as clinical overlaps among bronchiectasis, asthma, and COPD.

The prevalence of bronchiectasis has been increasing over the past decade, in part due to enhanced detection through more frequent CT scans and improved awareness among clinicians (1). The disease exhibits a higher prevalence among women and the elderly population (2). Various underlying causes contribute to the development of bronchiectasis, including post-infective, COPD, autoimmune disease, immunodeficiency, severe asthma, and others (3).

Interleukin 33 (IL-33) is a pro-inflammatory cytokine that triggers and amplifies inflammatory responses in the innate and adaptive immune systems when epithelial cells are stressed or damaged due to exposure to inflammatory triggers. Itepekimab, a monoclonal antibody (mAb),

binds to IL-33 and inhibits IL-33 signaling. In a mouse model of chronic house dust mite induced airway inflammation, it was demonstrated that lung IL-33 plays a role in driving inflammation and tissue remodeling beyond the classical Type 2 immune response associated with IL-33 signaling. Blocking IL-33 with itepekimab normalized the established inflammation and improved remodeling of both the lung epithelium and lung parenchyma. Specifically, IL-33 blockade normalized persistent and exacerbating inflammatory markers, including eosinophilic, neutrophilic, and ST2+CD4+T-cell infiltration. Importantly, the study identified a crucial role of IL-33 in driving lung remodeling, both in lung epithelium and parenchyma, as itepekimab restored the presence of ciliated cells over mucus-producing cells and reduced the number of myofibroblasts, even in the context of continuous allergen exposure, leading to improved lung function (4).

Currently, there are no approved therapies for the treatment of bronchiectasis. The available treatments, including bronchodilators, mucolytics, antibiotics, and inhaled corticosteroids, have limited evidence supporting their efficacy. Inhaled antibiotics have shown mixed results, with inhalation induced bronchoconstriction being a common complication. Patients with bronchiectasis frequently experience pulmonary exacerbations (PEs), which are associated with worsened quality of life, daily symptoms, decline in lung function, and increased mortality, particularly in those with more severe and frequent exacerbations (5).

To develop itepekimab as a potential treatment for non-cystic fibrosis bronchiectasis (NCFB), a randomized, placebo-controlled study is planned. This study aims to assess the effect of itepekimab in addition to standard-of-care background therapy, including bronchodilators, inhaled corticosteroids, mucolytics, and/or maintenance antibiotics. This proof-of-concept (PoC) study will explore the efficacy and safety profile of two different dosage regimens of itepekimab compared to placebo over a period of 24-52 weeks. Participants with NCFB who require additional treatment will be enrolled in the study, while continuing to receive standard-of-care background medication. The primary endpoint of the study will be a reduction in the annualized rate of moderate or severe PEs. Additionally, the study design allows for the assessment of itepekimab's efficacy in multiple other domains of NCFB, including symptom control, lung function, and quality of life.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB	• Annualized rate of moderate or severe PEs[a] over the treatment period
Secondary	
• Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB	• Time to first moderate or severe PE over the treatment period [Key secondary endpoint] • Percentage of participants who are PE free over the treatment period • Annualized rate of severe PEs over the treatment period • Percentage of participants who are severe PE free over the treatment period • Time to first severe PE over the treatment period

Objectives	Endpoints
• Evaluate the efficacy of itepekimab compared with placebo on pulmonary function in NCFB	• Change From Baseline in Pre- and Post-bronchodilator FEV1 at Week 8 and Week 24
• Evaluate the efficacy of itepekimab compared with placebo on reduction in antibiotic use in NCFB	• Number of days of new and/or added (in participants with maintenance antibiotic use) antibiotic use
• Evaluate the efficacy of itepekimab compared with placebo on HRQoL and health status as assessed by QoL-B, and SGRQ in NCFB	• Change from Baseline in QOL-B Respiratory Symptoms Domain Score in Adult Participants at Week 24 • Change from baseline in SGRQ total score at Week 24 • Percentage of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24
• Evaluate the safety and tolerability of itepekimab in NCFB	• Incidence of TEAEs, AESIs, SAEs, and AEs leading to permanent study treatment discontinuation in the treatment-emergent period
• Evaluate the PK profile of itepekimab in NCFB	• Serum concentrations of itepekimab from baseline to end of study
• Evaluate immunogenicity to itepekimab in NCFB	• Incidence of treatment-emergent anti-itepekimab antibodies (ADA) responses throughout the study

Abbreviations: AE = adverse event; AESI = adverse event of special interest; FEV1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life; NCFB = non-cystic fibrosis bronchiectasis; PE = pulmonary exacerbation; PK = pharmacokinetic(s); QOL-B = Quality-of-Life Questionnaire – Bronchiectasis; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire; TEAE = treatment-emergent adverse event

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

*Moderate PE in this study is defined as:

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

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

AND

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

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

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

For China, please see Section 10.8.1 details.

Overall design synopsis:

ACT18018 is a Phase 2 study conducted in multiple countries. It is a randomized, double-blind, placebo-controlled trial with parallel groups (consisting of 3 groups) aimed at evaluating the efficacy, safety, and tolerability of 2 different dosing regimens of itepekimab in participants diagnosed with NCFB who are receiving standard-of-care therapy, including bronchodilators, inhaled corticosteroids, mucolytics, and/or maintenance antibiotics. The study treatments consist of subcutaneous administration of itepekimab at a dose of 300 mg every 2 weeks (Q2W),

itepekimab 300 mg every 4 weeks (Q4W), or a matching placebo (1:1:1 randomization). A total of approximately 300 participants will be randomized in this study, and the treatment duration will be a minimum of 24 weeks and a maximum of 52 weeks. Following the treatment period, there will be a 20-week safety follow-up period. The variable treatment duration allows for maximizing data collection for the primary endpoint, which is the annualized rate of PEs, in a time-efficient manner.

Brief summary:

ACT18018 is a multinational, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study with 3 treatment groups. The purpose of this study is to evaluate efficacy, safety and tolerability with 2 dosing regimens of itepekimab compared with placebo in male and/or female participants with NCFB aged 18 years of age up to 85 years of age (inclusive).

During the randomization process, participants will be stratified based on their geographical region, documented history of COPD and/or asthma (if asthma is resolved before 18 years of age and has not recurred, it will not be taken into consideration), and whether they are receiving maintenance macrolide antibiotic therapy (macrolide antibiotics or non-macrolide antibiotics or no antibiotic) at the start of the study.

A cap for participants with asthma and/or COPD is in place, to ensure a preplanned subgroup analysis in participants without a documented history of COPD and/or asthma which can provide a reasonable estimate of the treatment effect. The number of participants with asthma, or COPD or both should not exceed approximately 60 participants (approximately 20%).

To ensure that the cap is not exceeded, the enrollment of participants with a documented history of COPD and/or asthma in each stratification group will be closely monitored and controlled throughout the recruitment phase of the study. If needed, enrollment in a stratum can be put on hold temporarily.

Study details include:

A) The study duration (screening, 24-52 week treatment, 20-week safety follow-up) will be up to 47-77 weeks.

B) The treatment duration will be up to 24-52 weeks.

C) The safety follow-up duration will be 20 weeks.

The number of visits will be up to 12 site visits and up to 5 phone/remote visits.

Number of participants:

Approximately 300 participants will be randomized.

Study arms and duration:

Participants who satisfy the inclusion criteria will be randomized (1:1:1) to one of the following IMP treatment groups to be administered for the planned 24-52 week treatment duration:

- 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, administered as a single SC injection of matching placebo to itepekimab Q2W.

Study intervention(s)

Investigational medicinal product(s)

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 or 0 mg/mL.

- 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. Participants on Q4W will receive alternating doses of IMP and placebo.

AxMP

No AxMP is provided. Participants must continue their established bronchodilators (short and long acting), inhaled corticosteroids, mucolytics and/or maintenance antibiotics (not to be provided by Sponsor).

Devices

The itepekimab prefilled syringe is classified as a combination product with an integral medical device where the principal mechanism of action is that of itepekimab. See Section 8.4.8 Guidelines for Reporting Product Complaints for reporting of product complaints. Medical devices for diagnostic interventions (eg, spirometry, ECG) are not considered as 'investigational devices' in the context of this study.

Post-trial access to study medication

Depending on evidence of the participant's unmet medical need, the non-availability of suitable alternative therapies, and an assessment of what is known about the benefits and risks of itepekimab, participants who have successfully completed their participation in this clinical trial will be eligible for post-trial access to itepekimab.

The Investigator/treating physician will determine if benefit of continued access to itepekimab can be expected and access to itepekimab is the best medical option for the participant and will then submit a request to Sanofi.

Provision of itepekimab will be in compliance with all applicable national and local laws and regulations, including safety reporting obligations.

A participant will not be eligible for post-trial provision of itepekimab if his/her participation in the trial is terminated prematurely.

Sanofi's post-trial access responsibilities will need to be periodically re-evaluated. Based on new information about the investigational product (including adverse reactions), the continued health benefit to the individual, and market availability of the product or alternative therapies, post-trial access may be terminated. This includes situations where the trial may be stopped due to safety concerns or other issues.

Duration of study intervention

Every participant will receive minimally 24 weeks of treatment, and maximally 52 weeks of treatment in the study. Once the last participant in the study has reached the minimum required treatment duration, all participants still on treatment will have an end of treatment visit and transfer into the 20-week safety follow-up period.

Statistical considerations:

- **Primary endpoint:**

The primary estimand for the primary endpoint of the annualized rate of moderate or severe PEs over the treatment period compares the rate of PE for the participants randomly assigned to an itepekimab regimen versus the participants randomly assigned to the placebo arm. For this analysis, adjudicated moderate or severe exacerbation endpoints will be considered. A adjudicated moderate PE in this study is defined as A) having 3 or more of the following symptoms for at least 48 hours: 1. Increased cough, 2. Increased sputum volume or change in sputum consistency, 3. Increased sputum purulence, 4. Increased breathlessness and/or decreased exercise tolerance, 5. Fatigue and/or malaise, 6. Hemoptysis AND B) A physician's decision to prescribe antibiotics (or addition of antibiotic or change in antibiotic). An adjudicated severe PE is defined as a PE as described above but resulting in intravenous antibiotic treatment, or hospitalization, or observation for >24 hours in emergency department/urgent care facility, or death. Subjects on chronic antibiotic therapy whose only change in therapy is dose or frequency adjustment in response to worsening of respiratory symptoms will not meet the definition of exacerbation.

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

The annualized rate of moderate or severe PEs will be analyzed using a negative binomial regression. The primary analysis model will include the total number of moderate or severe PE events that occur during the planned treatment period as the response variable, with treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), *Pseudomonas aeruginosa* (PA) chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (Yes or No), number of exacerbations in the prior year, and maintenance macrolide antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. Log-transformed observation duration will be the offset variable.

A positive PA carrier status is defined by the isolation of PA in randomization/baseline sputum culture (positive or negative). If no PA sputum culture was obtained at randomization/baseline, the outcome is indeterminate.

The estimated annualized event rate for each treatment group and its 2-sided 90% CIs will be derived from the negative binomial model. The event risk ratio (RR) of each itepekimab regimen versus placebo, and the corresponding 2-sided 90% CI and p-value will also be provided.

Sensitivity analyses for missing data in the primary endpoint will be performed.

In addition, a while-on-treatment estimand will be included as supportive estimand for this endpoint. Details of statistical analyses of this endpoint is specified in Section 9.2.2.

- **Main secondary endpoints:**

The primary estimand for the key secondary endpoint of time to first moderate or severe PE over the treatment period compares the time to first moderate or severe PE for the participants randomly assigned to an itepekimab regimen versus the participants randomly assigned to the placebo arm.

Operationally, regardless of treatment discontinuation, all participants will be followed-up according to the study procedures up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. That is, PE events and related data would be collected and reported over the entire planned treatment period for all study participants even if some participants may have discontinued the study treatment. Analytically, the time to first moderate or severe PE over the planned treatment period analysis is performed regardless of the occurrence of the ICEs and the timing of the ICE. For participants without any PE events, the time from randomization to the date of treatment completion or treatment discontinuation up to their planned treatment period (event time will be considered as censored at date of EOT or the last contact date within the planned treatment duration) will be used in the analysis.

The time to first moderate or severe PE will be analyzed using a Cox regression model.
The model will include the time to the first event as the dependent variable, with treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata, number of exacerbations in the prior year, and maintenance macrolide antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotic) at baseline as covariates.

The hazard ratio will be estimated for comparison of each itepekimab regimen to placebo. The Kaplan-Meier method will be used to derive the probabilities that a participant would experience an event up to specific time points for each treatment group.

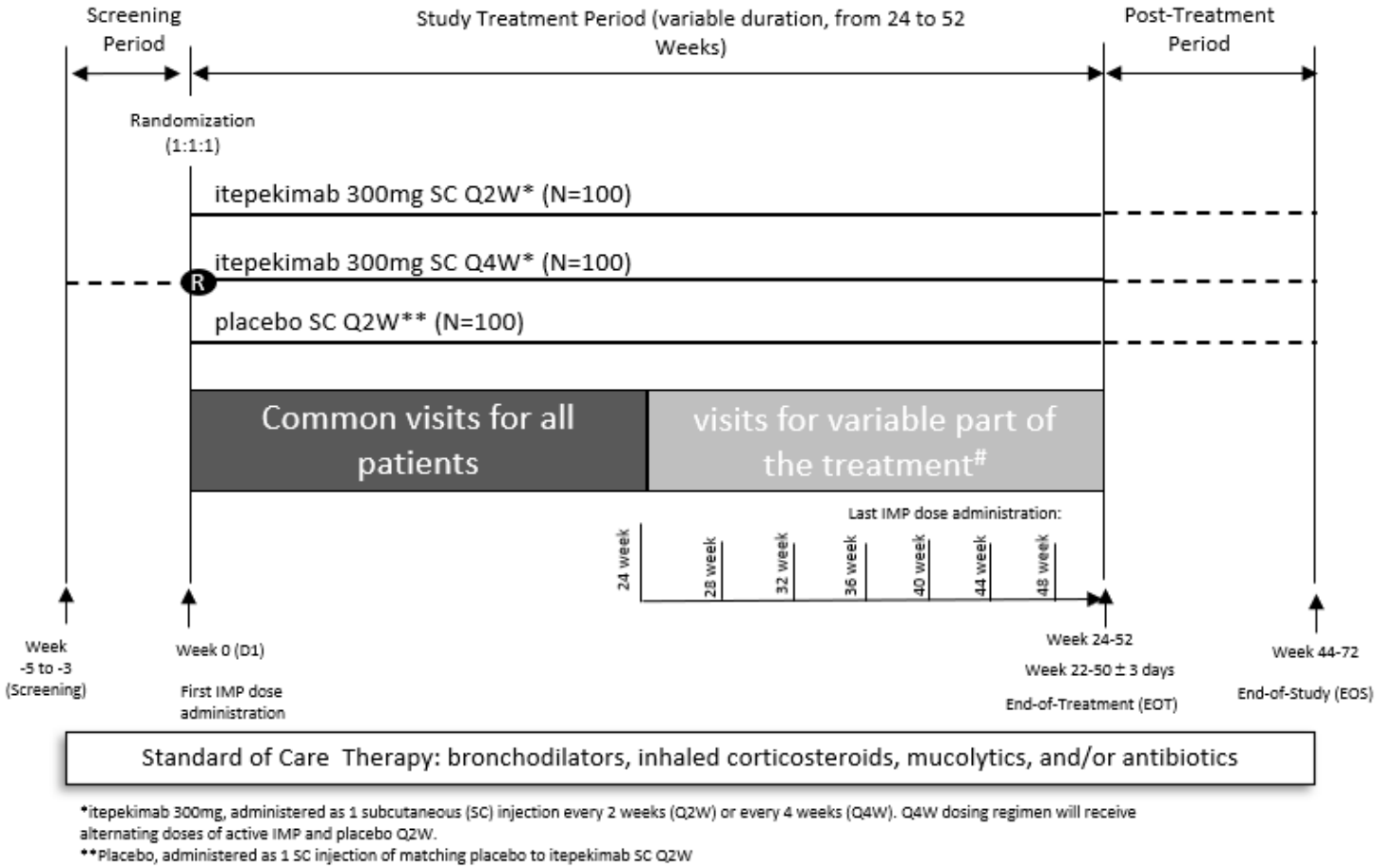
Data Monitoring committee:

For this study, an independent Data Monitoring Committee (DMC) will be established, which operates separately from the Sponsor. The DMC functions according to a DMC Charter and consists of external experts with relevant expertise in the diseases being studied, biostatistics, or clinical research. The main role of the DMC is to review safety data throughout the trial and, when necessary, assess efficacy, in order to evaluate the balance between benefits and risks. The DMC will also examine the trial results and provide appropriate recommendations to the Sponsor regarding the conduct of the clinical trial.

In their advisory capacity, the DMC provides recommendations to the Sponsor. It is the responsibility of the Sponsor to promptly review and consider the DMC's recommendations in a timely manner. The recommendations may pertain to continuing the trial as planned, making modifications to the trial design or procedures, or even potentially terminating the trial if deemed necessary.

1.2 SCHEMA

Figure 1 - Graphical study design



*itepekimab 300mg, administered as 1 subcutaneous (SC) injection every 2 weeks (Q2W) or every 4 weeks (Q4W). Q4W dosing regimen will receive alternating doses of active IMP and placebo Q2W.
**Placebo, administered as 1 SC injection of matching placebo to itepekimab SC Q2W

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (3-5 weeks)[w]	Interventional treatment period (up to 52 weeks)															Follow-up period (20 weeks)
	S	R/B[a]														EOT/ ETD[b]	EOS
VISIT	1	2[c]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
WEEK[c]	W-5 to -3	0	2	4[d]	8	12[e]	16	20[e]	24	28[e]	32	36[e]	40	44[e]	48	52	72
Informed consent	X																
Participant demographics	X																
Previous medical and surgical history	X																
Chest CT scan[f]	X																
BSI[g]	X																
Inclusion/exclusion criteria	X	X															
Participant-reported smoking status	X	X					X		X		X		X			X	X
Prior and concomitant medications	X	X	X	X	X		X		X		X		X		X	X	X
Study treatment administration																	
IVRS/IWRS	X	X	X	X	X		X		X		X		X		X	X	X
Randomization		X															
IMP administration[d]		X (Q2W Itepekimab/placebo administration up to Week 50)															
Safety																	
Physical examination[h] Full = mandatory Brief = if clinically indicated	Full	Full	Brief	Brief	Brief		Brief		Full		Brief		Brief		Brief	Full	Full
Vital signs[i]	X	X			X				X							X	X

Procedure	Screening (3-5 weeks)[w]	Interventional treatment period (up to 52 weeks)															Follow-up period (20 weeks)
	S	R/B[a]														EOT/ ETD[b]	EOS
VISIT	1	2[c]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
WEEK[c]	W-5 to -3	0	2	4[d]	8	12[e]	16	20[e]	24	28[e]	32	36[e]	40	44[e]	48	52	72
Electrocardiogram (12-lead)[j]	X	X							X							X	X
Hematology, clinical chemistry, urinalysis[k]	X	X		X	X				X		X					X	X
Hematology only[l]							X						X		X		
Routine urine cotinine dipstick test	X	X		X	X		X		X		X		X		X	X	X
Anabasine urine test[m]	X								X							X	
Tuberculosis testing (as per local guidelines)	X																
Hepatitis and HIV serology tests[n]	X																
Pregnancy (β-HCG blood) test[o]	X																
Urine pregnancy test[o]		X		X	X	X	X	X	X	X	X	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	X	X	X
Pharmacokinetics and ADA																	
Serum PK samples for itepekimab concentration[p]		X		X	X				X							X	X
Anti-itepekimab antibody[p]		X			X				X							X	X
Biomarkers																	
Blood biomarkers[q]		X		X					X								X
Sputum culture and sputum biomarkers (optional)[q]		X		X					X[r]								

Procedure	Screening (3-5 weeks)[w]	Interventional treatment period (up to 52 weeks)															Follow-up period (20 weeks)
	S	R/B[a]														EOT/ ETD[b]	EOS
VISIT	1	2[c]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
WEEK[c]	W-5 to -3	0	2	4[d]	8	12[e]	16	20[e]	24	28[e]	32	36[e]	40	44[e]	48	52	72
Sputum RNA (optional and for selected sites only)[s]		X		X					X[r]								
DNA for pharmacogenomic analysis (optional)[s]		X															
Plasma/serum for archival samples (optional)[s]		X		X					X								X
Efficacy																	
Exacerbation reporting by the Investigator		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry (pre-BD)[t]	X	X		X	X				X				X			X	X
Spirometry (post-BD)[t]	X	X		X	X				X				X			X	X
SGRQ[u]		X			X				X				X			X	
QOL-B[u]		X			X				X				X			X	
EQ-5D-5L[u]		X							X							X	
LCQ[u]		X							X							X	
SNOT-22[u]		X							X							X	
PGIC[u]					X				X				X			X	
PGIS[u]		X			X				X				X			X	
Healthcare Resource Utilization[v]		X			X				X				X			X	

Abbreviations: β-hCG = Human chorionic gonadotropin-beta; ADA = antidrug antibody; BID = twice daily assessments; BSI = Bronchiectasis severity Index; C = Consent; continuous = subsequent visits during the treatment period; cont. = continuous; DNA = Deoxyribonucleic acid ; EDTA = Ethylenediaminetetraacetic acid ; EOS = End of Study; EOT = End of treatment; ETD = Early treatment discontinuation; EQ-5D-5L = EuroQol 5-dimension 5-level quality-of-life Questionnaire; HIV = human immunodeficiency virus; IgE = Immunoglobulin E; IMP = Investigational Medical Product; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LABA = Long-acting β2 adrenergic agonist; LAMA = Long-acting muscarinic antagonist; LCQ = Leicester Cough Questionnaire; NCFB = Non-Cystic-Fibrosis

Bronchiectasis; PGIC = Participant Global Impression of Change; PGIS = Participant Global Impression of Severity; PK = Pharmacokinetic; RNA = Ribonucleic acid; R/B = Randomization/Baseline; S = Screening; SABA = Short-acting beta-agonists; SAEs = Serious adverse events; SC = subcutaneous; SGRQ = St. George's Respiratory Questionnaire; SNOT-22 = 22-item sino-nasal outcome test; QOL-B = Quality-Of-Life-Bronchiectasis;

a Randomization/baseline Visit is defined as Day 1. All subsequent visits will be calculated using this as a reference. The visit schedule should be adhered to within ±3 days for the screening period and randomized IMP treatment period, and ±5 days for the EOS visits during the post IMP treatment period. Determination of expected visit dates will be based on the date of randomization/baseline visit. After ETD, the participant is encouraged to attend all preplanned visits within ±5 days.

b End-of-treatment visit: See Section 7.1 for participants who discontinue treatment early. At the end of the study treatment period, a pre-planned clinic visit will be replaced by an early EOT visit for participants who are still on treatment.

c All assessments at Visit 2 (Day 1) are to be conducted pre-IMP dose.

d IMP (itepekimab or placebo) to be administered every 2 weeks at the site. Last dose will be given 2 weeks prior to planned EOT visit eg, for participants with 52-week treatment period the last dose will be taken at Week 50, or earlier, as directed by the Sponsor. Participants should be monitored by site personnel for at least 30 minutes after administration of the first 3 IMP injections. Monitoring period may be extended as per country specific requirements. Starting after Visit 4 (Week 4), 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. 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 by way of unscheduled visits.

e Can be performed with a phone call.

f Chest CT scan (if subject does not have prior radiological confirmation by means of CT of bronchiectasis diagnosis within 5 years prior to screening). Participants enrolling in the trial after amendment 04 and consenting to optional collection of chest CT imaging should have chest CT images used to determine eligibility submitted to the central portal, if available. If informed consent is re-obtained from previously enrolled participants (ie, prior to amended protocol 04), chest CT scan images used for eligibility should also be submitted to the central portal, if available. All participants consenting to the optional imaging collection should also have any additional chest CT scans performed for clinical care during the time period of the trial submitted to the central portal, if available. Both central reading and automated analysis will be performed. See Section 8.12 for further details.

g BSI to be calculated prior to baseline. For BSI calculation BMI needs to be obtained (height/weight), post BD FEV1 % predicted, Medical Research Council (MRC) dyspnea score, and colonization status (historical). Score will be entered into eCRF.

h Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Brief physical examinations will be conducted only if clinically indicated and will include respiratory, cardiovascular symptoms while additional systems may be examined as per clinical judgement of Investigator.

i Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate. Height (cm) will be measured at screening (Visit 1) only. Body weight (kg) will be measured at screening (Visit 1), Visit 9 (Week 24) and at EOT/ETD visits.

j ECG to be locally collected & read.

k Hematology will include hemoglobin, hematocrit, platelet count, total red blood cell count, and total white blood cell count with differential. Serum clinical chemistry will include creatinine, blood urea nitrogen, glucose (fasting), lactate dehydrogenase, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, bicarbonate, C-reactive protein (CRP), and creatine phosphokinase. Blood eosinophils will be blinded after Visit 2. Urinalysis will be tested locally by dipstick and include specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen, and bilirubin. Routine urinalysis will be performed in a central laboratory for participants in China. Cotinine will be tested locally by dipstick at the site in the urine sample.

l Hematology will include hemoglobin, hematocrit, platelet count, total red blood cell count, and total white blood cell count with differential.

m Anabasine Testing Guidelines: in case of negative cotinine test result, do not use anabasine test result for screening/randomization. In case of positive cotinine test result, ask the participant about NRT or non-smoked nicotine use. If the participant is using NRT or non-smoked nicotine and has a positive anabasine test result, exclude the participant. If the participant is using NRT or non-smoked nicotine and has a negative anabasine test result, the participant is eligible as per E 02. If the participant does not claim to smoke nor use NRT/chewing tobacco, exclude the participant.

n Clinical laboratory testing at Screening (Visit 1) 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. See Section 10.8.4 for country-specific requirements for Czechia.

o Only for women of childbearing potential: a serum pregnancy test will be performed at Screening (Visit 1); urine pregnancy tests will be performed at the visits listed in the SoA table. A negative result must be obtained at Visit 1 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. Sufficient amount of urine pregnancy test kits will be provided for visits that can be performed with a phone call.

p Systemic drug concentration and ADA samples are to be collected prior to dosing. If an SAE and/or AESI occurs related to anaphylaxis, systemic hypersensitivity reaction, and/or severe ISR lasting more than 24 hours) occurs in participant, additional blood samples may be collected for determination of functional itepekimab concentration (PK), and/or ADA assessment at or near the onset of the event. For China, these assessments can be considered optional.

q Blood biomarkers: proteinase 3, cathepsin G, CRP, fibrinogen, IL-6, IL-8, TNF-α, IFN-γ, IL-17A, IL-5, IL-13, IL-33, sST2, TARC, eotaxin-3, IgE, E-selectin, ICAM-1, VCAM-1, neutrophil elastase, eosinophils, neutrophils, and monocytes. Sputum biomarkers (only in participants willing and able to cough up fresh sputum): IL-5, IL-13, IL-33, TARC, eotaxin-3, IgE, IL-6, IL-8, TNF-α, IL-17A, IFN-γ, neutrophil elastase, proteinase 3, cathepsin G, MMP-8, MMP-9, MUC5B, MUC5AC, eosinophils, neutrophils, macrophages, and procalcitonin. Selected site will be requested to participate in determining the cellular components of sputum, depending upon their ability and willingness to locally prepare and analyze the sputum samples. Sputum microbiology culture will be performed with the sputum sample obtained at Randomization/Baseline. Subjects will be required to provide a sputum sample during the specified visits. On Day 1, the sputum sample should be collected prior to the first dosing of the study drugs. If a subject is unable but willing to provide a spontaneous sputum sample during any visit, chest physiotherapy can be performed to facilitate expectoration. For China, blood and sputum biomarkers can both be considered optional. In case Visit 9 (Week 24) coincides with EOT visit (eg, for last patient in), blood biomarkers (mandatory) and sputum biomarkers/RNA (both optional) should be obtained for these participants.

r Sputum should be collected at Week 24. If unsuccessful, sputum can be collected up to Week 32.

s Optional sputum RNA samples (selected sites only) and optional plasma/serum samples may be used for research purposes related to respiratory diseases such as bronchiectasis 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. Optional DNA sample may be collected once during the study. Optional sputum RNA and blood DNA will not be obtained from participants in China. In case Visit 9 (Week 24) coincides with EOT visit (eg, for last patient in), plasma/serum for archival samples (optional) should be obtained for these participants.

t 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). During the screening period, a successful spirometry (meeting American Thoracic Society (ATS)/European Thoracic Society (ERS) acceptability criteria with at least 3 acceptable flow-volume curves with at least 2 meeting the ATS/ERS repeatability criteria for FEV1 during Screening) should be obtained prior to 1st IMP administration. If the participant is unable to provide a successful spirometry, 1st IMP administration should be postponed or participant should be screen failed as per E 26. Following randomization and during the treatment period - if spirometry is not performed at the scheduled visit it should be performed at the following visit during the treatment period. Spirometry will be centrally collected & read.

u Participant's answers to the SGRQ, QOL-B, EQ-5D-5L, LCQ, SNOT-22, PGIC, and PGIS questionnaires will be recorded in an electronic format.

v Healthcare resource utilization/productivity will be recorded in the eCRF.

w Screening period may be extended by 4 weeks to a maximum duration of 9 weeks in case of an intercurrent PE occurs during the screening period.

2 INTRODUCTION

Itepekimab, also referred to as REGN3500 or SAR440340, is a monoclonal antibody (mAb) of the human immunoglobulin G4P (IgG4P) class. It binds with high affinity to interleukin 33 (IL-33), effectively inhibiting IL-33 signaling. This antibody is currently being investigated as a potential innovative therapy for chronic obstructive pulmonary disease (COPD).

2.1 STUDY RATIONALE

Bronchiectasis is a chronic and potentially life-threatening disease with high unmet medical need despite available standard of care therapies such as bronchodilators, mucolytics, and antibiotics. Patients with bronchiectasis frequently experience PEs, and exacerbations lead to worsened quality of life, daily symptoms, decline in lung function, and increased mortality.

Interleukin 33 (IL-33) is a pro-inflammatory cytokine that triggers and amplifies inflammatory responses in both innate and adaptive immune systems when epithelial cells are stressed or damaged due to exposure to inflammatory triggers. There are clinical and etiological similarities between bronchiectasis and COPD, as well as clinical overlaps among bronchiectasis, asthma, and COPD. Itepekimab is a mAb that binds to IL-33 and inhibits IL-33 signaling. There is no relevant mouse model for NCFB, however, in a mouse model of airway inflammation, it was demonstrated that lung IL-33 plays a role in driving inflammation and tissue remodeling beyond the classical Type 2 immune response associated with IL-33 signaling. Blocking IL-33 with itepekimab normalized the established inflammation and improved remodeling of both the lung epithelium and lung parenchyma (4). Itepekimab was investigated in patients with moderate-to-severe COPD and demonstrated reduced number of exacerbations of COPD, as well as improved function in patients who were former smokers (6).

Considering itepekimab's potential effect on both Type 2 and Type 1 inflammation, as well as its ability to normalize established inflammation and improve lung epithelium and parenchyma remodeling, it is hypothesized that administering itepekimab may have beneficial effects on patients with NCFB.

To develop itepekimab as a potential treatment for NCFB, a randomized, placebo-controlled study is planned. The study aims to assess the effect of itepekimab in addition to standard-of-care background therapy, which includes bronchodilators, inhaled corticosteroids, mucolytics, and/or maintenance antibiotics. This proof-of-concept (PoC) study will explore the efficacy, evaluate the safety profile, and investigate two different dosage regimens of itepekimab compared to placebo over a period of 24-52 weeks. The study will enroll participants with NCFB who require additional treatment in addition to their current management. Throughout the study, all participants will continue to receive standard-of-care background medication. The primary endpoint of the study will be the annualized rate of moderate or severe PEs. Additionally, the study design allows for the assessment of itepekimab's efficacy in multiple other domains of NCFB, including symptom control, lung function, and quality of life.

2.2 BACKGROUND

2.2.1 Bronchiectasis

Non-cystic fibrosis bronchiectasis, referred to here as bronchiectasis, is characterized by the permanent abnormal dilation of the bronchi and bronchioles, resulting from a destructive cycle of transmural infection and inflammation accompanied by the release of pro-inflammatory mediators (eg, cytokines, chemokines, prostaglandins, leukotrienes, histamine, and proteases). This process leads to the deterioration of the muscular and elastic components of the bronchial walls as well as aberrant epithelial remodeling with impaired mucociliary architecture in both large and small airways in patients with refractory NCFB. Bronchiectasis can cause obstructed breathing due to the production and clearance of abnormal mucus, rendering the airways susceptible to pathogen acquisition. Common symptoms of bronchiectasis include a chronic non-productive or productive cough, along with shortness of breath, haemoptysis, and chest pain. Wheezing and nail clubbing may also manifest. Individuals with bronchiectasis frequently experience lung infections, which can be of viral, bacterial, or mixed origin. These infections may trigger acute exacerbations characterized by a sudden worsening of symptoms, necessitating acute treatment such as antibiotics, supplemental oxygen, and, in some cases, hospitalization. Although many bronchiectasis patients have chronic stable-state lung infections, bacterial and viral isolations occur more frequently during exacerbations (7).

The prevalence of bronchiectasis has been steadily increasing over the past decade, primarily due to enhanced detection through more frequent CT-scans and improved awareness among clinicians. This rise in prevalence may also be attributed to an increase in the underlying causes of the condition (1). According to a report by Henkle et al. in 2018, the prevalence of bronchiectasis in the United States was documented to be 701 cases per 100 000 individuals (8). Similar or higher rates have been reported in other countries such as the United Kingdom (1), Germany (9), Spain (10), Singapore (11), and China. In China, it has been estimated that there are 1 100 cases per 100 000 women and 1 500 cases per 100 000 men of bronchiectasis (physician diagnosed) in the general population (12). The disease exhibits a higher prevalence among women and the elderly population (2), with older and frailer patients tending to experience more severe and symptomatic forms of the disease (13). Additionally, it is noteworthy that many bronchiectasis patients have never smoked.

Bronchiectasis is a pathological condition that serves as a common outcome for various disorders (14, 15, 16, 17). In a significant number of patients, the etiology of bronchiectasis is unknown (idiopathic) and accounts for 40% of cases. Other identified causes include post-infective (20%), COPD (15%), autoimmune disease (10%), immunodeficiency (6%), severe asthma (<5%), allergic bronchopulmonary aspergillosis (ABPA), ciliary dysfunction, and the presence of bronchiectasis as a comorbidity in patients with inflammatory bowel disease (15). There is a considerable overlap between bronchiectasis and COPD as well as asthma. Approximately 19-58% of bronchiectasis patients also have concurrent COPD, and 17-43% have concurrent asthma (1, 2, 18, 19, 20).

This study excludes patients with bronchiectasis who have comorbid cystic fibrosis (CF), which is caused by various mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and is associated with significant morbidity. These patients usually receive specialized care

(including treatment with cystic fibrosis transmembrane conductance regulator if possible) in dedicated centers (21). Therefore, this study focuses specifically on patients with non-CF bronchiectasis.

Currently, there are no approved therapies for the treatment of bronchiectasis. Common treatment approaches involve the use of bronchodilators (long-acting β2-agonists [LABA] and/or long-acting muscarinic antagonists [LAMA]), mucolytic agents (combined with expectorants and/or mucokinetics), and antibiotics. In situations of recurrent exacerbations, long-term oral (eg, macrolides) or inhaled antibiotics (eg, tobramycin) are often employed (22, 23). Trials involving inhaled antibiotics have yielded mixed results, with some showing positive outcomes. However, treatment with inhaled antibiotics has been complicated by relatively high frequencies of bronchospasm ranging from 10% to 40% (23). Guidelines from the British Thoracic Society and the European Respiratory Society recommend the long-term use of inhaled antibiotics for patients with chronic *Pseudomonas aeruginosa* (PA) infection who experience three or more exacerbations per year. It is important to note that none of these treatments are currently approved by regulatory agencies for the specific treatment of bronchiectasis (5). Inhaled corticosteroids are often prescribed, despite the lack of clinical trial evidence supporting their chronic use (24). Systemic corticosteroids are not recommended unless they are intended for the treatment of comorbid asthma or COPD (25). The 2017 European Respiratory Society guidelines for adult bronchiectasis recommend pulmonary rehabilitation as a therapeutic approach (25). Airway clearance techniques with or without pulmonary rehabilitation and muco-active treatment are advised for the treatment of bronchiectasis depending upon severity and number of exacerbations (eg, active cycle of breathing techniques or oscillating positive expiratory pressure) (5). In select cases, surgical resection may be performed to remove localized disease areas (26). Patients with end-stage disease may be considered for lung transplantation (27).

Bronchiectasis represents a condition with a significant unmet medical need. Patients affected by bronchiectasis exhibit a substantial disease burden, leading to increased mortality rates and high healthcare costs, particularly among individuals with compromised lung function and a history of smoking (13, 28, 29, 30). Subjects diagnosed with bronchiectasis commonly experience PEs, with an average frequency ranging from 1.5 to 6 per year (14, 31, 30). Some of these exacerbations are so severe, that hospitalization is required. Approximately 26% of patients had at least one hospital admission due to an exacerbation in the previous year (32). More severe exacerbations requiring hospitalization and those occurring more frequently (over 2 per year) are associated with a significant decline in quality of life, daily symptoms, deterioration of lung function, and increased mortality rates (31).

2.2.2 Itepekimab – Anti-IL-33 monoclonal antibody

Itepekimab, a human IgG4P monoclonal antibody that binds to IL-33 and inhibits IL-33 signaling, is currently being investigated as a potential novel treatment for COPD in two large-scale Phase 3 trials. Previously, a proof-of-concept study (ACT15104) was conducted to assess the effects of blocking the IL-33 pathway on exacerbations and lung function in participants with moderate-to-severe COPD who were already receiving controller therapy with LAMA, LABA, and/or ICS (6).

There are similarities in the underlying mechanisms of bronchiectasis and COPD, characterized by predominantly neutrophilic inflammation, with approximately 20% of bronchiectasis patients exhibiting eosinophilic inflammation. Both bronchiectasis and COPD are characterized by severe pulmonary dysfunction caused by a significant inflammatory response. A common histological feature of these inflammatory lung diseases is the accumulation of neutrophils in the lung's interstitium and alveoli. Neutrophils are the primary inflammatory cells found in the airways of most individuals with bronchiectasis (33, 34). Patients with these conditions exhibit higher numbers of neutrophils and other inflammatory cells compared to healthy individuals, resulting in elevated levels of neutrophil-derived products such as neutrophil elastase (NE) (33), myeloperoxidase, matrix metalloproteinases (35), cathepsins, antimicrobial peptides (eg, LL-37) (36), and neutrophil-derived DNA. NE is known to impact ciliary beat frequency, mucus production, clearance of apoptotic cells, and activation of other proteases, including matrix metalloproteinases (37, 38, 39). In a study involving 433 bronchiectasis patients in Scotland, increased levels of NE in sputum were associated with higher scores on the Bronchiectasis Severity Index, worse dyspnea scores, greater lung-function abnormalities, and more extensive radiologic disease. NE levels also increased during exacerbations and responded to antibiotic treatment (33). IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G (40).

In patients with bronchiectasis associated with pulmonary hypertension, the expression of IL-33 and its receptor (ST2) is elevated in lung tissues (41). Similar findings were reported by Green et al., who demonstrated strong expression of IL-33 in the airway epithelia, particularly in chronic lung diseases with an infectious origin such as cystic fibrosis (CF) and bronchiectasis (42).

In a mouse model of airway inflammation, it was demonstrated that lung IL-33 plays a role in driving inflammation and tissue remodeling beyond the classical Type 2 immune response associated with IL-33 signaling. Blocking IL-33 with itepekimab normalized the established inflammation and improved remodeling of both the lung epithelium and lung parenchyma. Specifically, IL-33 blockade normalized persistent and exacerbating inflammatory markers, including eosinophilic, neutrophilic, and ST2+CD4+T-cell infiltration. Importantly, the study identified a crucial role of IL-33 in driving lung remodeling, both in lung epithelium and parenchyma, as itepekimab restored the presence of ciliated cells over mucus-producing cells and reduced the number of myofibroblasts, even in the context of continuous allergen exposure, leading to improved lung function (4).

The majority of PEs in bronchiectasis are believed to be triggered by bacterial and viral airway infections. Other factors contributing to exacerbations include host inflammatory responses and environmental influences such as air pollutants (43). It is hypothesized that blocking IL-33, which is released locally in the airways in response to environmental triggers such as bacterial and viral infections in bronchiectasis patients, may represent a novel therapeutic approach to prevent PEs in patients with bronchiectasis.

2.3 BENEFIT/RISK ASSESSMENT

To date, no risks with itepekimab have been regarded as identified important risks. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of itepekimab may be found in the investigator's brochure (IB).

2.3.1 Risk assessment

Based on our completed clinical studies, the AE profile indicates that itepekimab is generally well-tolerated in participants with COPD and asthma. Like other monoclonal antibodies (mAbs), there is a potential risk of systemic hypersensitivity reactions (including immunogenicity) associated with itepekimab administration. Due to its mechanism of action as an IL-33 antagonist, which inhibits downstream inflammatory pathways in damaged epithelial tissue, serious infections, including opportunistic infections, are considered important potential risks specific to itepekimab. To manage these risks, careful participant selection, close monitoring, and prompt identification and treatment of AEs are implemented in the clinical study. Risk minimization, monitoring, and management plans are outlined in the IB. The IB also addresses all pertinent safety data collected during clinical development thus far, including observed adverse reactions from completed clinical trials.

To assess the effects on fertility, surrogate parameters were evaluated in a 26-week subcutaneous (SC) toxicology study conducted in monkeys, followed by a 13-week recovery period.
No itepekimab-related effects were observed on menstrual cycle length in females or on sperm motility, morphology, concentration, or volume in males. There were no microscopic effects on reproductive organs. Therefore, there is no evidence suggesting that itepekimab affects surrogate parameters of fertility. Additionally, an extended pre- and postnatal development (ePPND) toxicity study in cynomolgus monkeys revealed no embryo-fetal lethality, developmental toxicity, or growth retardation up to postnatal day 180. The no-observed-adverse-effect level (NOAEL) was determined to be 100 mg/kg/week SC. After the 18th dose, the maternal area under the concentration-time curve (AUCtau) at a dose of 100 mg/kg/week SC was measured to be 22 900 day*µg/mL.

It is important to note that monoclonal antibodies can cross the placenta and potentially harm the fetus. Therefore, risk minimization measures have been implemented in the study, excluding females who are lactating, breastfeeding, or pregnant. Women of childbearing potential (premenopausal females capable of becoming pregnant) are only eligible if they use one of the specified highly effective contraception methods outlined in the protocol's Inclusion criterion I 05.

Male contraception is not required for the study. It is expected that extremely low levels of itepekimab will reach the fetus through seminal fluid. Monoclonal antibodies have specific physicochemical characteristics that limit their passive transmission through biological membranes. For therapeutic antibodies to reach the fetus through seminal transfer, they would need to undergo vaginal absorption, which poses a significant barrier. Based on conservative assumptions and using the highest dose of itepekimab tested in Study R3500 HV-1551 (10 mg/kg intravenous [IV]), and assuming 100% transfer from maternal exposure to the fetus, the highest potential exposure of itepekimab to a fetus through seminal transfer would be approximately [redacted] µg/mL. This value is approximately [redacted] than the pharmacologically active concentration measured in vitro (44, 45).

During early human clinical studies, itepekimab demonstrated good tolerability in healthy adult subjects in the completed first-in-human single ascending dose study, where single IV doses of 0.3, 1, 3, 10 mg/kg, and 150 mg SC itepekimab or placebo were administered (Study R3500 HV 1551). It was also well-tolerated by participants with moderate asthma in the completed first-in-patient multiple ascending dose study, which assessed 75 mg or 150 mg SC itepekimab or placebo once every week (QW) for 4 weeks (R3500-AS-1619). No deaths or serious adverse events (SAEs) were reported.

In Study ACT15102, itepekimab monotherapy or co-administered with dupilumab for a period of 12 weeks, both at a dose of 300 mg once every 2 weeks (Q2W), was well tolerated by patients with moderate-to-severe asthma. The percentage of participants experiencing at least one treatment-emergent adverse event (TEAE) was well balanced across treatment groups. In Study ACT15104, the percentage of participants with at least one treatment-emergent SAE was similar between the itepekimab group (14.0%) and the placebo group (15.2%). There were no treatment-related antidrug antibodies (ADAs) observed in Studies ACT15102 and ACT15104. The full safety data and other potential risks for itepekimab are summarized in the IB.

Ongoing phase 3 studies (EFC16750 and EFC16819) and a Phase 2 mechanistic study (PDY16967) are actively monitoring safety. An independent data monitoring committee (DMC) has access to unblinded safety information, and, to date, the studies could be continued without amendments to the protocol. The ACT18018 study will also fall within the purview of the same DMC, which will regularly evaluate the balance of benefits and risks.

Considering the high mortality of patients with NCFB, all deaths will be adjudicated. Considering that cardiovascular disease is a frequent and important comorbidity of NCFB, 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. In the Good Laboratory Practice (GLP) toxicology studies, 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. No treatment-emergent ADA response was observed against itepekimab in any of the clinical studies completed to date.	Protocol exclusion criteria: • Known allergy to itepekimab or to excipients. Monitoring: • Participants should be monitored for any signs or symptoms of a hypersensitivity reaction for at least 30 minutes for all investigational medicinal product (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 following injection including rules on definitive discontinuation in case of anaphylaxis or systemic hypersensitivity and the recommendation to determine ADA level measurements using a validated assay (see Section 8.9). • Analysis of correlation of ADA status with safety and efficacy data.
Serious infections, including opportunistic infections	There were no preclinical findings suggestive of infections. In ACT15102, 3 participants with an event of infection SAEs were reported among a total of 11 participants with events of SAEs: infection SAEs were similar between the four groups: 0 events placebo, 1 event itepekimab 300 mg Q2W, 1 event in itepekimab 300 mg Q2W + dupilumab 300 mg Q2W, and 1 event in dupilumab 300 mg Q2W. There were no reported cases of opportunistic infections. In ACT15104, 19 participants with events of infection SAEs were reported among a total of 65 participants with a SAEs during the study: 10 in placebo and 9 in itepekimab. One participant each in the placebo group and two participants in the itepekimab group experienced an opportunistic infection: herpes zoster. All cases were of	Protocol exclusion criteria: • Participant with known or suspected immunodeficiency disorder, including history of systemic/invasive opportunistic infections. • Participant with nontuberculous mycobacteria (NTM) lung infection, allergic bronchopulmonary aspergillosis (ABPA), or tuberculosis (TB). • Participants with HIV infection or HIV seropositivity at Screening (Visit 1).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	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. For the overall susceptibility for serious and/or opportunistic infection, refer to the relevant section in this table. With increasing severity of NCFB the risk of respiratory tract infection in general is known to be increased. Adequate treatment for NCFB may result in the reduction of exacerbations which are largely of infectious etiology.	• Participants with a positive hepatitis B surface antigen or core antibody or hepatitis C antibody at Screening (Visit 1). Management of infections • Monitoring of participants for events related to/suggestive of serious infections or opportunistic infections. • The protocol contains rules on definitive discontinuation in case of opportunistic infections.
Study intervention(s) Itepekimab		
None	None	None
Study procedures		
None	None	None
Other		
None	None	None

Abbreviations: ADA = antidrug antibody; AESI = adverse event of special interest; 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 a proof-of-concept study conducted in patients with moderate-to-severe COPD (ACT15104), itepekimab demonstrated a 19.2% reduction in the risk of experiencing moderate-to-severe acute exacerbations of COPD (AECOPD) compared to placebo over a treatment period of up to 52 weeks. However, this difference did not reach statistical significance (relative risk [RR]: 0.808, 95% confidence interval [CI] 0.613 to 1.065; p=0.1296). Subgroup analysis based on smoking status revealed a significant effect in former smokers. Specifically, in former smokers, itepekimab showed a 42.5% risk reduction in moderate-to-severe AECOPD compared to placebo (RR 0.575, 95% CI 0.388 to 0.853, nominal p=0.0061). However, in the current smoker population, itepekimab did not demonstrate a reduction in the annualized rate of moderate-to-severe AECOPD (-9.4%, RR 1.094, 95% CI 0.743 to 1.612, nominal p=0.6472), and no benefits were observed in other evaluated endpoints indicating that active smoking may diminish the efficacy of itepekimab.

In the proof-of-concept study involving patients with moderate-to-severe asthma that was not well controlled on ICS + LABA therapy (ACT15102), itepekimab administered as monotherapy (300 mg Q2W) or in combination with dupilumab (300 mg Q2W) significantly decreased the likelihood of experiencing loss of asthma control (LOAC) and improved pre-bronchodilator forced expiratory volume in 1 second (FEV1) compared to placebo in patients gradually withdrawn from their baseline controller therapy.

There are similarities in the underlying mechanisms of bronchiectasis and COPD, characterized by predominantly neutrophilic inflammation, with approximately 20% of bronchiectasis patients exhibiting eosinophilic inflammation. Both bronchiectasis and COPD are characterized by severe pulmonary dysfunction caused by a significant inflammatory response.

Considering itepekimab's potential effect on both Type 2 and Type 1 inflammation, as well as its ability to normalize established inflammation and improve lung epithelium and parenchyma remodeling in a pre-clinical model, it is hypothesized that administering itepekimab may have beneficial effects on patients with NCFB. These effects may include reducing inflammation and mucus hypersecretion, leading to decrease in exacerbation rate, improvements in respiratory symptoms (such as cough and sputum production) and lung function (eg, FEV1). In a pre-clinical model, treatment with itepekimab has also been shown to restore the presence of ciliated cells over mucus-producing cells and reduce myofibroblast numbers, even in the presence of continuous allergen exposure, highlighting the role of IL-33 in lung remodeling (4).

2.3.3 Overall benefit/risk conclusion

Considering the risk mitigation measures implemented to ensure participant safety in the study, the identified potential risks associated with itepekimab are justified by the expected benefits that it may provide to participants with NCFB.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

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

Objectives	Endpoints
	• Change from baseline at Week 4, Week 24-32 in the following: - Sputum (optional): IL-5, IL-13, IL-33, TARC, eotaxin-3, IgE, IL-6, IL-8, TNF-α, IL-17A, IFN-γ, eosinophil, neutrophil and macrophage count, neutrophil elastase, proteinase 3, cathepsin G, MMP-8, MMP-9, MUC5B, MUC5AC, and procalcitonin
• Evaluate the efficacy of itepekimab compared with placebo on FEV1 slope in NCFB • Evaluate the efficacy of itepekimab compared with placebo on healthcare utilization in NCFB • To characterize the effects of itepekimab on gene expression and to study genetic factors that may predict itepekimab safety/efficacy • Evaluate the efficacy of itepekimab compared with placebo on HRQoL and health status as assessed by SGRQ, QoL-B, and LCQ in NCFB • Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB	• Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4-12 weeks • Annualized number of days of healthcare resource utilization over the treatment period • Pharmacogenomics analysis (optional) • Blood DNA sampling (optional) • Sputum RNA sampling (optional and selected sites only) • Change from baseline in QoL-B Physical, Role, Emotional, and Social Functioning, Vitality, Health Perceptions and Treatment Burden Domain score in adult participants at Week 24 • Change from baseline in LCQ total score at Week 24 • Annualized rate of all exacerbation (as recorded by Investigator) • Annualized rate of all exacerbations leading to prescription with antibiotics • Annualized rate of all exacerbations leading to prescription of antibiotics and/or systemic corticosteroids + meeting footnote a Part A criterion of a moderate exacerbation

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

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

* Moderate PE in this study is defined as:

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

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

AND

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

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

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

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

Other exploratory endpoints including but not limited to the PGIS, PGIC, EQ-5D-5L, SNOT-22 and alternative timepoints for secondary endpoints will be described in the SAP.

For China, please see Section 10.8.1 for details.

Primary estimands defined for primary and key secondary efficacy endpoints are summarized in Table 3 below. More details are provided in Section 9.2.

Table 3 - Summary of primary estimands for main endpoints

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

Endpoint	Estimands			
Category (estimand)	**Endpoint**	**Population**	**Intercurrent event(s) (ICEs) handling strategy**	**Population-level summary (Analysis and missing data handling)**
			c) If a participant takes study treatment not as randomized for any reason, the participant will be included in treatment group as initially randomized. d) For participants with change in background therapy, all the data observed during their planned treatment period (as defined above) will be included in the analyses.	compared to other strategies, missing data may nevertheless occur as a result of participants withdrawing from the study. To account for a shorter duration of follow-up of participants who withdraw from the study prior to their planned treatment duration, the primary analysis negative binomial model will include an offset term for the logarithm of follow-up duration. No further imputation will be performed for the unobserved PE events that may happen after study discontinuation and up to end of the planned treatment duration. **Sensitivity estimators**: Sensitivity analyses focusing on the assumptions about missing data will be performed to assess the robustness of the conclusion of the primary analysis using tipping point analysis and/or a pattern mixture model by multiple imputation. Details will be specified in the SAP.
Secondary objective: Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB				
Key secondary endpoint (primary estimand: treatment policy)	Time to first moderate or severe PE over the treatment period	ITT	The 4 ICEs specified above will be handled in the same way using treatment policy strategy. Operationally, regardless of treatment discontinuation, all participants will be followed-up according to the study procedures up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. That is, PE events and related data would be collected and reported over the entire planned treatment period for all study participants even if some participants may have discontinued the study treatment. Analytically, the time to first moderate or severe PE over the planned treatment period analysis is performed regardless of the occurrence of the ICEs and the timing of the ICE. For participants without any	**Below population-level summaries** will be derived using a Cox regression model. • The hazard ratio of each itepekimab regimen versus placebo, and the corresponding 2-sided 90% CI and p-value. The model will include the time to the first event as the dependent variable, with treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and

Endpoint	Estimands			
Category (estimand)	Endpoint	Population	Intercurrent event(s) (ICEs) handling strategy	Population-level summary (Analysis and missing data handling)
			PE events, the time from randomization to the date of treatment completion or treatment discontinuation up to their planned treatment period (event time will be considered as censored at date of EOT or the last contact date within the planned treatment duration, whichever comes first) will be used in the analysis.	maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. The Kaplan-Meier method will be used to derive the probabilities that a participant would experience an event up to specific time points for each treatment group.

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 patients with NCFB and have been used or are being used in similar designed Phase 2 and 3 studies using brensocatib, HSK31858 and BI 1291583 (46; NCT05238675, NCT04594369, NCT05601778).

4 STUDY DESIGN

4.1 OVERALL DESIGN

ACT18018 is a Phase 2 study conducted in multiple countries. It is a randomized, double-blind, placebo-controlled trial with parallel groups (consisting of 3 groups) aimed at evaluating the efficacy, safety, and tolerability of two different dosing regimens of itepekimab in participants diagnosed with NCFB who are receiving standard of care therapy, including bronchodilators, inhaled corticosteroids, mucolytics, and/or maintenance antibiotics. The study treatments consist of subcutaneous administration of itepekimab at a dose of 300 mg every 2 weeks (Q2W), itepekimab 300 mg every 4 weeks (Q4W), or a matching placebo (1:1:1 randomization). A total of approximately 300 participants will be randomized in this study, and the treatment duration will be a minimum of 24 weeks and a maximum of 52 weeks. Following the treatment period, there will be a 20-week safety follow-up period. The variable treatment duration allows for maximizing data collection for the primary endpoint, which is the annualized rate of moderate or severe PEs, in a time-efficient manner.

The primary endpoint is the annualized rate of adjudicated moderate or severe PEs over the treatment period. All exacerbations defined as worsening of respiratory symptoms leading to prescription of antibiotics (new, addition or change in) and/or systemic corticosteroids will be captured by the Investigator. An adjudication committee will determine if following criteria are met: a moderate PE in this study which is defined as: A) having 3 or more of the following symptoms for at least 48 hours: 1. Increased cough, 2. Increased sputum volume or change in sputum consistency, 3. Increased sputum purulence, 4. Increased breathlessness and/or decreased exercise tolerance, 5. Fatigue and/or malaise, 6. Haemoptysis, AND B) A physician’s decision to prescribe antibiotics (or addition of antibiotic or change in antibiotic). Severe PE is defined as PE as described above that require intravenous antibiotics treatment, or hospitalization, or observation for >24 hours in emergency department/urgent care facility, or result in death. For both moderate and severe PE events to be counted as 2 separate events, they must be separated by at least 14 days between any course of antibiotics or 14 days between discharge and new admission in case of hospitalization (severe events only). Subjects on chronic antibiotic therapy whose only change in therapy is dose or frequency adjustment in response to worsening of respiratory symptoms will not meet the definition of exacerbation.

For efficacy endpoint analysis, the primary population will be the ITT population (see Section 9.1). The efficacy analysis of subgroups will be detailed in the SAP. During the randomization process, participants will be stratified based on their geographical region, documented history of COPD and/or asthma (if asthma is resolved before 18 years of age and has not recurred, it will not be taken into consideration), and whether they are receiving maintenance macrolide antibiotic therapy at the start of the study. To ensure that the proportion of participants with a documented history of COPD and/or asthma does not exceed approximately 20%, the enrollment of participants with a documented history of COPD and/or asthma in each stratification group will be closely monitored and controlled:

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

This will ensure a preplanned subgroup analysis in participants without a documented history of COPD and/or asthma which can provide a reasonable estimate of the treatment effect.

The study duration is outlined below:

- Screening period (3-5 weeks).
- Treatment period (24-52 weeks).
- Post-IMP treatment safety follow-up (20 weeks).

Participants who satisfy the inclusion criteria will be randomized (1:1:1) to one of the following IMP treatment groups to be administered for the planned 24-52 week treatment duration:

- 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, administered as a single SC injection of matching placebo to itepekimab Q2W.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, placebo-controlled study design where the effect of the IMP is assessed on top of standard-of-care background therapy is considered to be the most appropriate design to examine the efficacy and safety of a novel biologic therapy in NCFB. Annualized rate of moderate-to-severe PEs was selected as the primary endpoint as it is generally considered to be the most clinically relevant outcome in NCFB. NCFB exacerbations have major short-term and long-term effects on patients and are an important measure of the clinical burden of NCFB. They determine disease-associated morbidity, mortality, resource burden, and healthcare costs (28, 29, 30, 13). More severe exacerbations requiring hospitalization and those occurring more frequently (over 2 per year) are associated with a significant decline in quality of life, daily symptoms, deterioration of lung function, and increased mortality rates (31).

Similar study designs and endpoints have been employed for recent studies with other drugs and are considered “state-of-the-art” for studies in NCFB (46; NCT05238675, NCT04594369, NCT05601778). 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. On top of that, all patients will remain on their standard-of-care therapy for the duration of the study. The 24-52-week duration of this study allows for assessment of the broad range of short-term and midterm effects itepekimab may have on PE, lung function, HRQoL, and symptom control. This study is targeting non-smokers and former smokers. For the current study, a smoking cessation of ≥6 months prior to screening was chosen because on the one hand it is generally believed that a majority of reversible alteration in the lung has a recovery period of a few weeks after smoking cessation (47, 48). 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 (49).

Itepekimab has demonstrated efficacy in patients with asthma (50) and in patients with COPD (6). There are clinical and etiological similarities between bronchiectasis and chronic obstructive pulmonary disease (COPD), as well as clinical overlaps among bronchiectasis, asthma, and COPD. Participants will be stratified during the randomization process based on their documented history of COPD and/or asthma in order to prevent uneven distribution of this among the 3 treatment arms. Secondly, to ensure that the proportion of participants with a documented history of COPD and/or asthma does not exceed approximately 20%, the enrollment of participants in each stratification group will be closely monitored and controlled.

4.2.1 Patient input into design

As the design of this ACT18018 trial is very similar to previous trials which was or are being conducted with itepekimab in respiratory disease (ACT15104 and EFC16750/EFC16819), no feedback was requested specifically for the ACT18018 study.

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 [redacted] 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 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 Phase 3 COPD studies for confirmation. Both dose regimens of 300 mg SC Q2W and Q4W are expected to achieve a mean [redacted] Based on this information, the less frequent dosing regimen (Q4W) may provide a similar benefit/risk ratio in the former smoker participants with COPD.

These two dosage regimens used in the Phase 3 program in COPD will be used in this NCFB study as well, due to the clinical and etiological similarities between NCFB and COPD, as well as clinical overlaps among NCFB, asthma, and COPD.

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.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 to 85 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Clinical history consistent with NCFB (cough, chronic sputum production and/or recurrent respiratory infections) that is confirmed by chest computerized tomography (CT) scan (either historically within the past 5 years, or during screening), AND are mucopurulent sputum producers with a history of chronic expectoration.

I 03. Participants with a post-BD FEV1 % predicted ≥30% during Screening period (obtained in between Visit 1 but prior to Baseline/Randomization Visit 2).

I 04. At least 2 moderate or 1 severe PEs defined by need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 month before the Screening Visit. In case maintenance antibiotic is used, at least one exacerbation must have occurred while patient was on maintenance antibiotic therapy.

- Moderate PE = worsened respiratory symptoms leading to treatment with antibiotics, or addition of antibiotics, or change in antibiotics.
- Severe PE = worsened respiratory symptoms resulting in hospitalization or observation for >24 hours in emergency department/urgent care facility.

Note: Subjects on chronic antibiotic therapy whose only change in therapy is dose or frequency adjustment in response to worsening of respiratory symptoms will not meet the definition of exacerbation. Switch and/or add-on of a new antibiotic will meet the definition.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 05. All

a) Male participants:

- No contraceptive measures required for this study.

b) 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 women of child bearing potential (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 at least 20 weeks after the last dose of study intervention.

Informed Consent

I 06. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) 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. Have bronchiectasis due to CF, hypogammaglobulinemia, common variable immunodeficiency, known active nontuberculous mycobacteria (NTM) lung infection, or pulmonary fibrosis.

E 02. Participants who are currently smoking tobacco, or participants in whom smoking cessation has occurred <6 months prior to Screening (Visit 1) Note: Urine cotinine levels will be tested at Screening (Visit 1) and at various subsequent visits during the study (nicotine replacement therapy and/or non-inhaled tobacco product use are not considered current smoking of tobacco).

E 03. Known or suspected immunodeficiency disorder, including history of invasive/systemic opportunistic infections outside of the lungs.

E 04. Pulmonary exacerbation (PE) (as described in Section 8.2.1) which has not resolved clinically during screening period. Screening period may be extended by 4 weeks to a maximum duration of 9 weeks in case of an intercurrent PE.

E 05. Have significant haemoptysis (requiring medical intervention and/or requiring blood transfusion) within 6 weeks prior to Baseline (Visit 2).

E 06. Have any clinically significant abnormal laboratory values at Screening (Visit 1) or diseases or disorders (eg, cardiovascular, pulmonary, gastrointestinal, liver, kidney, neurological, musculoskeletal, endocrine, metabolic, psychiatric, physical impairment,) that, in the opinion of the Investigator, may put the subject at risk by participating in the study, or interfere with the subject's treatment, assessment, or influence the results of the study, or have compliance issues with the study.

E 07. History of lung transplantation.

E 08. History of malignancy within 5 years before Screening (Visit 1), 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 09. Unstable ischemic heart disease, including acute myocardial infarction within the past 1 year prior to Screening, or unstable angina in the 6 months prior to Screening (Visit 1), or during the screening period.

E 10. 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.

Prior/concomitant therapy

E 11. Currently being treated with antimicrobial therapy for tuberculosis (TB) (for tuberculosis, also E 22 is applicable), or on active treatment (any) for allergic bronchopulmonary aspergillosis (ABPA).

E 12. Are taking oral or inhaled antibiotics as chronic treatment for NCFB since less than 6 months prior to Screening (Visit 1). Participants on antibiotics as chronic treatment should be on such treatment for at least 6 months prior to enrolment while meeting all other inclusion and exclusion criteria.

E 13. Are not on a stable dose of inhaled corticosteroid and/or long-acting bronchodilators and/or long-acting anticholinergics for at least 4 weeks prior to Screening (Visit 1) (applicable only for participant who are using an inhaled corticosteroid and/or long-acting bronchodilators and/or long-acting anticholinergics. This is not a requirement for eligibility).

E 14. 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 15. Have recently started (<3 months prior to screening) participating in, or are scheduled to participate in a pulmonary rehabilitation program at Screening (Visit 1).

E 16. Live-attenuated vaccine(s) within 4 weeks prior to Screening (Visit 1) or plans to receive such vaccines during the study (see Appendix 13 [Section 10.13]).

E 17. Anti-IgE therapy (eg, omalizumab) within 130 days prior to Screening (Visit 1) or any other immune-directed biologic therapy (eg, anti-IL5, anti-IL5R, anti-IL4Ra, anti-TSLP) or systemic immunosuppressant (eg, methotrexate, any anti-tumor necrosis factor [anti-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 1), whichever is longer.

E 18. Participants receiving medications or therapy that are prohibited as concomitant medications (Section 6.9) at screening and/or during screening phase.

Prior/concurrent clinical study experience

E 19. Known allergy to itepekimab or to excipients.

E 20. Exposure to another investigative drug (monoclonal antibodies as well as small molecules) prior to Screening (Visit 1), within the period specified as follows: an interval of less than 6 months or <5 pharmacokinetic (PK) half-lives, whichever is longer, for investigative monoclonal antibodies, and an interval of less than 30 days or <5 PK half-lives, whichever is longer, for investigative small molecules.

Diagnostic assessments

E 21. Clinically significant new abnormal electrocardiogram (ECG) within 6 months prior to, or at Screening (Visit 1) that may affect the participant's participation in the study in the judgment of the Investigator.

E 22. TB assessment is mandatory to rule out active/latent TB and should be performed and assessed according to local guidelines. Participants with active or latent TB need to be excluded (see Section 10.8.4 for country-specific requirements for Czechia).

Note: If no local guidelines are available or TB testing in accordance with local guidelines is not able to be performed at the site, a blood sample for Quantiferon testing can be sent to the central laboratory.

Participants with a positive TB skin test or a positive Quantiferon assay are excluded from the study unless all of the following conditions are met:

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

AND

- Have obtained consultation with a specialist (eg, pulmonologist or infectious disease expert) to rule out active TBI,

AND

- For whom review and approval from Sponsor has been granted.

E 23. History of human immunodeficiency virus (HIV) infection or positive HIV1-2 serology at Screening (Visit 1).

E 24. Participants with any of the following result at Screening (Visit 1): Positive (or indeterminate) hepatitis B surface antigen (HbsAg) or positive IgM hepatitis B core antibody (HbcAb) or positive total 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) (see Section 10.8.4 for country-specific requirements for Czechia).

E 25. Clinically significant laboratory abnormalities at Screening (Visit 1):

- Alanine aminotransferase (ALT) or aspartate aminotransferase (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/mm^3 (<1000/mm^3 for those of African descent).
- Platelets <100 000/mm^3.
- Creatinine ≥150 μmol/L.

E 26. Are unable to perform technically acceptable spirometry meeting ATS/ERS acceptability criteria with at least 3 acceptable flow-volume curves with at least 2 meeting the ATS/ERS repeatability criteria for FEV1 during Screening period prior to first IMP administration.

Other exclusion criteria

E 27. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 28. Participant 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 29. 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 ICH-GCP Ordinance E6).

E 30. 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.

E 31. Any country-related specific regulation that would prevent the participant from entering the study – see Appendix 8 [Section 10.8] of the protocol (country-specific requirements).

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.3.1 Meals and dietary restrictions

Not applicable.

5.3.2 Caffeine, alcohol, and tobacco

Use of inhaled tobacco products (eg, smoking tobacco, vaping, heated tobacco, etc) and marijuana products will not be allowed from 6 months prior to Screening (Visit 1) until after the final follow-up visit. If abstinence is difficult for the participant, the participants may seek medical help

and receive supportive treatment with Nicotine Replacement Therapy (NRT), by oral, intranasal, or transdermal administration (but not inhalation). Use of alcohol and caffeine is allowed. However, 8 hours prior to spirometry, no alcohol should be consumed (for details, refer Section 8.2.2).

5.3.3 Activity

Not applicable.

5.3.4 Other restrictions

Not applicable.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequentlyrandomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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. Participants who fail any inclusion criteria 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.

Participants who are unable to perform technically acceptable spirometry meeting ATS/ERS acceptability criteria with at least 3 acceptable flow-volume curves with at least 2 meeting the ATS/ERS repeatability criteria for FEV1 during Screening period, can be retested during the screening period of the study. In the case of technical malfunction of equipment during spirometry, the participant may be retested. Subjects who need to repeat pulmonary function tests (PFTs) because they do not meet the Inclusion criterion I 03 can repeat the test without being screen failed. If spirometry during screening is impacted by a PE, participant needs to be screen failed, but can be rescreened (see E 04).

If certain dynamic laboratory tests do not meet the inclusion criteria at Screening (Visit 1), 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.

If the participant experiences a PE (see Section 8.2.1) during the screening period, the screening period may be extended by 4 weeks (up to 9 weeks in total). If the exacerbation has clinically resolved (no symptoms and no treatment for exacerbation) during the extended screening period, screening assessments do not need to be repeated but patient can proceed to Baseline visit and randomization if all other eligibility criteria are still met.

It is intended to include approximately up to 80% of participants without a documented history of COPD and/or asthma and 20% or less of participants with a document history of COPD and/or asthma. This will be monitored and regulated throughout the recruitment period. Recruitment may be paused of 1 stratum temporarily if deemed necessary. If asthma is resolved before 18 years of age and has not recurred, it will not be taken into consideration. In case of misdiagnosis of COPD and/or asthma in the past (eg, for COPD no spirometry confirmation or diagnosis of COPD in absence of smoking history and/or smoke exposure, for asthma lack of reliable history of typical variable respiratory symptoms of asthma or confirmation of variable expiratory airflow limitation), the Investigator can document this in the source materials and enroll the patient in the stratum of 'NO COPD and/or asthma'. If one of the stratification groups is filled, the IRT will close enrollment in this group. As previous studies have demonstrated efficacy of itepekimab in COPD and asthma, and since there is clinical overlap between NCFB and COPD/asthma, it is important to be able to demonstrate efficacy in NCFB participants without co-morbid COPD and/or asthma. By including approximately 80% of participants without documented history of COPD and/or asthma, it is expected to have adequate power to evaluate treatment effects in this subgroup of NCFB participants.

Participants who are in the screening period at the moment of stratum closure or at time of meeting the anticipated total number of targeted participants (n=300) will not be guaranteed randomization, even if they meet all inclusion criteria and none of the exclusion criteria, because over recruitment may not be allowed.

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

For exceptional emergency situations (examples are provided in Appendix 9, Section 10.9) where the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 9 (Section 10.9) should be considered for temporarily delaying screening/enrollment/randomization/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, IMPs and noninvestigational medicinal products (AxMPs), medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 STUDY INTERVENTION(S) ADMINISTERED

The IMP is to be administered every 14 ±3 days (Q2W) (up to 26 doses) or 28 ±3 days (Q4W) (up to 13 doses) with placebo injection in between during the treatment period (Table 4). Each prefilled syringe contains a deliverable volume of 2 mL with an itepekimab concentration of 150 mg/mL or 0 mg/mL.

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 left or right upper thighs, 4 quadrants of the abdomen, or the left or right 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 onsite 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 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 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 should only perform the injection in the abdomen, or left or right upper thighs. The caregiver can perform the injection in left or right upper thighs, the abdomen, or left or right 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).

For doses not given at the study site, paper form will be provided to record information related to the injections. The forms will be collected and 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 participants and at next site visit check the completed forms.

Table 4 - Study intervention(s) administered

Intervention label	300 mg Q2W	300 mg Q4W	Placebo
Intervention name	Itepekimab	Itepekimab	Placebo matching itepekimab
Type	Biological/Vaccine	Biological/Vaccine	Biological/Vaccine
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 AxMP	IMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in prefilled syringes. Each prefilled syringe will be labelled as required per country requirement.	Study intervention will be provided in prefilled syringes. Each prefilled syringe will be labelled as required per country requirement.	Study intervention will be provided in prefilled syringes. Each prefilled syringe will be labelled as required per country requirement
[Current/former name(s) or alias(es)]	Itepekimab	Itepekimab	Not applicable

Table 5 - Study arm(s)

Arm title	300 mg Q2W	300 mg Q4W	Placebo
Arm type	Experimental	Experimental	Placebo
Type of intervention	Participants will receive itepekimab 300 mg Q2W as SC injection for up to 52 weeks	Participants will receive itepekimab 300 mg Q4W with alternating placebo administration at the 2-week interval between active IMP as SC injection for up to 52 weeks	Participants will receive placebo Q2W as SC injection for up to 52 weeks
Associated intervention labels	NA	NA	NA

The IMP may be supplied at the site or from the PI/site/Sponsor to the participant (DTP) via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.1.1 Devices

The itepekimab prefilled syringe is classified as a combination product with an integral medical device where the principal mechanism of action is that of the itepekimab. See Section 8.4.8 Guidelines for Reporting Product Complaints for reporting of product complaints. Medical devices for diagnostic interventions (eg, spirometry, ECG) are not considered as "investigational device" in the context of this study.

6.2 PREPARATION, HANDLING, STORAGE, AND 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.
3. 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.
4. 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 8.4.8).

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 ASSIGNMENT TO STUDY INTERVENTION

All participants will be centrally assigned to randomized study intervention using an 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.

Definition of a randomized participant is a participant from screened population who has been allocated to a randomized intervention regardless of whether the intervention was received or not. A participant cannot be randomized more than once in the study. The randomized intervention kit number list is generated centrally by Sanofi. The IMPs are packaged in accordance with this list. Study intervention will be dispensed at the study visits as summarized in the SoA.

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

Returned study intervention should not be re-dispensed to the participants.

6.4 BLINDING

This is a double-blind study in which participants/care providers/Investigators are blinded to study intervention. 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 (eg, in case of available antidote). Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at the Investigator's discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

The bioanalyst and pharmacokineticist responsible for the sample analysis and pharmacokinetic evaluation will be unblinded. They will, however, agree not to disclose the randomization schedule or the individual unblinded analytical results before the database lock.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE for the purpose of expedited regulatory reporting (see Section 8.4.4). Sponsor staff involved in the conduct of the study will remain blinded to the participant intervention assignment.

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 above in this section.

6.5 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 participants and at next site visit check the completed paper administration form(s).

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each subsequent phone of site visit. Compliance will be assessed by direct questioning and counting returned PFSs during the site visits and documented in the source documents and relevant form. Deviations from the prescribed dosage regimen have to be recorded.

A record of the quantity of IMP dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.6 DOSE MODIFICATION

No dose modification or interval modification is allowed for IMP. After 1 severe or 2 moderate exacerbations of NCFB, adjustments in baseline inhaled corticosteroid and/or long-acting bronchodilators and/or long-acting anticholinergics therapy (start, stop and/or dose adjustments) will be permitted for symptom control and as needed for the remainder of the trial period and will be documented. Short-acting bronchodilator and/or short acting anticholinergic medication and mucolytics dose and interval may be modified as needed.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Depending on evidence of the participant's unmet medical need, the non-availability of suitable alternative therapies, and an assessment of what is known about the benefits and risks of itepekimab, participants who have successfully completed their participation in this clinical trial will be eligible for post-trial access to itepekimab.

The Investigator/treating physician will determine if benefit of continued access to itepekimab can be expected and access to itepekimab is the best medical option for the participant and will then submit a request to Sanofi.

Provision of itepekimab will be in compliance with all applicable national and local laws and regulations, including safety reporting obligations.

A participant will not be eligible for post-trial provision of itepekimab if his/her participation in the trial is terminated prematurely.

Sanofi's post-trial access responsibilities will need to be periodically re-evaluated. Based on new information about the investigational product (including adverse reactions), the continued health benefit to the individual and market availability of the product or alternative therapies, post-trial access may be terminated. This includes situations where the trial may be stopped due to safety concerns or other issues.

6.8 TREATMENT OF OVERDOSE

Symptomatic overdose is an AESI (defined in Section 8.4.7). 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.

6.9 PRIOR AND CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, 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:

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

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen, at doses of ≤2 grams/day, is permitted for use any time during the study. Other concomitant medications may be considered on a case-by-case basis by the Investigator in consultation with the medical monitor.

Use of inhaled corticosteroid and/or long-acting bronchodilator and/or long-acting anticholinergic or antibiotic controller medication is not required. If a subject uses controller medication, they should continue their maintenance doses of oral or inhaled antibiotics or inhaled corticosteroids and/or bronchodilators (LABA/LAMA) during the study. Subjects can continue to use PDE4 inhibitors when applicable (but not start or stop), and use their inhaled short-acting medication when applicable (SABA, and/or SAMA) at will. Subjects are also allowed to continue their airway clearance maintenance treatment/procedures such as use of hypertonic saline/isotonic saline, and mucolytics when applicable. However, except under unforeseeable clinical circumstances, the airway clearance maintenance treatment/procedures and pulmonary rehabilitation should continue unchanged throughout the duration of the study until Visit 31 (EOS).

The following treatments are not permitted during the screening and treatment periods (except for the acute treatment of a PE):

- Any inhaled corticosteroid and/or long-acting bronchodilators and/or long-acting anticholinergics medication other than those used at study entry (LABA and/or LAMA and/or ICS).
- New use of the following (stable, chronic use for >6 months prior to Screening [Visit 1] are allowed, but discontinuation of the following during treatment phase is strongly discouraged):
  - Chronic (≥4 weeks) use of antibiotics (inhaled or oral).
  - Oral or inhaled PDE-3 and/or PDE-4 inhibitors (roflumilast, ensifentrine, etc).
  - LTRA (eg, montelukast).

- Methylxanthines (eg, theophylline, aminophylline) except for short term (≤2 weeks) use in case of PE.
- Systemic corticosteroids except for short term (≤2 weeks) use for various reasons.
- Anti-IL5 or IL5R mAb (eg, benralizumab, mepolizumab, reslizumab).
- Anti-thymic stromal lymphopoietin (TSLP) (Tezepelumab)
- Anti-IgE therapy (eg, omalizumab).
- Anti-IL4 receptor mAb (eg, dupilumab).
- DPP1 inhibitors (brensocatib)
- Systemic immunosuppressants (eg, methotrexate, any anti-TNF mAbs, B- and/or T-cell targeted immunosuppressive therapies, JAK inhibitors), other immune-directed biologic therapy such as anti-IL-6 (tocilizumab, sarilumab, siltuximab), anti-IL-17 (bimekizumab, brodalumab, ixekizumab, secukinumab), anti-IL-23 (guselkumab, mirikizumab, risankizumab, tildrakizumab), anti-IL-12/IL-23 (ustekinumab).
- Live-attenuated vaccines: refer to the Appendix for List of Prohibited Live-Attenuated Vaccines, Appendix 13 (Section 10.13).
- Other investigational drugs.

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

- Antihistamines are permitted.
- Short-acting bronchodilator or short-acting anti-cholinergic medication (SABA, SAMA).
- NRT (chew tobacco is allowed as well).
- Ocular, intranasal, and topical application of corticosteroids to areas of the skin/mouth.
- Inactivated and other nonlive-attenuated vaccines (including any future nonlive-attenuated severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) vaccines.

Table 6 - Minimum time intervals for restricted medication use prior to reversibility/spirometry testing

Medication	Minimal Time Interval from Last Medication Dose
	Pre-Bronchodilator Testing
Inhaled SABA (salbutamol/albuterol, levosalbutamol/levalbuterol, terbutaline)	6 hours
Inhaled LABA (formoterol, salmeterol), including ICS/LABA combination products	24 hours
Vilanterol, indacaterol, olodaterol (ultra-long)	36 hours
Inhaled SAMA (ipratropium) including SABA/SAMA combinations	12 hours
Inhaled LAMA (aclidinium, tiotropium, glycopyrrolate, umeclidinium), including LAMA/LABA and ICS/LAMA combination products	36 hours

Medication	Minimal Time Interval from Last Medication Dose
	Pre-Bronchodilator Testing
Xanthines (prohibited concomitant medication)	
twice daily	12 hours
once daily	24 hours
Roflumilast (chronic use only is allowed)	24 hours

Abbreviations: ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; NA = not applicable; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist.

6.9.1 Rescue medicine

Pulmonary exacerbations (PEs) of NCFB should be treated as deemed necessary by the Investigator avoiding, if possible, the list of non-permitted concomitant medications (see Section 6.9). After successful management of a PE of NCFB (eg, with antibiotics and oxygen suppletion), all efforts should be made to resume the initial controller treatment regimen if this is medically acceptable in the Investigator's opinion. After 1 severe or 2 moderate PEs of NCFB, 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 NCFB will be captured on the exacerbation page in the eCRF (including, but not limited to requiring use of antibiotics, requiring hospitalization, or emergency room [ER] visit, or resulting in death).

Protocol defined moderate and severe PE events are collected as efficacy endpoints via the exacerbation page in the eCRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

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 and follow-up and for any further evaluations that need to be completed.

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 12 [Section 10.12]).
- 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]). Certain pulmonary infections which are frequently observed in bronchiectasis don't automatically qualify for treatment discontinuation (such as, but not limited to aspergillosis and mycobacteria infections).
- Serum ALT >3 × upper limit of normal (ULN) and total bilirubin >2 × ULN (see Appendix 6 [Section 10.6]).
- Serum ALT >5 × ULN if baseline ALT ≤2 × ULN or ALT >8 × ULN if baseline ALT >2 × ULN (see Appendix 6 [Section 10.6]).

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (within 48 hours) before making a decision of permanent discontinuation of the IMP for the concerned participant.

In case of exposure to prohibited concomitant medication such as, but not limited to immunomodulating monoclonal antibodies or immunosuppressants as listed in the prohibited medications from Section 6.9, a decision should be made on the need for temporary or permanent discontinuation of IMP. The decision to resume the treatment with IMP will be made by the Principal Investigator based on the clinical judgment and potential risks of drug interactions.

Handling of participants after permanent 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 permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate.

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 may be reduced. For site visits, under exceptional circumstances when a participant cannot or does not want to come to the site for a scheduled visit, a phone contact can be made. During the phone contact, at least information about AEs, concomitant medications, and exacerbation events should be collected.

All cases of permanent 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 QTc stopping criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula (QTcF) after enrollment), the Investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4 Temporary discontinuation

Temporary discontinuation decided by the Investigator corresponds to 1 or more dose not administered to the participant. Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs, use of prohibited medication (see Section 7.1.1), or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 Contingency measures for a regional or national emergency that is declared by a governmental agency [Section 10.9]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.5 Rechallenge

Reinitiation of intervention with the IMP 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 adverse event was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

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 the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent from the study, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent, as per applicable clinical regulation(s).

If a participant withdraws from the study, the participant 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.

The Investigators should discuss with them 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 e-CRF 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 the participant 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, 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. The recommendation is to have 3 attempts to contact the participant at minimum.

- 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, 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, the participant will be considered to have withdrawn from the study.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ADMINISTRATIVE AND GENERAL/BASELINE PROCEDURES

- 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.
- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) 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 timeframe defined in the SoA (Section 1.3).
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements (see Appendix 9 [Section 10.9]).
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded, unless these are considered critical.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

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.
- Safety and laboratory assessments.
- Sputum collection (optional: only in participants able and willing to produce non-induced sputum. Sputum can be collected during the visit, or in the morning prior to the visit; date of collection and processing need to be obtained). In case the patient is unable to produce sputum, a morning sputum sample can be brought to the clinic within 1 week after the planned collection date for post randomization visits.

- 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:

- 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.

8.1.1 Smoking history and status

The smoking history and status for each subject will be obtained at Visit 1 (Screening), Visit 2 (Randomization/Baseline), Visit 7, Visit 9, Visit 11, Visit 13, Visit 16 (EOT/ETD), and Visit 17 (EOS).

Subject smoking history will be evaluated and grouped into three categories based on their response to the following; Current Smoker, Former Smoker, and Never Smoker (51).

Subjects who report smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, smoke either every day or occasionally are defined as a Current Smoker. Subjects who reported smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, do not smoke at all are defined as a Former Smoker. Subjects who report never having smoked 100 cigarettes are defined as Never Smoker. Subjects who are determined to be Current Smokers at Visit 1 (Screening) are not eligible for participation in the study and will be added into the eCRF as a screen failure.

For subjects who are Former Smoker or Current Smoker, their smoking history will be assessed using the number of pack-year criteria.

The pack-year is calculated by multiplying the number of packs of cigarettes smoked per day (1 pack =20 cigarettes) by the number of years the person has smoked. For example, 1 pack year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year. Subject smoking history will be documented into the study source document and the eCRF.

Current smokers are not eligible for the ACT18018 study. Former smokers are only eligible in whom smoking cessation has occurred ≥6 months prior to Screening (Section 5.2; E 02).

8.2 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA.

8.2.1 Disease-specific efficacy measures

Severity of PE of NCFB as defined by the protocol

All exacerbations (defined as an acute worsening of respiratory symptoms) leading to a prescription in antibiotics (new, addition or change in) and/or systemic corticosteroids will be recorded by the Investigator. An adjudication committee will determine if following criteria are met: moderate exacerbation is defined as: A) having 3 or more of the following symptoms for at least 48 hours: 1. Increased cough, 2. Increased sputum volume or change in sputum consistency, 3. Increased sputum purulence, 4. Increased breathlessness and/or decreased exercise tolerance, 5. Fatigue and/or malaise, 6. Haemoptysis, AND B) A physician's decision to prescribe antibiotics (or addition of antibiotic or change in antibiotic). Subjects on chronic maintenance antibiotic therapy whose only change in therapy is dose or frequency adjustment in response to worsening of respiratory symptoms will not meet the definition of exacerbation. Severe exacerbation is defined as PEs as described above which results in intravenous antibiotics treatment, or hospitalization or observation for >24 hours in emergency department/urgent care facility, or 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 antibiotics and/or systemic corticosteroids, 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 PE of NCFB

In addition to the protocol-defined PE of NCFB listed above, clinical signs and symptoms of PE of NCFB will be captured in the exacerbation eCRF (including, but not limited to, increase in breathlessness and/or decreased exercise tolerance, increase in fatigue and/or malaise, increase in wheezing, increase in cough, increase in sputum volume and/or increase in sputum purulence).

Management of PE of NCFB

Pulmonary exacerbation (PE) of NCFB should be treated as deemed necessary by the Investigator taking into account, if possible, the list of non-permitted concomitant medications (see Section 6.9). After successful management of a PE of NCFB (eg, with antibiotics and nebulization with SABA/SAMA medication and oxygen), all efforts should be made to resume the initial NCFB treatment regimen if this is medically acceptable in the Investigator's opinion. After 1 severe or 2 moderate PEs of NCFB, adjustments in ICS/LABA/LAMA therapy will be permitted for symptom control and as needed for the remainder of the trial period. The treatment of the PE of NCFB 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). It is not required to postpone IMP administration in case of a PE, but IMP can temporarily be postponed if deemed necessary by the Investigator.

Protocol defined moderate and severe PE events are collected as efficacy endpoints via the exacerbation page in the eCRF. The reporting of mild, moderate and severe events as AEs are left to the discretion of the Investigator. Guidance on reporting requirements and timelines is provided in Section 8.4.

8.2.2 Spirometry

Spirometry at clinical site visits should be performed in accordance with the European Respiratory Society (ERS)/American Thoracic Society (ATS) 2005 guidelines and prior to administration of investigational product (52).

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 European Respiratory Society/American Thoracic Society (ERS/ATS) 2019 guidance (53). 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:

- Smoking and/or vaping and/or water pipe use within 1 hour before testing (to avoid acute bronchoconstriction due to smoke inhalation) Note: smoking is exclusion criterion (Section 5.2) 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 technically acceptable flow-volume curves meeting ATS/ERS acceptability criteria with at least 2 meeting the ATS/ERS repeatability criteria for FEV1 should be obtained at every visit, if possible.

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

8.2.3 Participant-reported outcome questionnaires

All PRO questionnaires will be provided to the study subjects in an electronic format after Randomization. Subjects will complete the questionnaires at the dedicated visits as shown in the SoA (Section 1.3). The subjects will complete the questionnaire while they are in the clinic. The completed questionnaires will be reviewed. Subjects will be retrained on how to complete the questionnaires correctly, if needed.

8.2.3.1 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 (54, 55). 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 quality of life (see Appendix 14 [Section 10.14]).

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 two 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 psychosocial 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 was 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.

8.2.3.2 Quality-Of-Life-Bronchiectasis (QOL-B)

The QOL-B is a validated, self-administered patient reported outcome (PRO) that assesses symptoms, functioning and health-related QOL for subjects with NCFB (56, 57). The QOL-B contains 37 items in 8 domains (Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions and Treatment Burden) (see Appendix 15 [Section 10.15]).

8.2.3.3 Leicester Cough Questionnaire

The Leicester Cough Questionnaire is a validated PRO questionnaire evaluating cough on quality of life in subjects with NCFBE (58) (See Appendix 16 [Section 10.16]).

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

8.2.3.4 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 NCFB 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 = "Much better", 2 = "A little better", 3 = "No change", 4 = "A little worse", 5 = "Much worse", 6 = "Very much worse".

The PGIS is a 1-item questionnaire that asks participants to provide the overall self-assessment of their NCFB symptom severity on a 4-point scale for the past week. Response choices are 1 = "None", 2 = "Mild", 3 = "Moderate", 4 = "Severe" (see Appendix 17 [Section 10.17]).

8.2.3.5 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, selfcare, 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 18 [Section 10.18]).

8.2.3.6 22-Item Sino-nasal Outcome Test (SNOT-22)

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on HRQoL (Appendix 19 [Section 10.19]). The SNOT-22 has 22 items on a 5-category scale applicable to sino-nasal conditions and surgical treatments. The range of the global score is 0 to 110 and a minimal important difference (MID), the smallest difference between clinical trial arms mean change from baseline (point estimates) that will be interpreted as important, of 8.9 (59). Lower scores indicate less impact and the recall period is the past 2 weeks. There are 5 domains that can be described within SNOT-22, including nasal, ear, sleep, general and practical, and emotional.

8.2.3.7 Bronchiectasis Severity Index

Bronchiectasis severity index is a scoring system based on a combination of clinical, radiological and microbiological features that can be used to assess subjects' NCFBE severity. The BSI can be predictive of mortality and hospital admissions and be predictive of exacerbations and QOL giving a broad assessment of disease severity (31).

The BSI score will be calculated during the screening period in order to estimate disease severity. The BSI score calculation is described in Appendix 20 (Section 10.20) and will be entered into the eCRF directly.

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.4

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

8.3.1 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. Weight will also be measured and recorded at Week 24 and EOT visits.
- A brief physical examination will include, at a minimum, assessments of the respiratory and cardiovascular system while additional systems may be examined as per clinical judgement of Investigator.
- Investigators should pay special attention to clinical signs related to previous serious illnesses and intercurrent infections.

8.3.2 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 blood pressure (mmHg) will be recorded.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- 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).
- For blood pressure measurements, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute. The average of the 3 blood pressure readings will be recorded.

8.3.3 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 finding that meet the definition of an AE (Section 8.4) 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 preexisting condition at Screening (Visit 1) that does not affect the conduct of the study per the Investigator's judgment will need to be well documented in the source documentation.

8.3.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents. See Appendix 3 (Section 10.3) for abnormal laboratory results reporting. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 20-week after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant 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 tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests 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 Negative or Indeterminate: Eligible
HCV antibody: positive	Test for HCV RNA If HCV RNA Positive: Excluded If HCV RNA Indeterminate: Eligible

Abbreviations: DNA = deoxyribonucleic acid; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBsAb = hepatitis B surface antibody; HCV = hepatitis C virus; Ig = immunoglobulin. See Section 10.8.4 for country-specific requirements for Czechia.

8.3.5 Pregnancy testing

Pregnancy testing will be performed in all WOCBP 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) (see SoA, Section 1.3). Participant will be instructed to not administer next IMP in case of suspected/confirmed pregnancy and contact the site.

8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.4.7.

The definitions of unsolicited and solicited adverse events can be found in Appendix 3 (Section 10.3).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) 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 IMP in ACT18018 (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

8.4.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the informed consent form (ICF) until the EOS visit at the timepoints specified in the SoA (Section 1.3).

All SAEs and 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 information on AEs or SAEs 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 the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of detecting AEs and SAEs

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

8.4.3 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 pre-specified study end-date, all SAEs and AEs of special interest (as defined in Section 8.4.7), 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).

8.4.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an 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 Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious 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 an 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.

8.4.5 Pregnancy

- Details of all pregnancies in female participants will be collected during the intervention period and during the 20 weeks safety follow-up period.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner (after obtaining the necessary signed informed consent from the female partner) will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner 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 8.4.4. While the Investigator is not obligated to actively seek this information in former participant/pregnant female partner, 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.

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

Not applicable.

8.4.7 Adverse events of special interest

An adverse event of special interest (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/non-investigational medicinal product (AxMP):
  - 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.
- Significant ALT elevation:
  - ALT >3 × the ULN associated with total bilirubin >2 × ULN;

    or
  - ALT >5 × the ULN if baseline ALT ≤2 × ULN;
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- Other project specific AESI(s)
  - Anaphylactic reactions or systemic allergic reactions that require treatment (see Appendix 12 [Section 10.12]).
  - 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).

8.4.8 Guidelines for reporting product complaints

Any defect in the IMP/device 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.

8.5 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	[redacted]
Blood sample volume	
Blood handling procedures	
Serum aliquot split	
Serum shipment condition	

Abbreviations: 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	[redacted]
Analytical technique	
Site of bioanalysis	

Abbreviations: [redacted]; 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 is such a case 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.

- Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and for possible exploratory analysis of drug metabolites. The exploratory data will not be included in the study report but will be kept on file.

For China, please see Section 10.8.1 for details.

8.6 PHARMACODYNAMICS

The following biomarkers will be assessed to explore the pharmacodynamics of itepekimab:

- Blood eosinophil, neutrophil, and monocyte counts will be measured as part of the standard 5-part WBC differential cell count on a hematology auto analyzer.
- Serum proteinase 3, cathepsin G, C-reactive protein (CRP), fibrinogen, IL-6, IL-8, Tumor necrosis factor alpha (TNF-α), Interferon gamma (IFN-γ), interleukin-17A (IL-17A), IL-5, IL-13, IL-33, sST2, thymus and activation-regulated chemokine (TARC), eotaxin-3, Immunoglobulin E (IgE), E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and neutrophil elastase.
- Sputum (optional): IL-5, IL-13, IL-33, TARC, eotaxin-3, IgE, IL-6, IL-8, TNF-α, IL-17A, IFN-γ, neutrophil elastase, proteinase 3, cathepsin G, MMP-8, Matrix Metalloproteinase 9 (MMP-9), mucin-5B (MUC5B), MUC5AC, eosinophils, neutrophils, macrophages, and procalcitonin.

Analysis will be stepwise and depending upon outcome some analyses may be skipped.

8.7 GENETICS

Sputum samples for RNA analysis (at time points shown in the Schedule of Activities) will be collected from participants who have consented to participate in the optional genetic analysis component of the study in selected sites only. In addition, a separate blood sample for DNA isolation will be collected from participants who have consented to participate in the optional genetic analysis component of the study. Participation in each of these assessments is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

For participants who have consented to participate in the optional genetic analysis component of the study, sputum samples for RNA analysis will be collected in selected sites only as indicated in the SoA (see Section 1.3). In addition, for those participants who have consented to the optional genetic analysis, a separate blood sample for DNA isolation will also be collected. For DNA samples, in the event of technical problems during sample processing, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Sputum RNA and whole blood DNA samples may be used to determine a possible relationship between gene expression levels and/or genetic variation and

- Response to treatment with itepekimab (which may include aspects such as biologic effects and clinical efficacy).
- How the body processes itepekimab.
- Possible side effects of itepekimab, and/or,
- Features of bronchiectasis and related diseases.

Analysis of sputum RNA (using RNA sequencing) may be used to determine a possible relationship between gene expression and clinical response to treatment with itepekimab, identify changes in gene expression from baseline and identify potentially predictive and response-associated gene signatures.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual. Results of these exploratory analyses may be presented in reports separate from the CSR.

Genetic analyses will not be done for participants enrolled in China.

8.8 BIOMARKERS

- Blood samples will be collected to perform analysis of markers associated with bronchiectasis and/or itepekimab activity in order to determine the effect of itepekimab on the biomarkers. Biomarkers will include: proteinase 3, cathepsin G, CRP, fibrinogen, IL-6, IL-8, TNF-α, IFN- γ, IL-17A, IL-5, IL-13, IL-33, sST2, TARC, eotaxin-3, IgE, E-selectin, ICAM-1, VCAM-1, and neutrophil elastase. Samples will be collected according to the

schedule described in the SoA (see Section 1.3) and as detailed in laboratory manual provided separately to sites. Analysis will be stepwise and depending upon outcome some analyses may be skipped.

- Blood eosinophils, neutrophils, and monocytes will be assessed pre-dose and at time points described in the SoA (see Section 1.3).
- Samples for analysis of sputum markers will be collected, which may include sputum proteins IL-5, IL-13, IL-33, TARC, Eotaxin-3, IgE, IL-6, IL-8, TNF-α, IL-17A, IFN-γ, neutrophil elastase, proteinase 3, and cathepsin G, MMP-8, MMP-9, MUC5B, MUC5AC, procalcitonin) and/or cells (eg, eosinophils, neutrophils and macrophages). Selected site will be requested to participate in determining the cellular components of sputum, depending upon their ability and willingness to locally prepare and analyze the sputum samples. Analysis will be stepwise and depending upon outcome some analyses may be skipped.
- Optional samples for biomarker research that should be collected from participants who signed the optional pharmacogenetic/pharmacogenomic informed consents (1 for blood, 1 for sputum) are the following:
  - Whole sputum 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 bronchiectasis or other 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.

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.

For China, please see Section 10.8.1 for details.

8.9 IMMUNOGENICITY ASSESSMENTS

Antibodies to itepekimab will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. 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	[redacted]
Blood sample volume	
Blood handling procedures	
Serum aliquot split	
Serum shipment condition	

Abbreviations: 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	[redacted]
Analytical technique	
Site of bioanalysis	

Abbreviations: 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. More details will be provided in the SAP.

Instructions for the collection and handling of these samples will be provided by the Sponsor in a separate document. These samples will be tested by the Sponsor using a validated assay method.

Samples for immunogenicity analyses and their derivatives may be stored for up to 5 years after LPLV for potential re-analyses.

A 3-tiered approach will be employed to assess the immunogenicity of itepekimab when applicable: Samples will be screened and then confirmed for antibodies binding to itepekimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of itepekimab.

All samples collected for detection of antibodies to itepekimab may also be evaluated for itepekimab serum concentrations to enable interpretation of the antibody data.

For China, please see Section 10.8.1 for details.

8.10 HEALTHCARE RESOURCE UTILIZATION

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

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

[redacted]

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of data/sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

Data protection – Processing of coded clinical data

The study participant will be provided will all mandatory details of the data processing in Section 2 of the core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in Section 2 of the Core ICF.

Study participant data will be stored for up to 25 years for regulatory purposes and future research. Biological samples for future use will be stored for up to 25 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 case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

For China, please see Section 10.8.1 for details.

8.12 IMAGING ASSESSMENTS

A chest CT scan as outlined in the schedule of activities (see footnote *f*) is required for participation in the study and may be historical within the past 5 years or if no historical chest CT scan is available, performed as part of screening.

Participants enrolling in the trial after amendment 04 and consenting to optional collection of chest CT imaging should have chest CT images used to determine eligibility submitted to the central portal, if available. If informed consent is re-obtained from previously enrolled participants (ie, prior to amended protocol 04), chest CT scan images used for eligibility should also be submitted to the central portal, if available.

All participants consenting to the optional imaging collection should also have any additional chest CT scans performed for clinical care during the time period of the trial submitted to the central portal, if available. Both central reading and automated analysis will be performed. Results will be used to further characterize aspects including but not limited to the severity of bronchiectasis, location and type of bronchiectasis, and degree of mucus impaction. This information will not be used to overrule the PI’s determination of eligibility.

No specific imaging protocols will be used to guide the collection of these images.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and important secondary endpoints.

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined.

Table 12 - Populations for analyses

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

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

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

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

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

9.2 STATISTICAL ANALYSES

The statistical hypotheses to be tested on the primary endpoint of annualized rate of moderate or severe PE over the treatment period are as follows:

- Null hypothesis: $r_{itepekimab}/r_{placebo} = 1$
- Alternative hypothesis: $r_{itepekimab}/r_{placebo} \neq 1$

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

The statistical hypotheses to be tested on the key secondary endpoint of time to first moderate or severe PE are as follows:

- Null hypothesis: $h_{itepekimab}/h_{placebo} = 1$
- Alternative hypothesis: $h_{itepekimab}/h_{placebo} \neq 1$

Where $h_{itepekimab}$ represents hazard of PE for itepekimab 300 mg Q2W or Q4W, $h_{placebo}$ represents hazard of PE for placebo.

The statistical hypotheses to be tested on other secondary endpoints, such as annualized rate of severe PE endpoint and time to first severe PE endpoint, can be specified similarly as those for the primary or key secondary endpoint.

For change from baseline in pre- and post- bronchodilator FEV1 at Week 24, change from Baseline in Quality-of-Life Questionnaire - Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score in Adult Participants at Week 24, change from Baseline in Quality-of-life Questionnaire - Bronchiectasis (QoL-B) Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden Domain score in Adult participants at Week 24 and change from baseline in SGRQ total and symptom scores at Week 24, the null hypothesis is the change from baseline value between itepekimab 300 mg Q2W or Q4W and placebo is equal, while the alternative hypothesis is the change from baseline value is unequal.

For the percentage of participants who are PE free over the treatment period and percentage of participants who are severe PE free over the treatment period, 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.

9.2.1 General considerations

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

Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).

The observation period will be divided into 4 segments:

- The **pre-treatment** period is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration +154 days (ie, to the end of 20-week safety follow-up period). The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP +14 days.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

9.2.2 Primary endpoint(s) analyses

9.2.2.1 Definition of endpoint(s)

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

9.2.2.2 Main analytical approach

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

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

  The following ICEs may occur:

  a) Early discontinuation of study treatment.

  b) Taking prohibited medications post randomization.

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

  d) Change in background therapy during the treatment period.

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

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

a) Participants who discontinue IMP before their planned treatment duration will be asked and encouraged to return to the clinic for all remaining study visits; all PE events during the planned treatment period (between 24-52 weeks depending on participants' enrollment date) will be included in the analysis irrespective of study treatment adherence; the observation duration (used as offset variable in the analysis model) is equal to the planned treatment duration, except when a participant withdraws early from the study, in which case, the observation duration is from randomization to the last contact date of the participant within the planned treatment duration.

b) For participants taking prohibited medications, all the data observed during their planned treatment period (as defined above) will be included in the analyses.

c) If a participant takes study treatment not as randomized for any reason, the participant will be included in treatment group as initially randomized.

d) For participants with change in background therapy, all the data observed during their planned treatment period (as defined above) will be included in the analyses.

- Population level summary: The annualized rate of moderate or severe PEs will be analyzed using a negative binomial regression. The primary analysis model will include the total number of moderate or severe PE events that occur during the planned treatment period as the response variable, with treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), number of exacerbations in the prior year, and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. Log-transformed observation duration will be the offset variable.

  The estimated annualized event rate for each treatment group and its 2-sided 90% CIs will be derived from the negative binomial model. The event risk ratio (RR) of each itepekimab regimen versus placebo, and the corresponding 2-sided 90% CI and p-value will also be provided.

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

9.2.2.3 Sensitivity analysis

Sensitivity analyses to assess the robustness of the conclusion of the primary analysis will be performed using tipping point analysis and/or a pattern mixture model by multiple imputation. Details will be specified in the SAP.

9.2.2.4 Supplementary analyses

A while-on-treatment estimand will be defined and analyzed as a supportive estimand for the primary endpoint to assess the efficacy of itepekimab excluding data measured when participants do not adhere to the treatment regimen. In this analysis, only the PEs 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 PEs 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.

9.2.2.5 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, race, ethnicity, weight, screening eosinophil (<300 cells/mm^3 or ≥ 300 cells/mm^3), PA chronic colonization status (yes or no or indeterminate), documented history of COPD and/or asthma strata (yes or no), number of exacerbations in the prior year (1 or 2 or ≥ 3), maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, and other factors.

A positive PA carrier status is defined by the isolation of PA in randomization/baseline sputum culture (positive or negative). If no PA sputum culture was obtained at randomization/baseline, the outcome is indeterminate.

Details will be specified in the SAP.

9.2.3 Secondary endpoint(s) analyses

9.2.3.1 Key secondary endpoint

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

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

  The following ICEs may occur:

  a) Early discontinuation of study treatment.
  b) Taking prohibited medications post randomization.

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

d) Change in background therapy during the treatment period.

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

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

Operationally, regardless of treatment discontinuation, all participants will be followed-up according to the study procedures up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. That is, PE events and related data would be collected and reported over the entire planned treatment period for all study participants even if some participants may have discontinued the study treatment. Analytically, the time to first moderate or severe PE over the planned treatment period analysis is performed regardless of the occurrence of the ICEs and the timing of the ICE. For participants without any PE events, the time from randomization to the date of treatment completion or treatment discontinuation up to their planned treatment period (event time will be considered as censored at date of EOT or the last contact date within the planned treatment duration) will be used in the analysis.

- Population-level summary: The time to first moderate or severe PE will be analyzed using a Cox regression model. The model will include the time to the first event as the dependent variable, with treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥ 300 cells/mm^3), PA chronic colonization status (yes or no or indeterminate), documented history of COPD and/or asthma strata (yes or no), number of exacerbations in the prior year, and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates.

  The 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.

9.2.3.2 Other secondary endpoints

Table 13 - Statistical analysis methods for other secondary endpoints

Endpoint	Statistical analysis methods
Annualized rate of severe PEs over the treatment period	Event rate will be analyzed similar to the primary endpoint of "Annualized rate of adjudicated moderate or severe PEs over the treatment period".
Time to first severe PE over the treatment period	Time to event will be analyzed similar to the key secondary endpoint of "time to first moderate or severe PE over the treatment period".

Endpoint	Statistical analysis methods
Percentage of participants who are PE free over the treatment period Percentage of participants who are severe PE free over the treatment period	The percentage of participants who are PE free over the treatment period and percentage of participants who are severe PE free over the treatment period will be analyzed using a logistic regression model. The model will include treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (yes or No or Indeterminate), documented history of COPD and/or asthma (yes or no) strata, number of exacerbations in the prior year, and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline as covariates. The odds ratio of being a responder comparing each itepekimab dose arm to placebo will be provided along with the corresponding 90% CI and p-value.
Change from baseline in pre- and post-BD FEV1 at Week 8 & Week 24 Change from Baseline in Quality-of-Life Questionnaire - Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score in Adult Participants at Week 24 Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24	The change from baseline for continuous endpoints will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline values up through Week 24 as response variables. The covariates to be included are treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, visit, treatment by-visit interaction, the corresponding baseline value and baseline-by-visit interaction as covariates. Sex and height will be included as covariates only in the models for spirometry parameters. Participants who discontinue IMP before the end of planned treatment period (between 24-52 weeks depending on participants' enrollment date) will be asked and encouraged to return to the clinic for all remaining study visits and the additional off treatment values measured up through the end of planned treatment period will be included in the analysis. For participants who withdraw from the study before the end of planned treatment period, values will be missing after study discontinuation or last contact. No imputation will be performed for missing values in this analysis. An unstructured correlation matrix will be used to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline will be derived from the mixed-effect model. Descriptive statistics including number of participants, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 90% CI and the p-value will be derived from the MMRM model for comparison of each itepekimab dose arm against placebo.
Number of days of new and/or added (in participants with maintenance antibiotic use) antibiotic use	The endpoint will be analyzed using ANCOVA model. To account for the potential different treatment duration by study design, the response variable will be the % of days of new and/or added antibiotics used with the denominator as the treatment duration in days. The covariates to be included are treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline. Descriptive statistics including number of participants, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 90% CI and the p-value will be derived from the ANCOVA model for comparison of each itepekimab dose arm against placebo.
Percentage of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 24	The percentage of participants with SGRQ improvement ≥4 points at Week 24, regardless of if the participant is still on treatment or not, will be analyzed using a logistic regression model. The model will include treatment group, age, region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, and baseline SGRQ total score as covariates. Participants with SGRQ improvement <4 points or missing SGRQ total score at Week 24 will be considered as non-responders. The odds ratio of being a responder comparing each itepekimab regimen to placebo will be provided along with the corresponding 90% CI and p-value.

Endpoint	Statistical analysis methods
Pharmacokinetics (PK)	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.
Antidrug antibody (ADA)	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.

9.2.4 Tertiary/exploratory endpoint(s) analyses

Pharmacodynamic, biomarker, and tertiary efficacy endpoints including change from baseline in QoL-B domain scores (other than the respiratory domain) at Week 24, change from baseline in LCQ total score at Week 24 and rate of change in post-BD FEV1 exploratory analyses are briefly described in Table 14. 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 14 - Tertiary/exploratory endpoints

Endpoint	Statistical Analysis Methods
Pharmacodynamics and biomarkers	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±SEM) on raw data, changes from baseline and percent changes from baseline will be provided by treatment group.
Rate of change in post-BD FEV1 (L) from baseline (post-BD FEV1 slope) after 4-12 weeks	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, 90% CIs, and p-values on the slope differences between active treatment groups and placebo will be derived from a mixed-effects model with repeated post-BD FEV1 measured during the treatment period after the initial bronchodilator effect period (up to Week 52) as the outcome, age, sex, baseline height (continuous variable), region, screening eosinophil (<300 cells/mm^3 or ≥300 cells/mm^3), PA chronic colonization status (Yes or No or Indeterminate), documented history of COPD and/or asthma strata (yes or no), and maintenance antibiotic therapy strata (macrolide antibiotics or non-macrolide antibiotics or no antibiotics) at baseline, 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.

Endpoint	Statistical Analysis Methods
Change from Baseline in Quality-of-life Questionnaire - Bronchiectasis (QoL-B) Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden Domain score in Adult participants at Week 24	These endpoints will be analyzed using the same MMRM model and analysis approach for continuous endpoints (such as pre-BD FEV1, etc.) as specified in Table 13.
Change from baseline in LCQ total score at Week 24	

9.2.5 Multiplicity adjustment

No adjustments for multiplicity are planned for this Phase 2 study. Reported p-values will be nominal p-values.

9.2.6 Safety analyses

Safety analyses will be descriptive, based on the safety population. The safety analysis will focus on the TEAEs reported during the treatment-emergent period.

9.2.6.1 Adverse events

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a PT or a prespecified grouping), all treatment emergent SAEs, all TEAEs leading to death, any TEAE related to IMP reported by the Investigator and all TEAEs leading to permanent treatment discontinuation.

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

9.2.6.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

When relevant, for laboratory variables, vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided for each planned visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables and ECG variables.

Analyses according to PCSA

PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

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

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

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

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

- Normal/missing.
- Abnormal.

Table 15 - Summary of safety analysis

Assessments	Statistical Analysis Methods
TEAEs, AESIs, SAEs, TEAEs leading to death, and TEAEs leading to permanent treatment discontinuation	Adverse event incidence tables will present by system organ class (SOC) (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. Percentage 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 SOC 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 SOC, HLGT, HLT, and PT showing number (%) of participants sorted by internationally. • Agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

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

9.2.7 Other analyses

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

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.

9.3 INTERIM ANALYSES

No interim analysis is planned.

9.4 SAMPLE SIZE DETERMINATION

To assess the power of the primary efficacy endpoint the annualized rate of moderate-to-severe PEs, we assume:

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

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

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

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

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.
  - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable.
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws.
  - Any other applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - 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 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

- Determining whether an incidental finding (as per Sanofi policy) 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 concerned 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.

As applicable, according to requirements of the Regulation No536/2014 of the European Parliament and the Council of the European Union, 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.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48h after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

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 ICF will be provided to the study participant in paper version. When feasible, an eConsent process may be used at global level and/or locally if permitted by country regulations.

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants and answer all questions regarding the study, including what happens to the participants when their participation ends (post-trial access strategy for the study).
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the General Data Protection Regulation (GDPR) and of the French law, 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 case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) must be provided to the participant.

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 future 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 checkboxes in CSICF Part 3, each checkbox corresponding to a specific use: consent for the performance of an optional exploratory research; consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research; consent for collection of additional biological samples for storage and use for future research, and consent for performance of genetic analyses on biological samples. The Investigator or authorized designee

will explain to each participant the objectives of the exploratory research and why data and samples are important for future 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.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). 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 trial participants, Investigators, nurses, experts, service providers, 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 personal 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 they are expected to modify the drug response/because they 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). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- Participants must be informed that their 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.

- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal 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 pre-contractual 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).
- 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

10.1.5.1 Data Monitoring Committee

Participant safety will be continuously monitored by the data monitoring committee (DMC) committee, which includes safety signal detection at any time during the study.

In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to itepekimab administration. An initial safety review for this study is planned for the first 10% of participants who are dosed.

All safety data collected will be summarized and reviewed by the DMC for agreement of next steps. The DMC will be unblinding during the above reviews.

DMC members' responsibilities and the process for data monitoring are described in the Data Monitoring Committee Charter.

10.1.5.2 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 PEs. Adjudicators will adjudicate all reported and suspected exacerbation events leading to prescription of antibiotics (new, addition or change) in a consistent and unbiased manner throughout the study and check if they meet the protocol definition of a moderate or severe exacerbation (see Section 8.2.1).

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.

10.1.6 Dissemination of clinical study data and results

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

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, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

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 anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. 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 undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Drug Clinical Trial Registration and Information Disclosure Management Practice (Trial Implementation)", requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

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 "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations".

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.
- Guidance on completion of CRFs will be provided in CRF Completion Instructions.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (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).
- 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 different 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 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.

- Definition of what constitutes source data can be found in monitoring guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF 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.

10.1.9 Study and site start and closure

First act of recruitment

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site termination

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:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
  - If circumstances beyond the control of the Sponsor make it unreasonable to require the study's continuation.
- 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 participant and should assure appropriate participant 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 16 will be performed by the central laboratory (inclusive of central laboratory in China), with the exception of sputum culture testing which may be performed in a local laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. 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 recorded.
- 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.
- 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 16 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	Platelet count
	Red blood cell (RBC) count
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
	Hemoglobin
	Hematocrit

Laboratory tests	Parameters
Clinical chemistry[a]	Blood urea nitrogen (BUN)
	Potassium
	Creatinine
	C-reactive protein (CRP)
	Glucose (fasting if feasible)
	Sodium
	Bicarbonate
	Creatinine phosphokinase
	Albumin
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)[a]
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)[a]
	Alkaline phosphatase
	Lactate dehydrogenase
	Total and direct bilirubin
	Total protein
	Total Cholesterol
Biomarkers	Blood biomarkers: proteinase 3, cathepsin G, CRP, fibrinogen, interleukin-6 (IL-6), interleukin (IL-8), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin -17A (IL-17A), interleukin-5 (IL-5), interleukin-13 (IL-13), interleukin-33 (IL-33), soluble suppressor of tumorgenicity 2 (sST2), thymus and activation-regulated chemokine (TARC), eotaxin-3, immunoglobulin e (IgE), E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1(VCAM-1), neutrophil elastase, eosinophils, neutrophils, and monocytes.
	Sputum biomarkers (only in participants willing and able to cough up fresh sputum): IL-5, IL-13, IL-33, TARC, eotaxin-3, IgE, interleukin-6 (IL-6), interleukin-8 (IL-8), TNF-α, IL-17A, IFN-γ, neutrophil elastase, proteinase 3, cathepsin G, matrix metalloproteinase-8 (MMP-8), matrix metalloproteinase-9 (MMP-9), mucin-5B (MUC5B), mucin-5AC (MUC5AC), eosinophils, neutrophils, macrophages, and procalcitonin
Routine urinalysis	Specific gravity
	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by local dipstick
Pregnancy testing	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Other screening tests	For women of childbearing potential: Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test at Screening (Visit 1) and urine pregnancy tests during the 24-52-week Treatment and the 20-week safety Follow-Up Periods as the plan in SoA[b]. A negative result must be obtained at Visit 1 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 should be performed as soon as possible to confirm the pregnancy. Pregnancy urine test at home administration/phone visits at Week 12, 20, 28, 36, and 44 will be performed by the participant herself at home. 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 1): 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 1): Human immunodeficiency virus (HIV) screen (anti-HIV-1 and HIV-2 antibodies)

Laboratory tests	Parameters
	Tuberculosis testing according to local guidelines (local laboratory) or if not available, in central laboratory (Quantiferon test) at Screening (Visit 1)
	Sputum microbiology culture will be performed with the sputum sample obtained at Randomization/Baseline (sputum samples are optional)
	Routine urine cotinine test (local dipstick)
	Urine anabasine test

NOTES:
a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 and Appendix 6 (Section 10.6)
b 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.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE definition

- An AE is any untoward medical occurrence in a 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.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The [participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined events for which the participant is specifically questioned.

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, or more severe than expected for the participant's condition), 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.
- New condition 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.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse and abuse with the IMP.
- 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 an AE or SAE if they fulfill the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any abnormal laboratory findings or other abnormal safety assessments that 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.
- 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.

10.3.1 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

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 admitted (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 or significant 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) that 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 by the Investigator 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.

- The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm.
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc).
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
    - Development of drug dependence or drug abuse.
    - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN.
    - Suicide attempt or any event suggestive of suicidality.
    - Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
    - Bullous cutaneous eruptions.

10.3.2 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.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's 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's 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 one of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- 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.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. 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's 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's representative**.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an 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's 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 health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology, if available.
- New or updated information will be recorded in the originally submitted documents.

- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.3 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's 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) 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's representative by telephone.
- Contacts for SAE reporting can be found in contact list in the Investigator Study File.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- 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 data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in contact list in the Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 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. Premenopausal 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. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

4. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal 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 one 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 postmenopausal status before study enrollment.

10.4.2 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).

10.5 APPENDIX 5: GENETICS

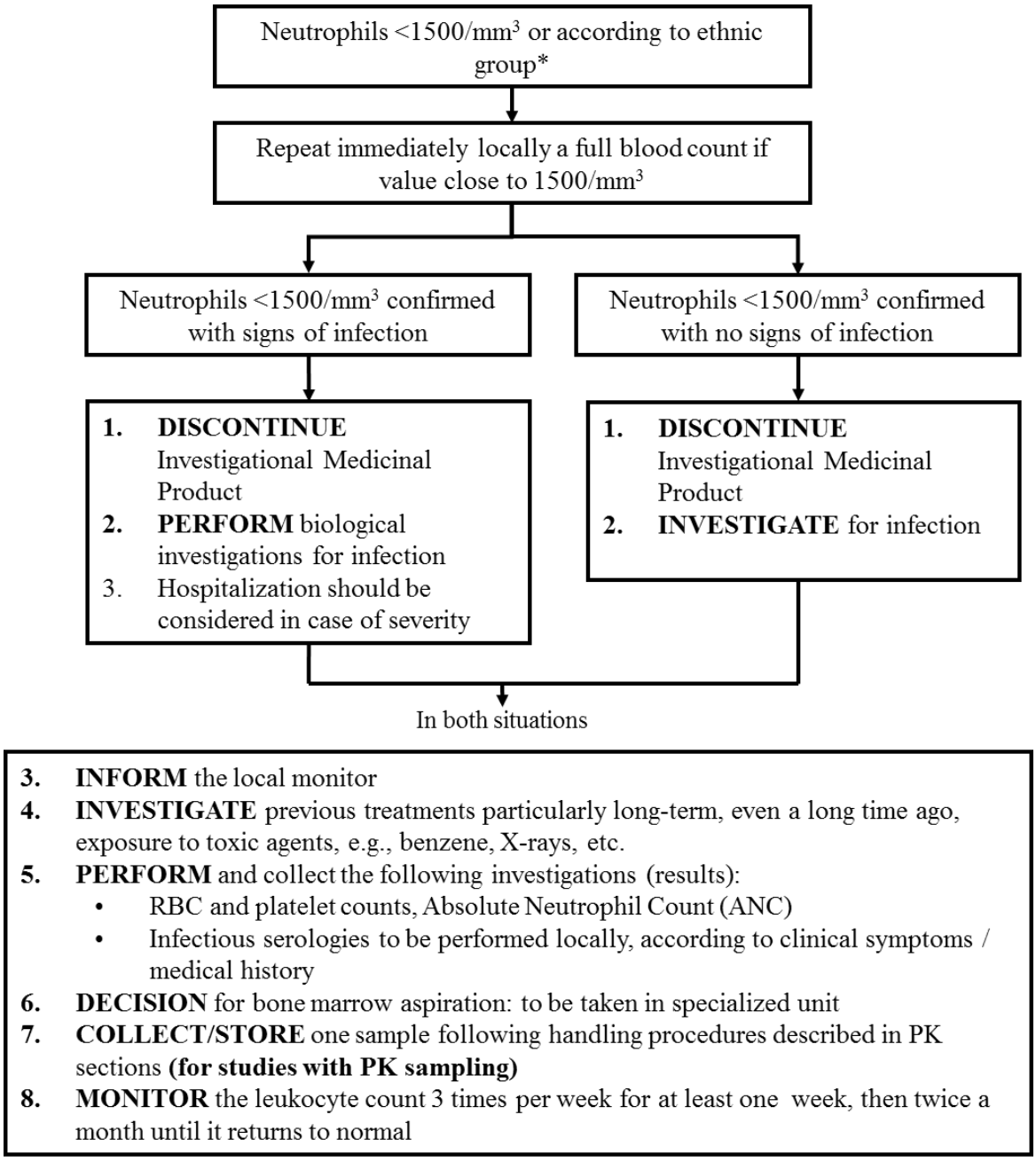
Use/Analysis of DNA

- 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, a blood sample will be collected for DNA analysis from consenting participants.
- RNA and DNA samples will be used for research related to itepekimab or bronchiectasis and related diseases. They may also be used to develop tests/assays including diagnostic tests related to itepekimab and/or interventions of this drug class and bronchiectasis. Genetic research may consist of DNA analysis of one or more candidate genes, the analysis of genetic markers throughout the genome, and RNA sequencing to determine expression levels of gene/s of interest.
- RNA and DNA samples will be used for research related to itepekimab or bronchiectasis and related diseases. They may be used to determine a possible relationship between gene expression levels (RNA) or gene variants (DNA) and response to treatment with itepekimab, how the body processes itepekimab and possible side effects of itepekimab. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

- The DNA and RNA samples may be analyzed as part of a multi-study assessment of genetic or transcriptomic factors involved in the response to itepekimab or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the RNA and DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on itepekimab and/or study interventions of this class or bronchiectasis continues but no longer than 25 years or other period as per local requirements.

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

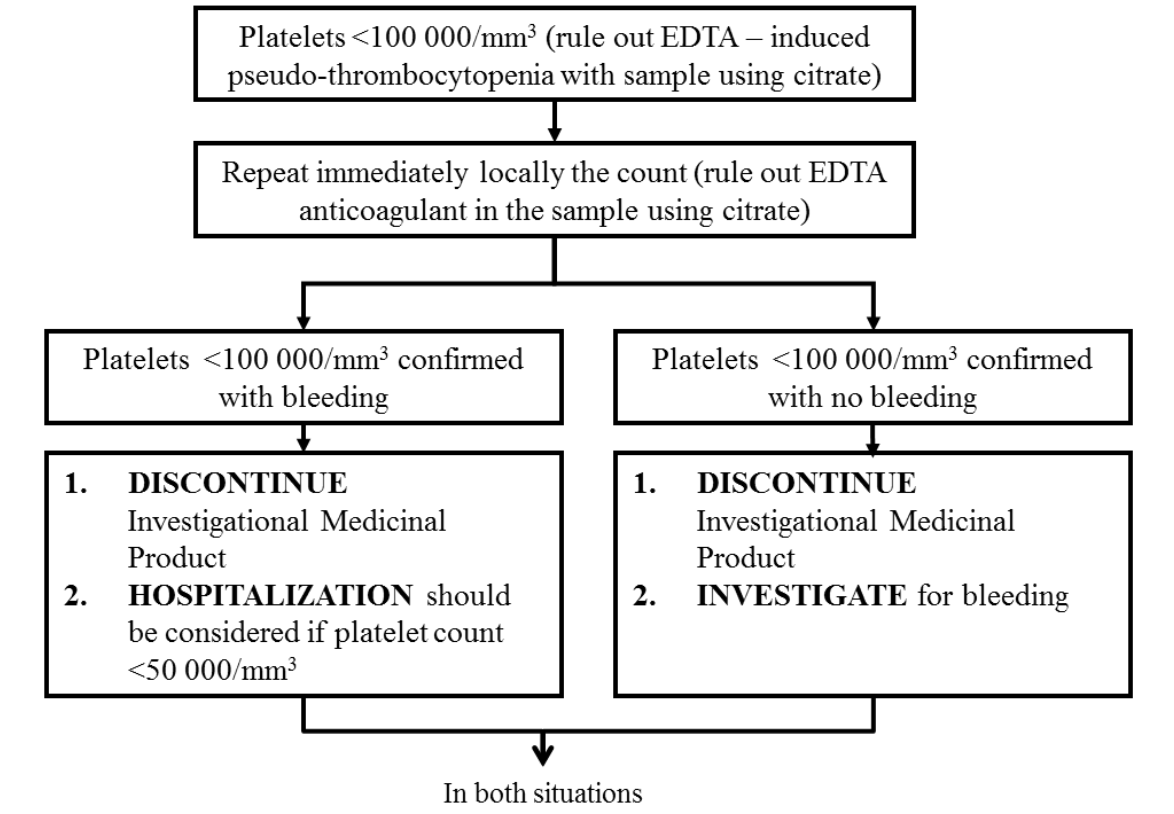
NEUTROPENIA



* For individuals of African descent, the relevant value of concern is <1000/mm3

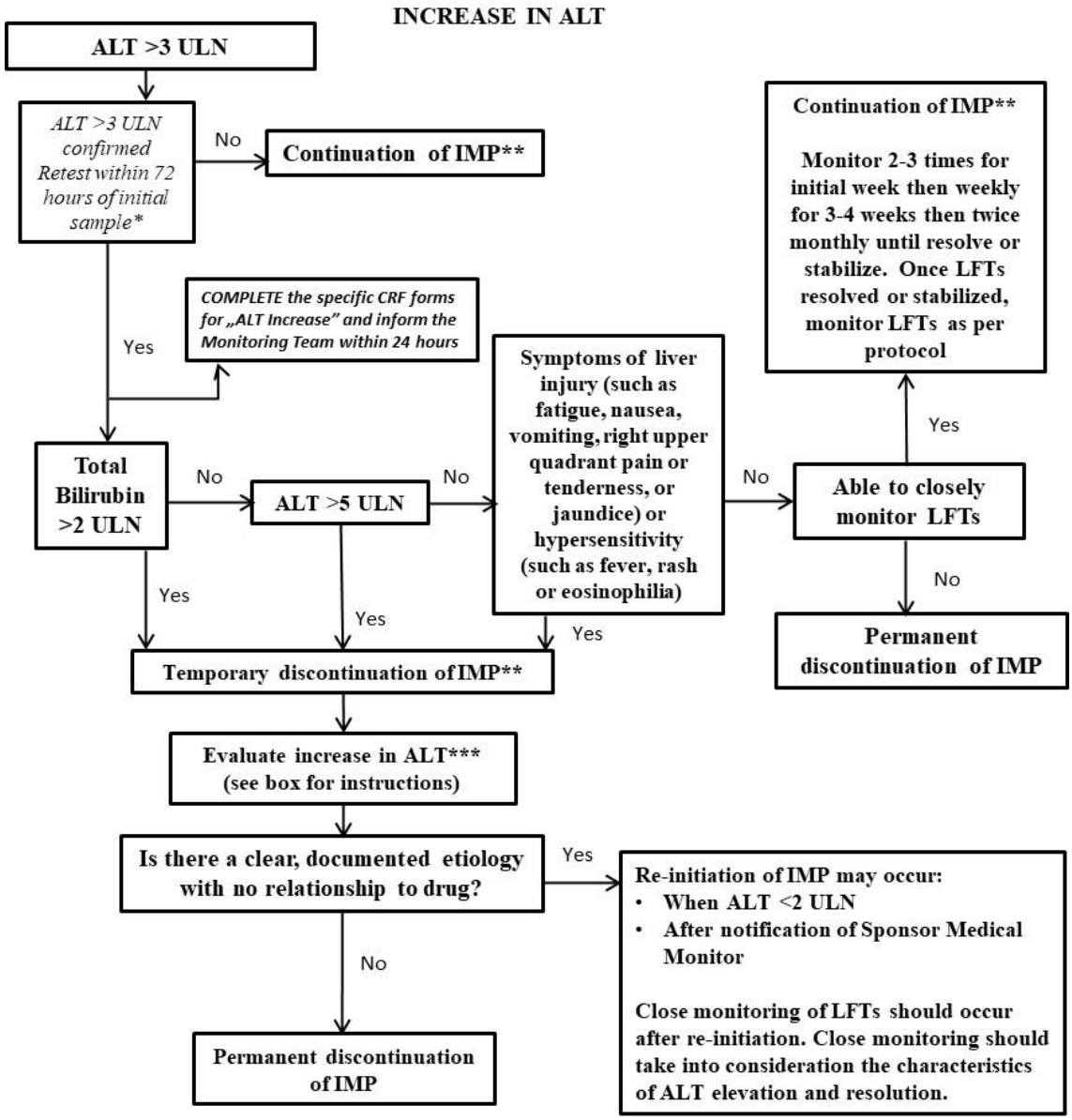
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

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 adverse events in Appendix 3 (Section 10.3) is met.



*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
** Unless a protocol-defined criterion for permanent discontinuation is met
*** See box below
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 Section 10.3 for guidance on safety reporting.

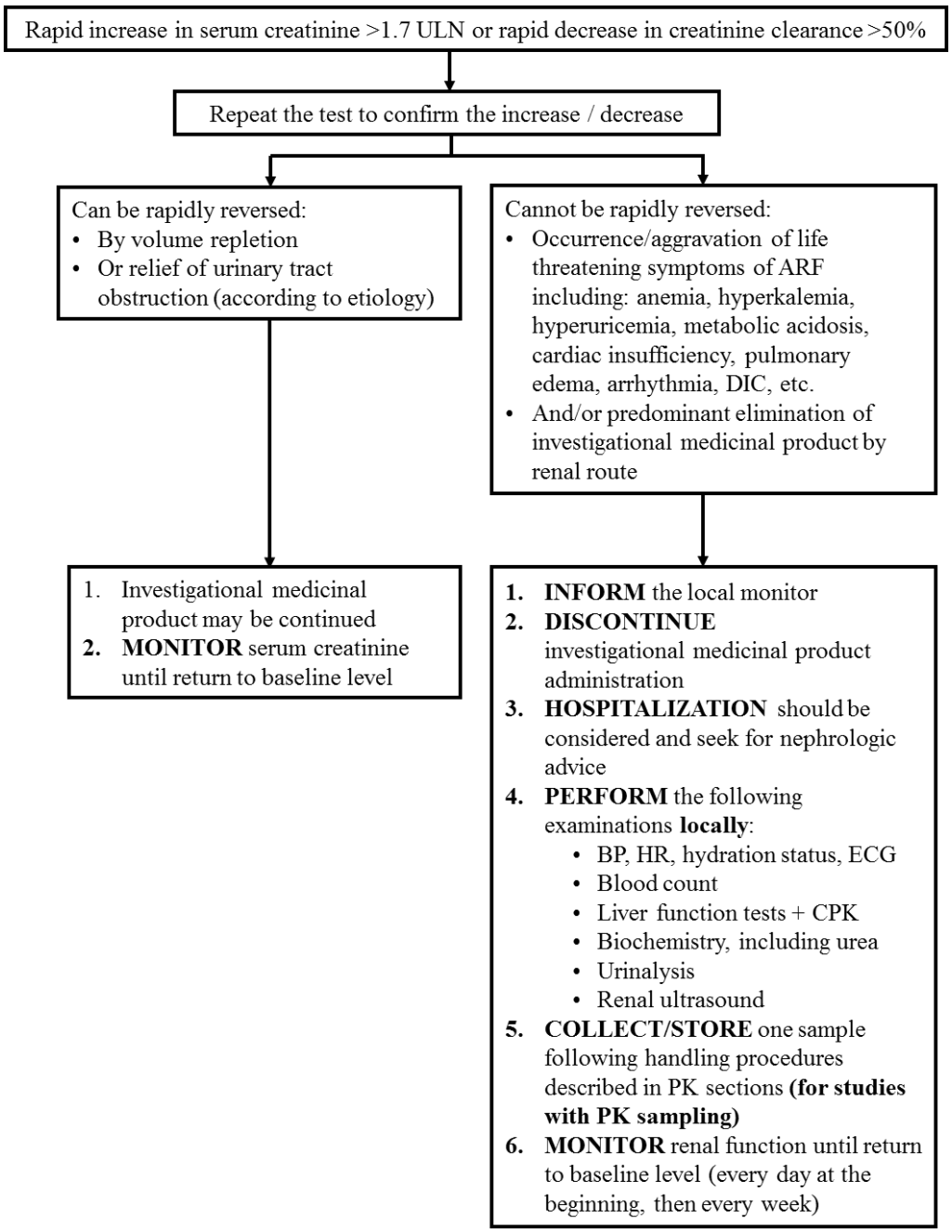
Evaluate Increase in ALT***

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any recent alcohol use or travel
4. **INVESTIGATE** if any use of non-prescription medications including herbal or dietary supplements
5. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, GGT, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** iron, ferritin and transferrin
6. **CONSIDER** biomarkers for alcohol use (eg, urine ethyl glucuronide (EtG)]
7. **CONSIDER** consulting with hepatologist
8. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
9. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to ≤ULN, baseline value (if baseline >ULN) or clinical resolution.
10. **FREEZE** serum sample (5ml x 2)
11. **In case of suspicion of GILBERT Syndrome**, a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
** Unless a protocol-defined criterion for permanent discontinuation is met.
*** See box below
Note:

a) "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.
b) See Section 10.3 for guidance on safety reporting.

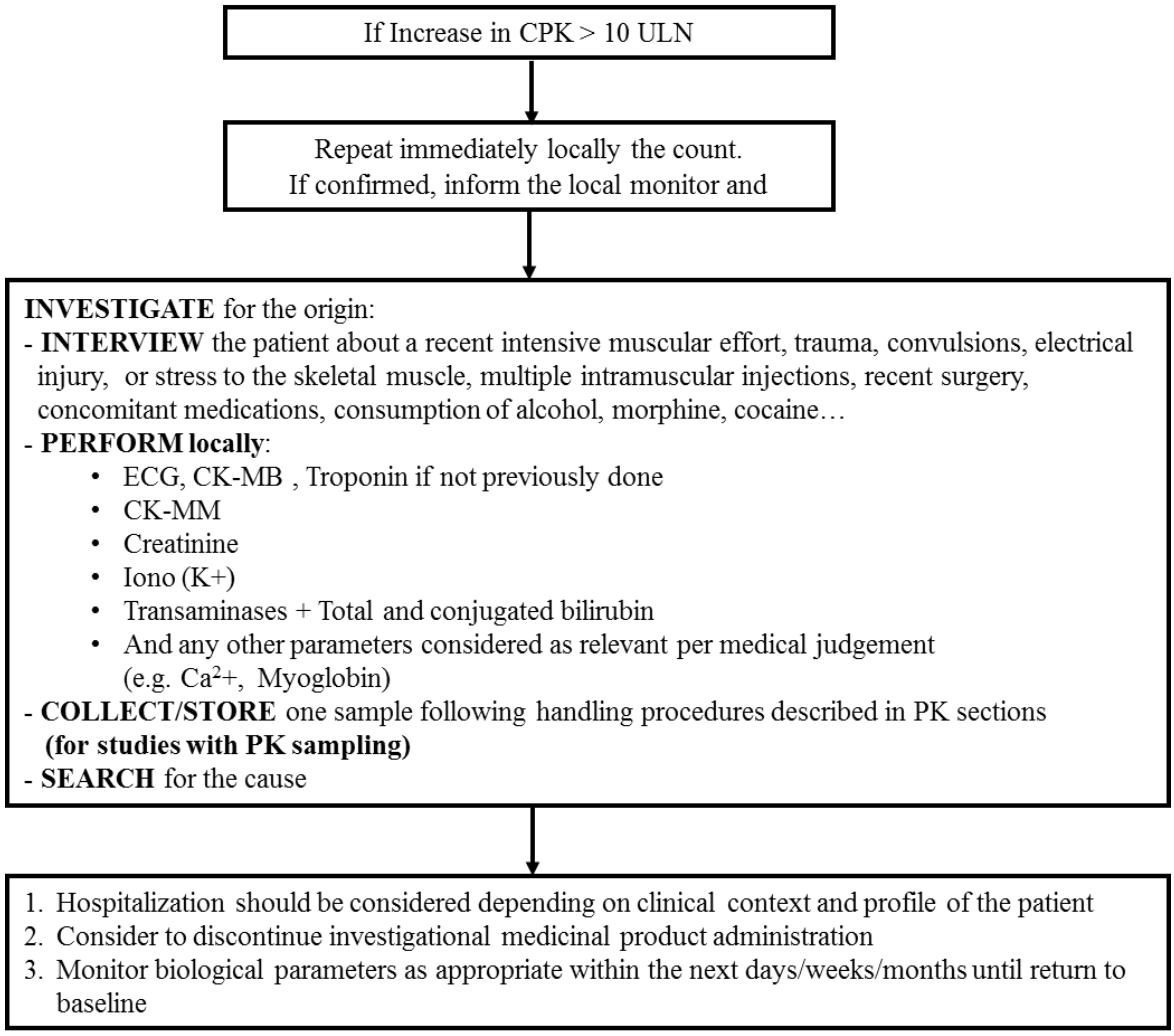
INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



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 adverse events 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 adverse events in Section 10.3 is met.

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.8.1 China

In China, a local central laboratory will be used.

Genetic analyses will not be done for participants enrolled in China. All biomarkers (except for blood neutrophil and eosinophil count), systemic drug concentrations, and ADA response can be considered optional in China.

Pregnancy testing will be performed at screening with a blood test using a local China based central laboratory, and at subsequent visits using a locally-provided urine test.

Future use of biological samples as described in Section 8.11 and genetics samples as described in Section 8.7 are not applicable participants in China. All residual mandatory samples collected from participants in China have to be destroyed upon clinical study report (CSR) completion at the latest.

Routine urinalysis will be performed in a central laboratory for participants in China.

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Drug Clinical Trial Registration and Information Disclosure Management Practice (Trial Implementation)", requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

10.8.2 Germany

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 10.9 (APPENDIX 9: Contingency measures), Section 7.1.1 (Permanent discontinuation), Section 10.1.3 (Informed consent process) and Section 8.4 (Adverse events reporting).

For Germany contingency measures are currently only applicable for the COVID-19 pandemic.

10.8.3 France

Additional exclusion criterion specific to France only:

1. The participant is not affiliated to a social security scheme.
2. The participant is under tutorship or curatorship; the participant is under safeguard of justice or deprived of his/her liberty by an administrative or court decision.

10.8.4 Czechia

In addition to E 22, the following is required for Czechia (see underlined text): Participants from Czechia with a positive TB skin test or a positive Quantiferon assay are excluded from the study unless all of the following conditions are met:

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

AND

- Have obtained consultation with a specialist to rule out active and latent TBI,

AND

- For whom review and approval from Sponsor has been granted.

In addition to E 24, the following is required for participants randomized in Czechia:

1. If a participant has anti-HBc Ab positivity at screening but is confirmed to have no detectable HBV DNA by PCR testing at screening, the participant must be willing to have repeat HBV DNA PCR testing performed at least every 3 months until the end of trial.
2. If a participant has anti-HBs Ab positivity at screening but is confirmed to have no detectable HBV DNA by PCR testing at screening, the participant must be willing to repeat HBV DNA PCR testing performed at least every 3 months until the end of trial, unless the participant has completed HBV vaccination previously as proven by medical records.
3. If a participant has total anti-HCV Ab positivity at screening but is confirmed to have no detectable HCV RNA by PCR testing, the participant will repeat HCV RNA PCR testing every at least every 3 months until the end of trial.

10.8.5 European Union

10.8.5.1 Safety reporting to the agency

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.

A single Annual Safety Report, aligned with ICH E2F, will include safety information for all IMPs (including the reference compound[s]). Fatal and life-threatening SUSARs must be reported within 7 calendar days, other SUSARs are to be reported within 15 calendar days.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

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

- A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.
- Contingency procedures are suggested in this appendix and in Section 8, for an emergency 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 emergency.
- During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be postponed, and screening/enrollment, 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 emergency (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 emergency, 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 emergency declared by a governmental agency for the duration of the emergency (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 for visits other than Screening visit (Visit 1 [Week -3 to -5]) and enrollment visit (Visit 2 [Week 0]), remote visits (eg, with home nurses, home health vendor) may be planned for the collection of possible safety and/or pharmacodynamic 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.
- If on-site visits are not possible, visit windows may be extended for assessment of safety and/or pharmacodynamic data that cannot be obtained remotely (eg, spirometry visit window ±2 weeks for the IMP Treatment Period, and ±2 weeks for the visits during the post IMP treatment Follow-up Period).
- Use of local clinic or laboratory locations may be allowed for hematology and clinical chemistry samples.

Contingencies implemented due to a regional or national emergency 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.

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (Article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

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: DEFINITION OF ANAPHYLAXIS

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (60). Clinical criteria for diagnosing anaphylaxis:

Table 17 - 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.

Abbreviations: 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.

10.13 APPENDIX 13: 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. Some conditions (eg, varicella) have multiple vaccine types available; only live vaccines are prohibited in this study.

10.14 APPENDIX 14: ST. GEORGES'S RESPIRATORY QUESTIONNAIRE

[redacted]

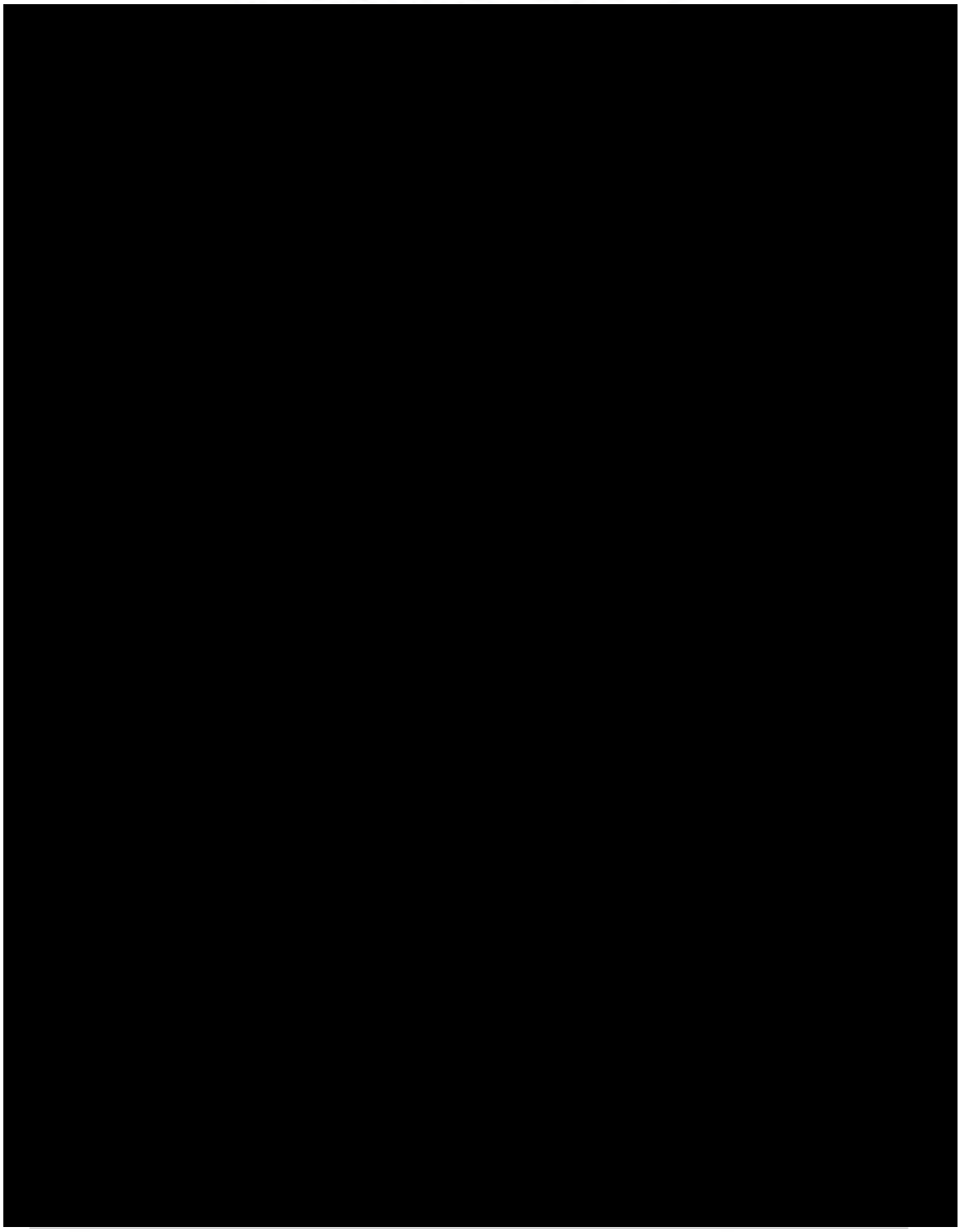
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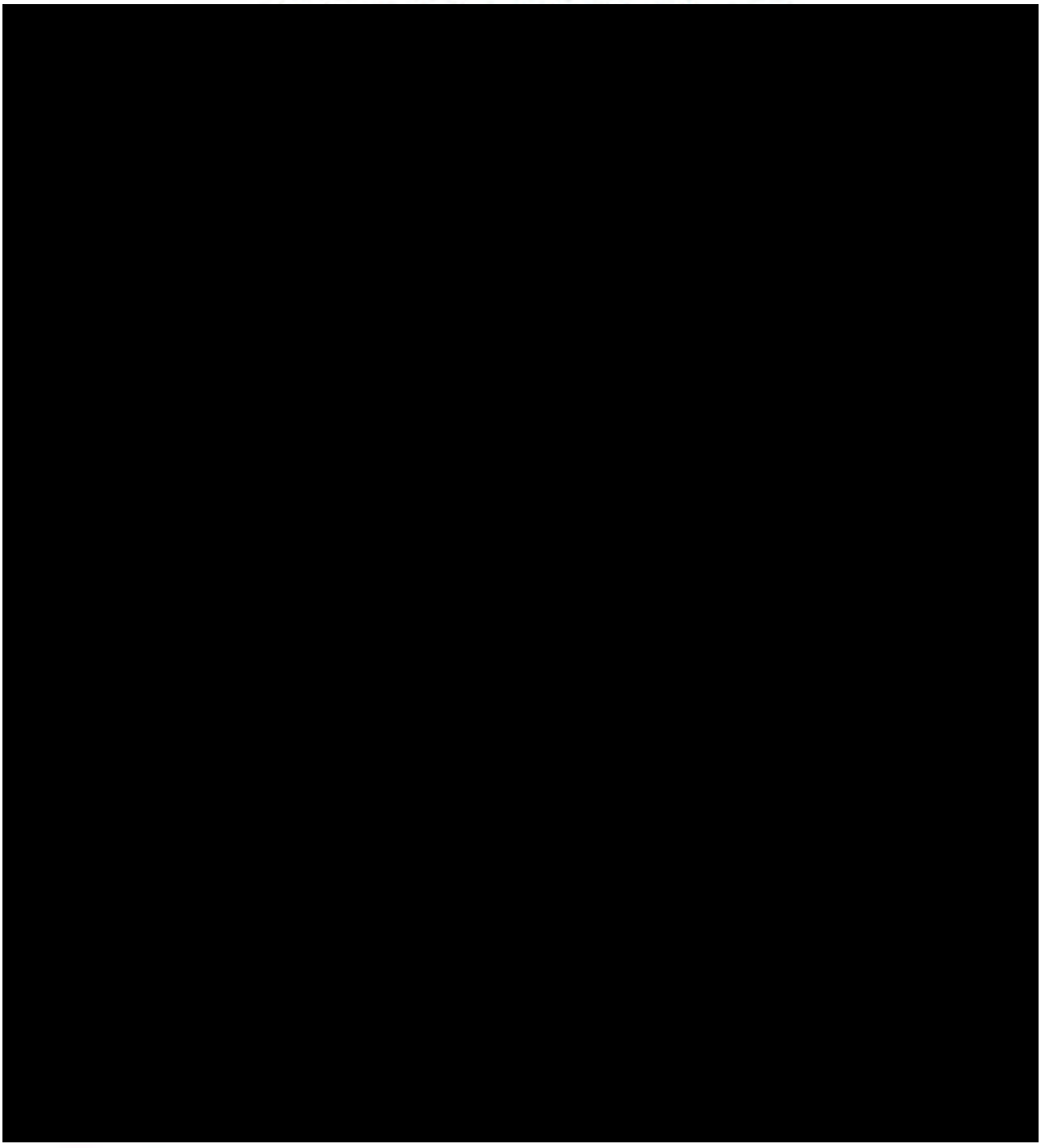
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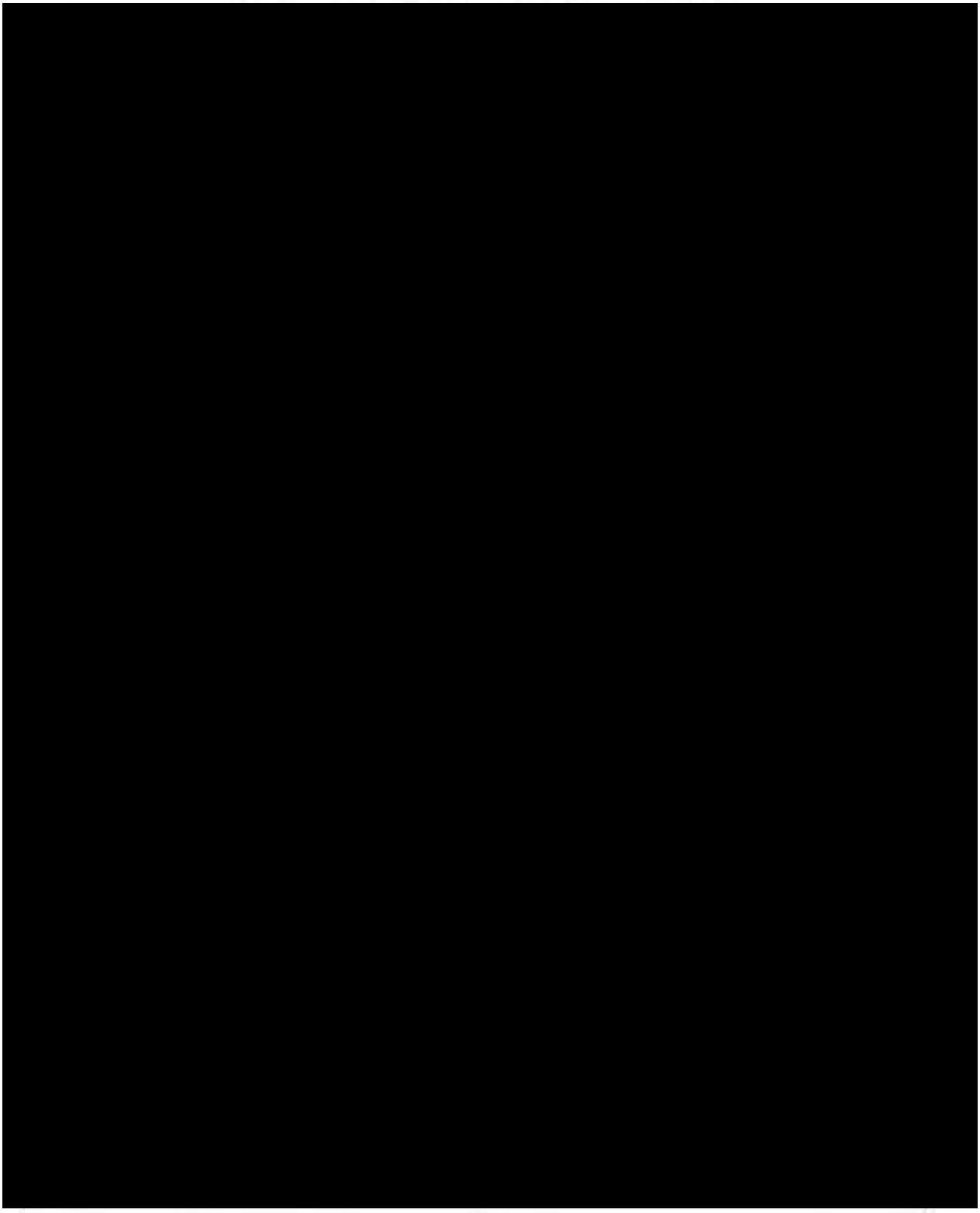
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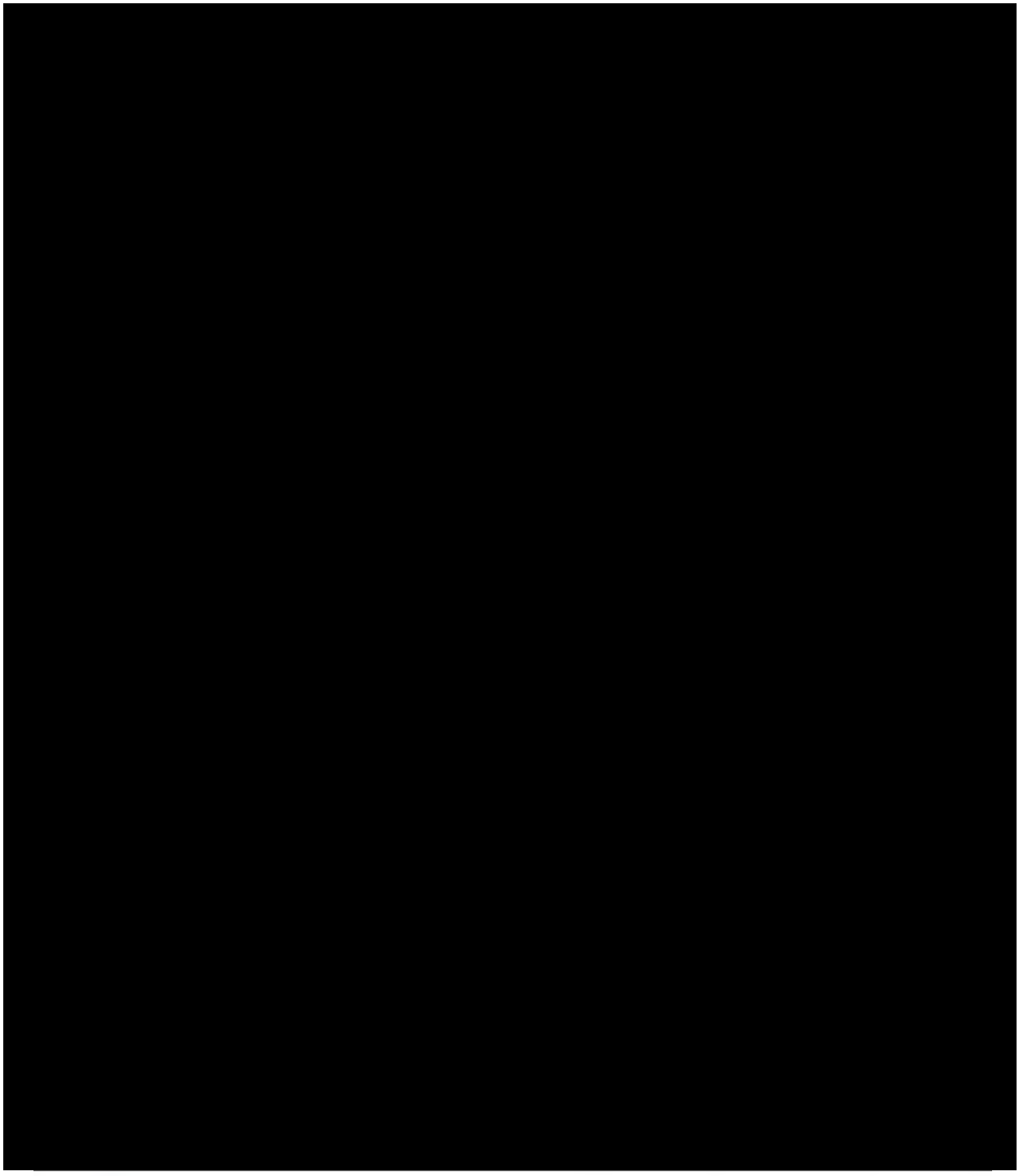


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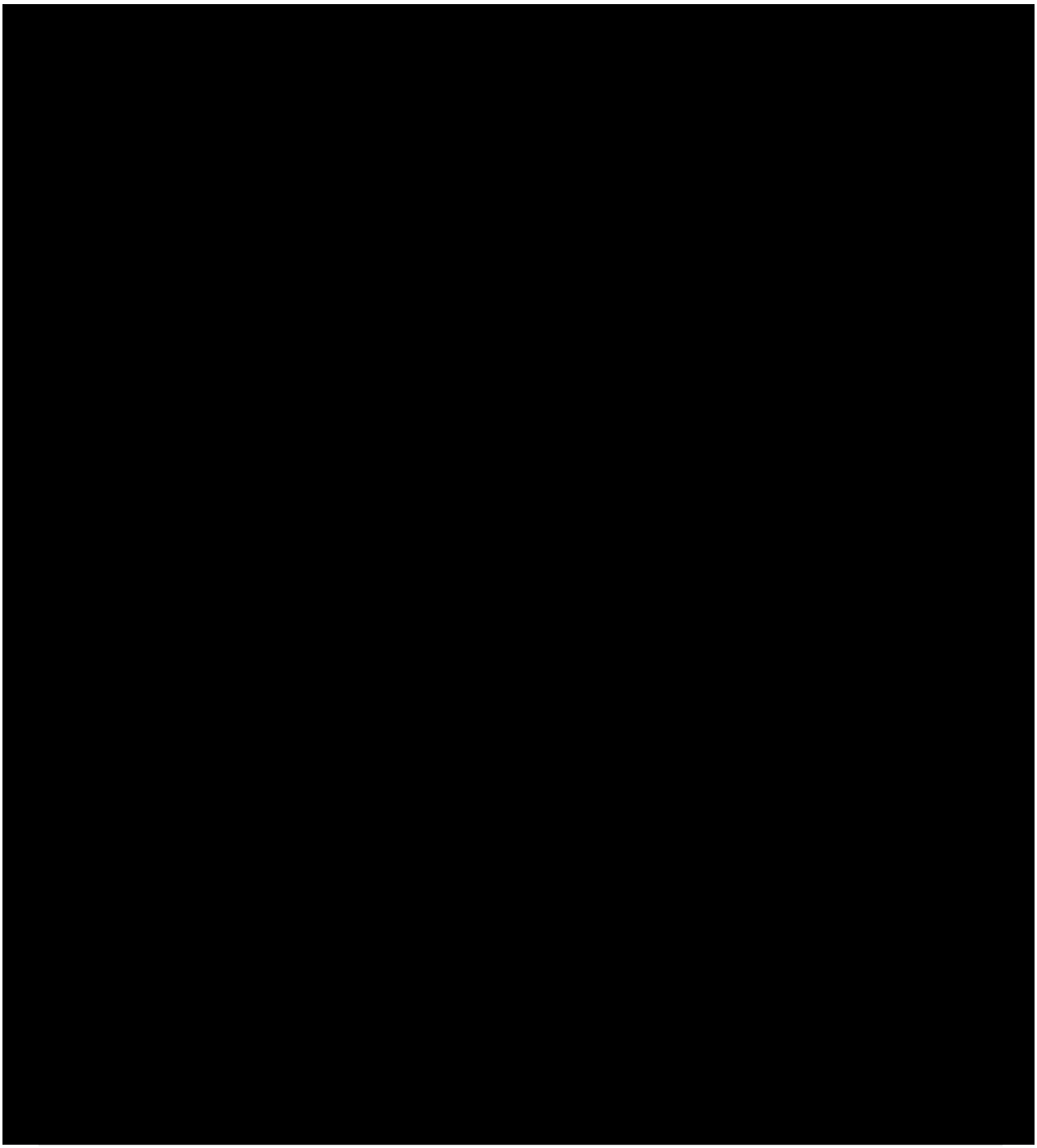




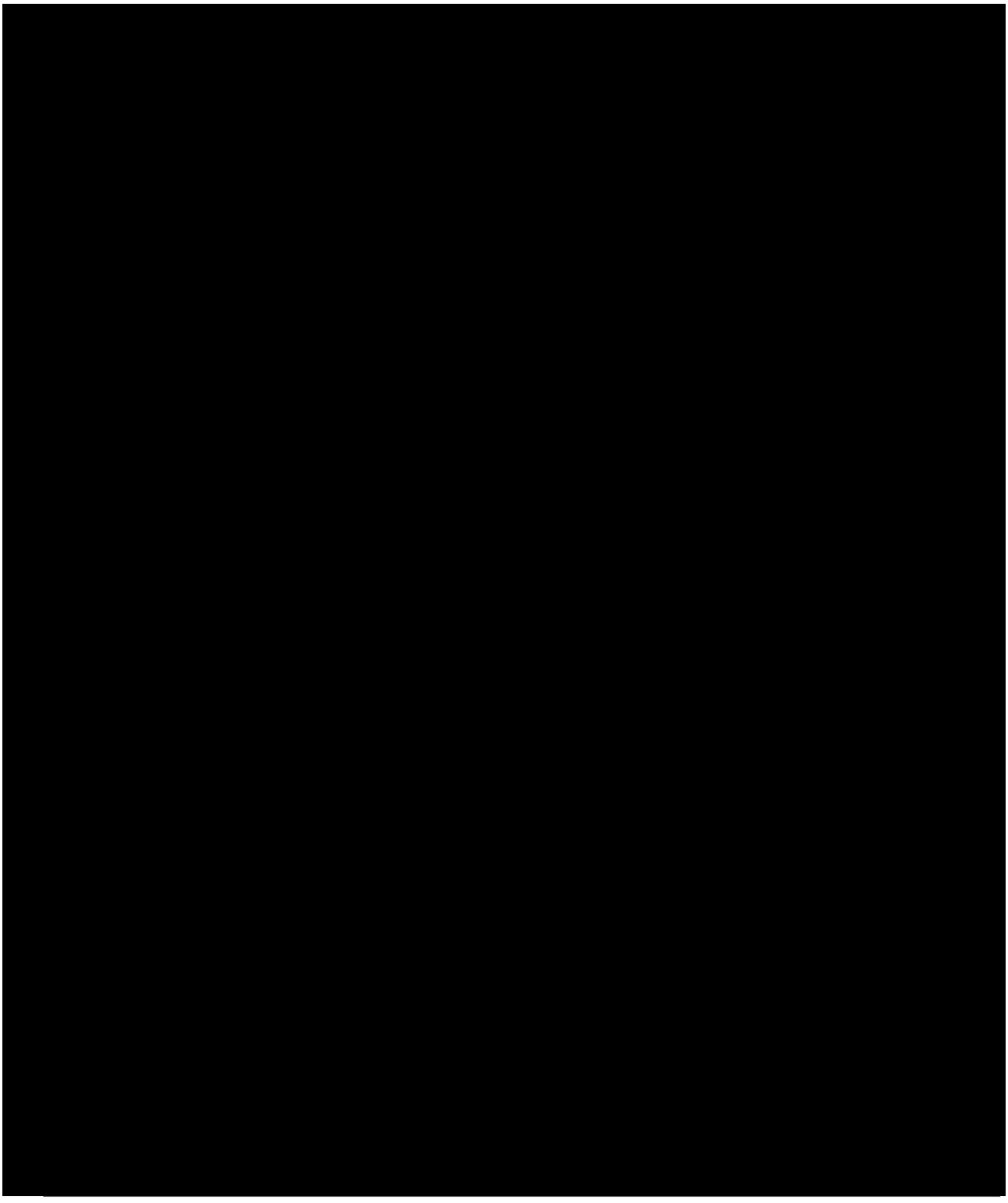
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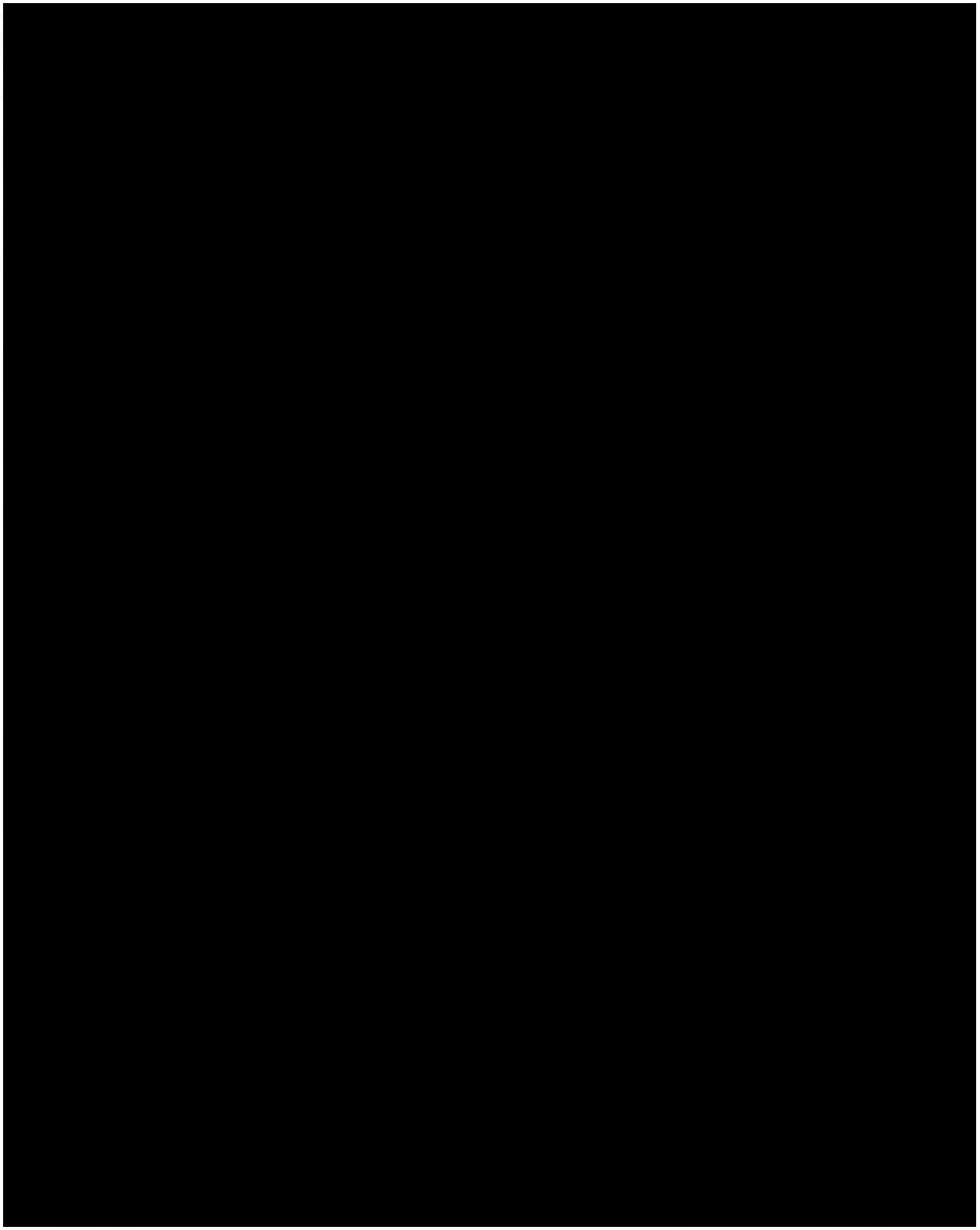
10.15 APPENDIX 15: QOL-B



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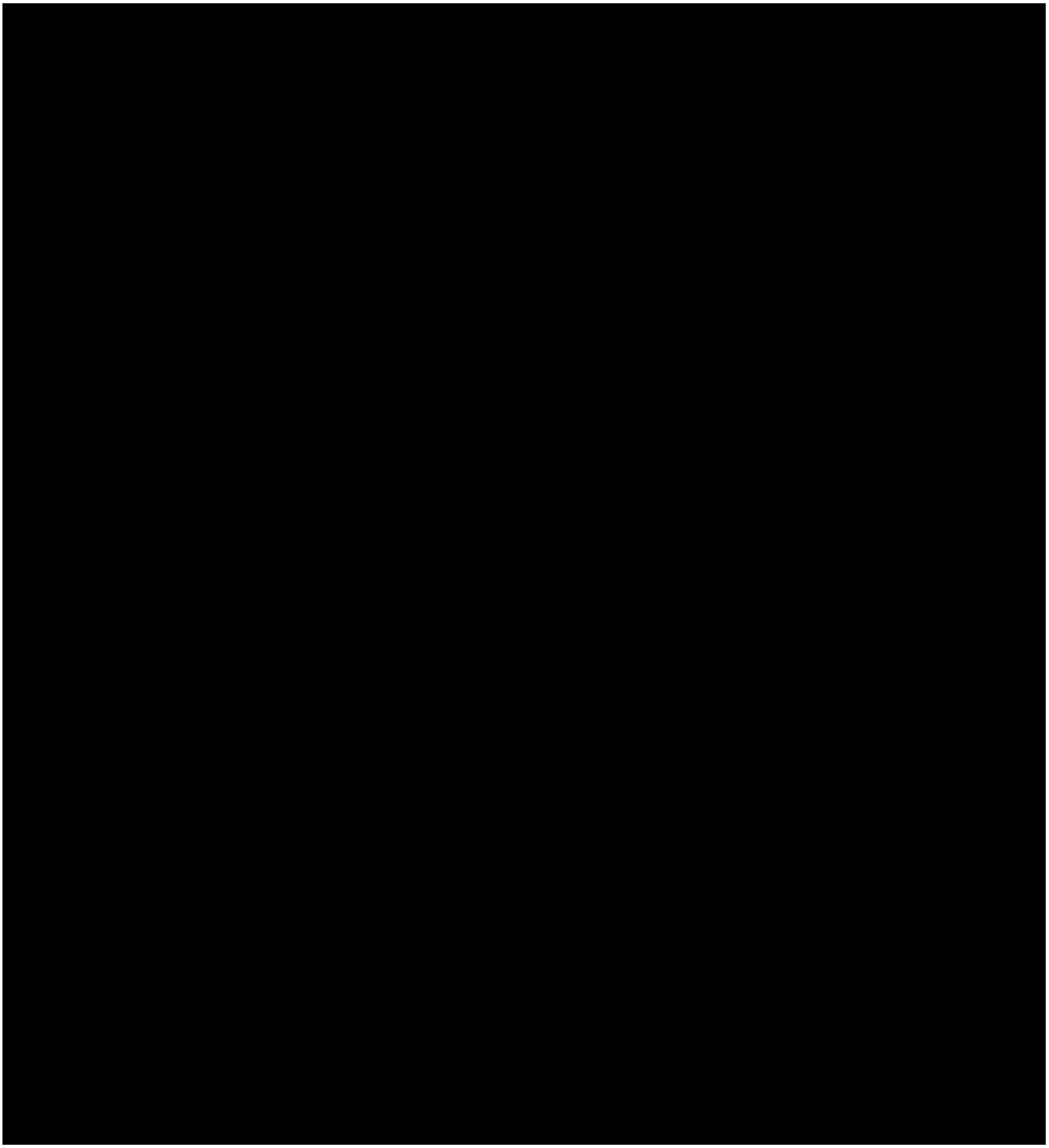
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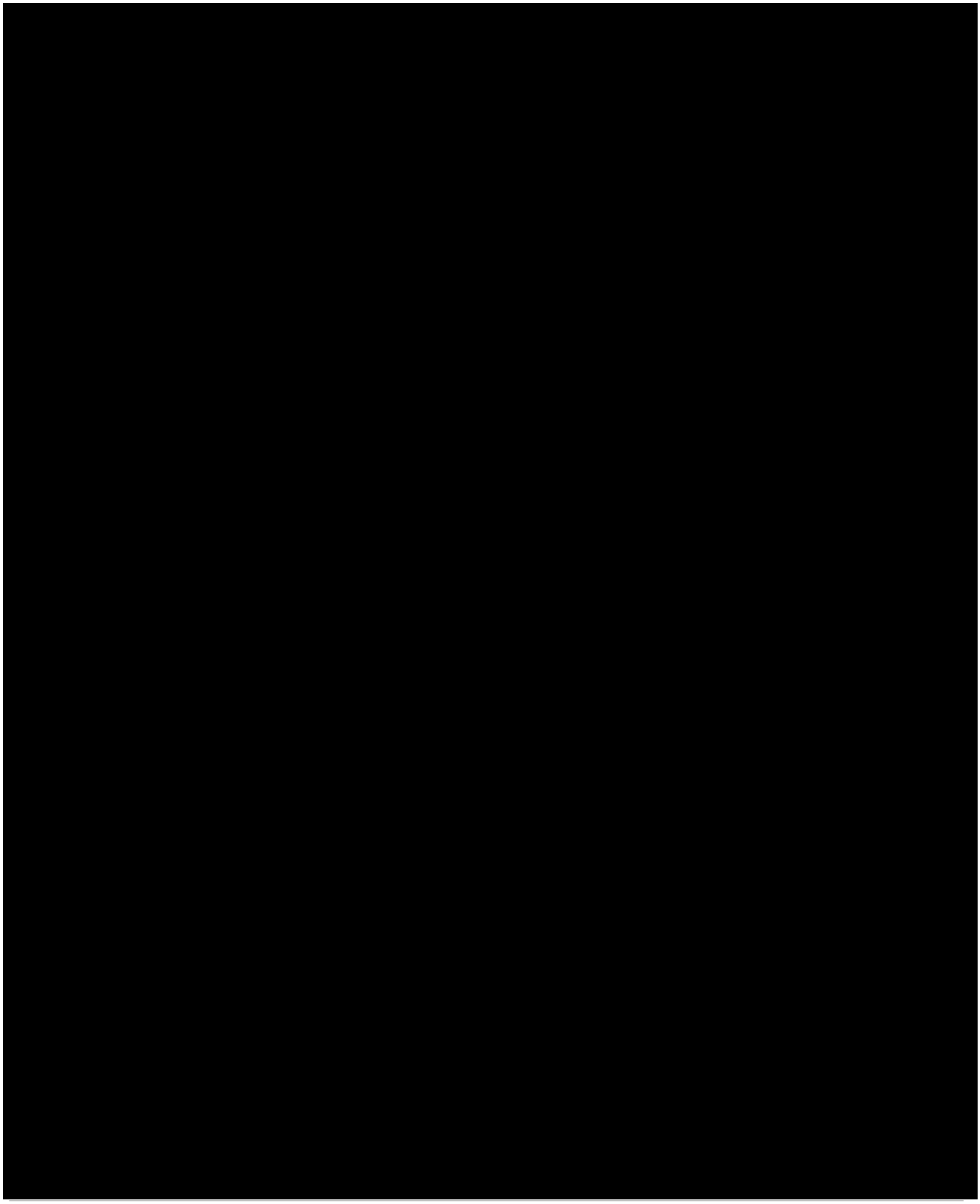
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10.16 APPENDIX 16: LEICESTER COUGH QUESTIONNAIRE



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10.17 APPENDIX 17: PGIC/PGIS

Patient Global Impression of Change (PGIC)

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

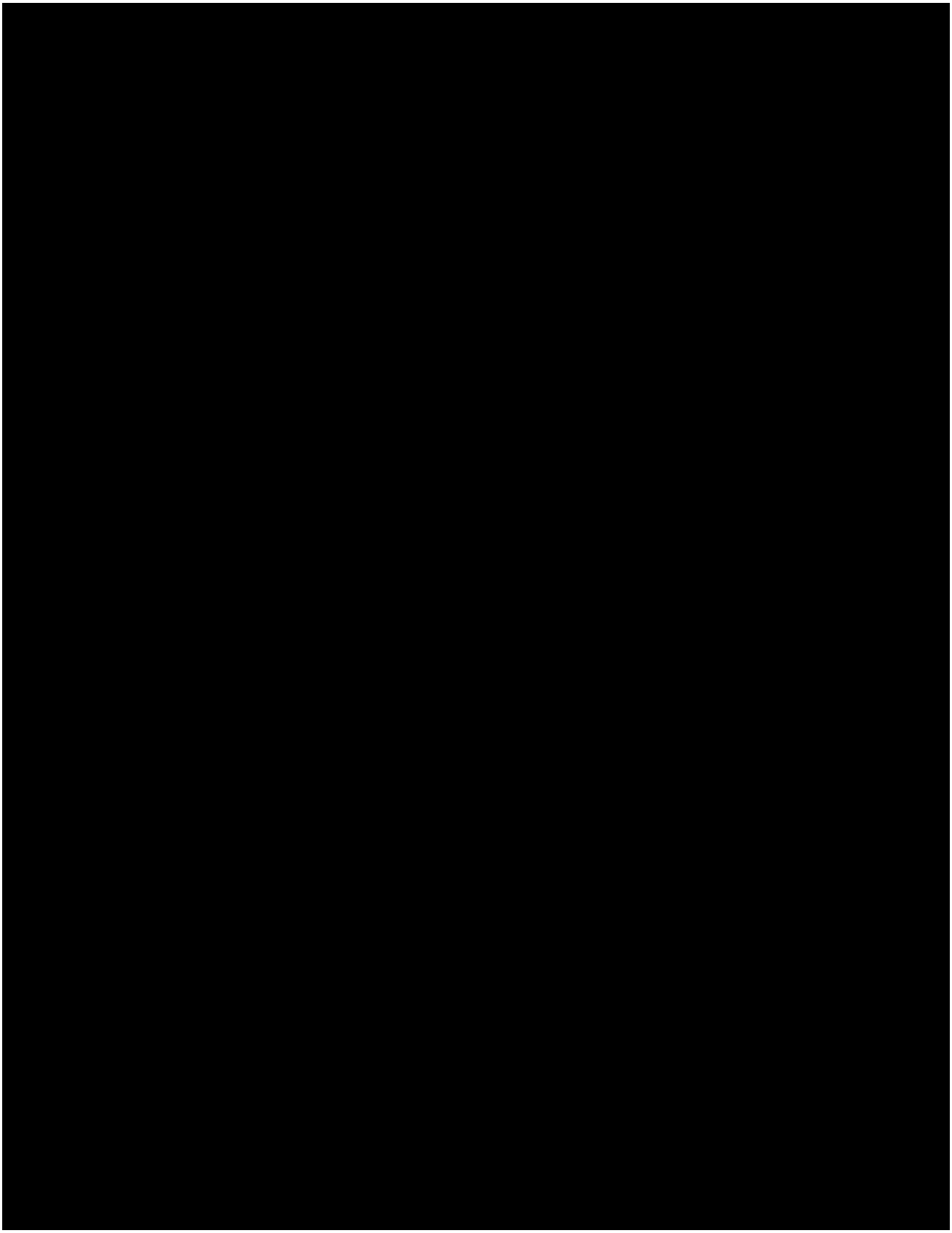
- ☐ Very much better (1)
- ☐ Much better (2)
- ☐ A little better (3)
- ☐ No change (4)
- ☐ A little worse (5)
- ☐ Much worse (6)
- ☐ Very much worse (7)

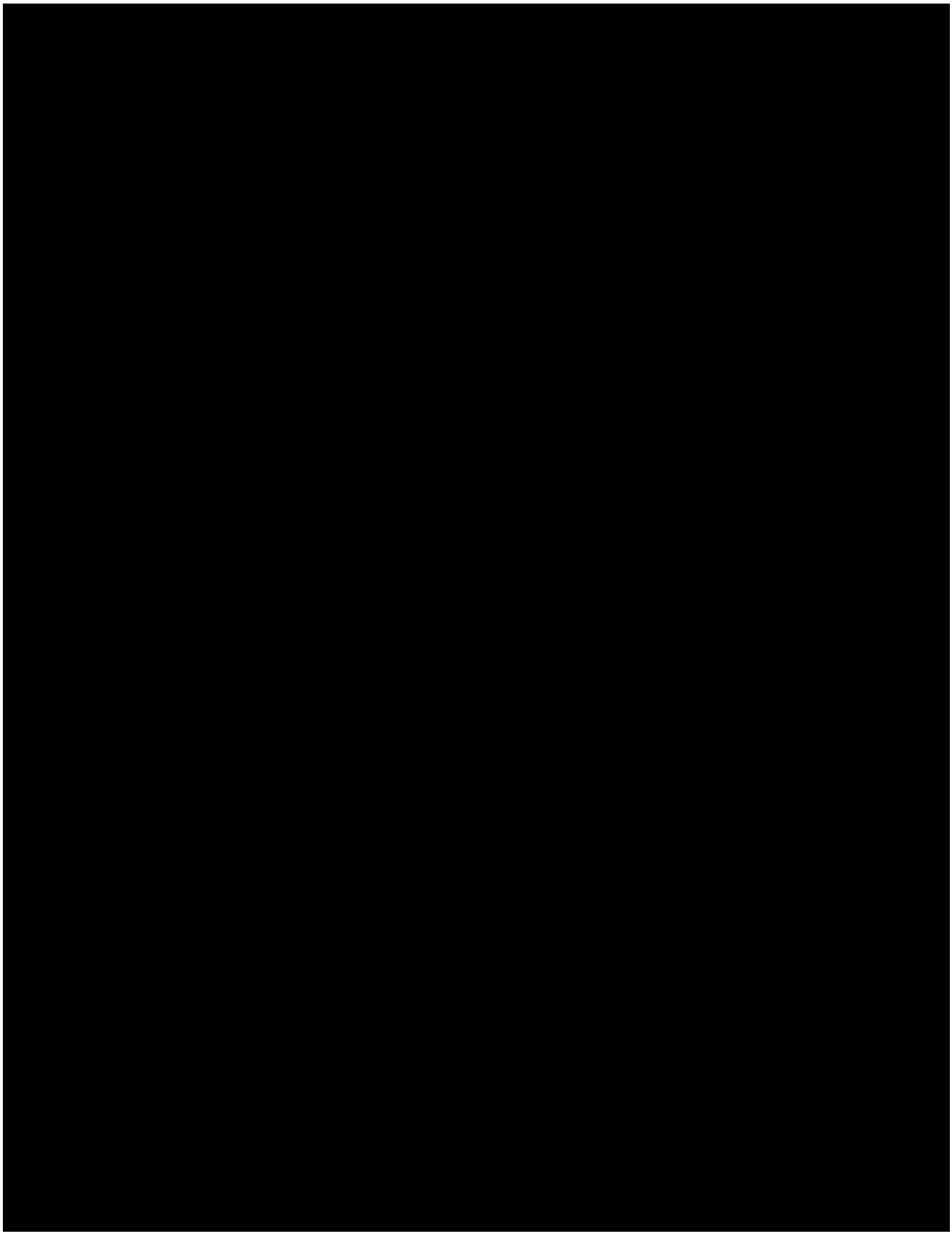
Patient Global Impression of Severity (PGIS)

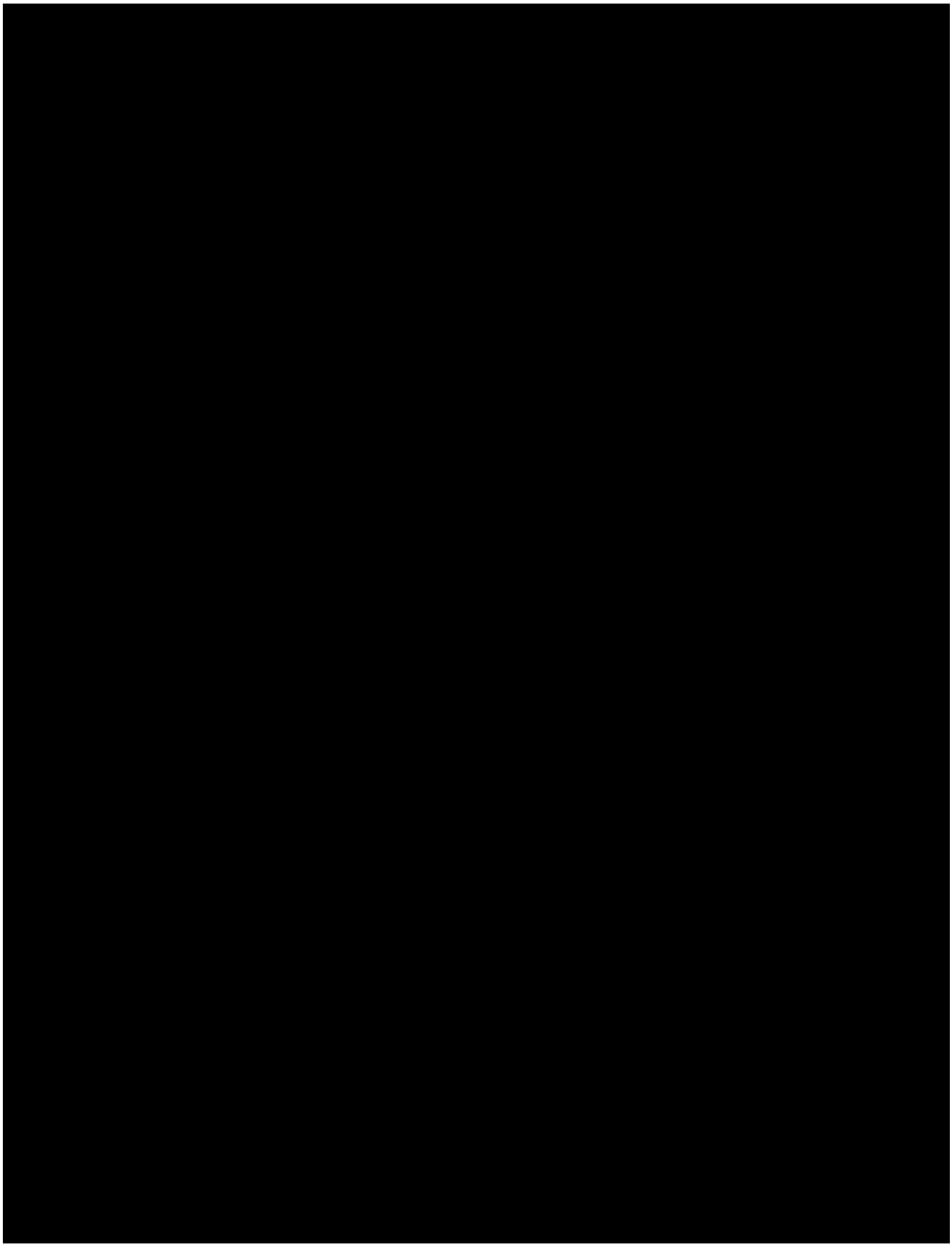
Please choose the response below that best describes the severity of your bronchiectasis symptoms over the past week.

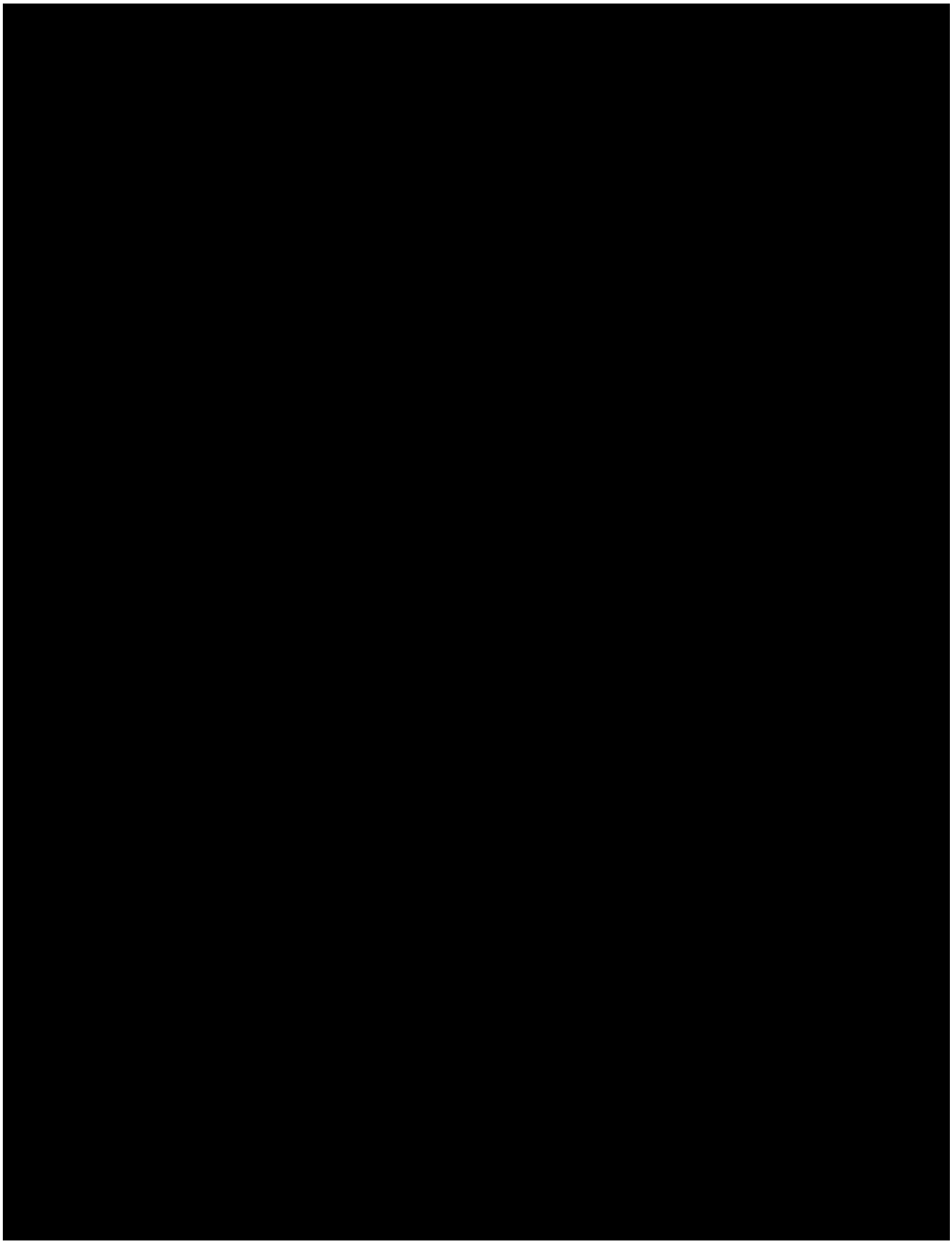
- ☐ None (1)
- ☐ Mild (2)
- ☐ Moderate (3)
- ☐ Severe (4)

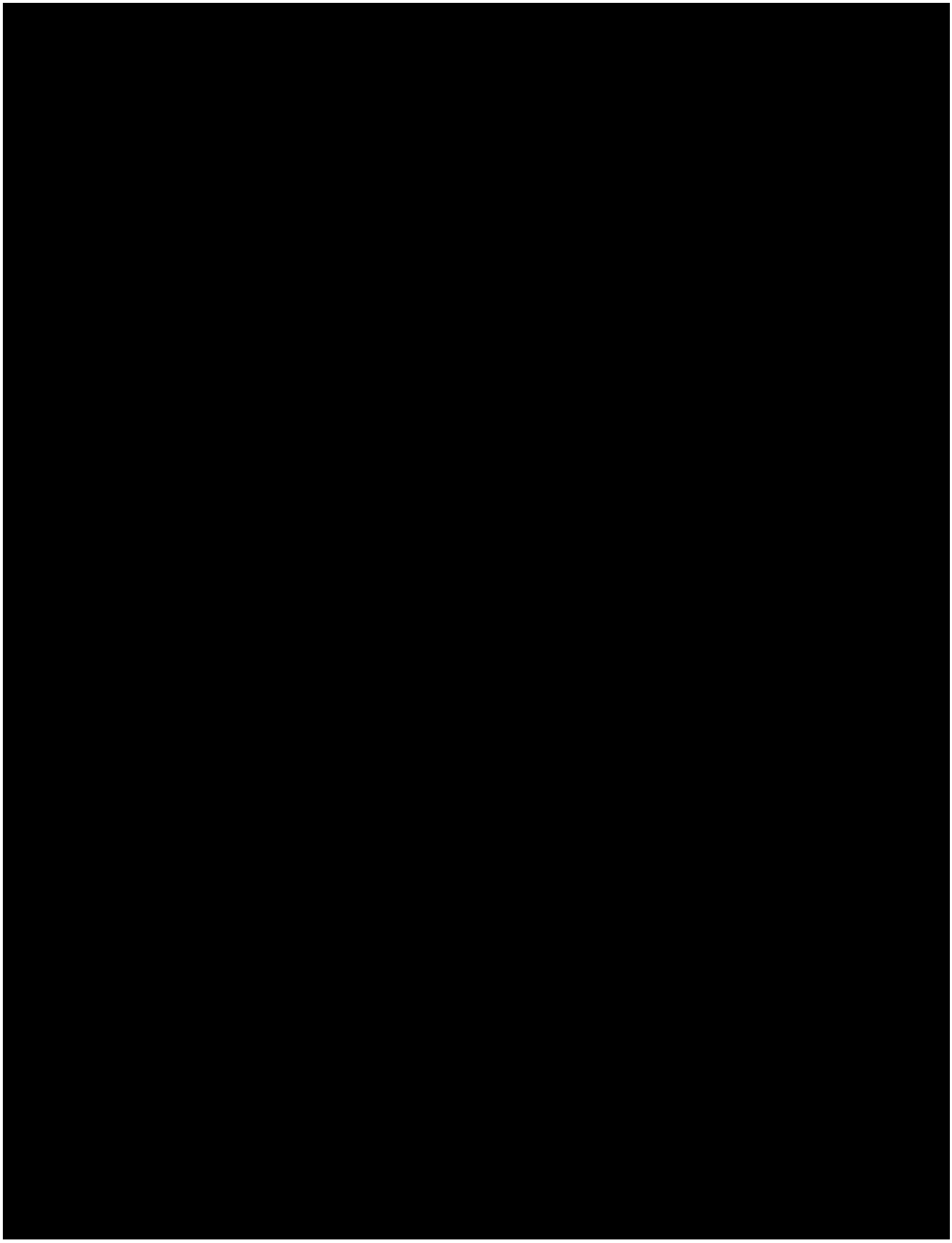
10.18 APPENDIX 18: EQ-5D-5L

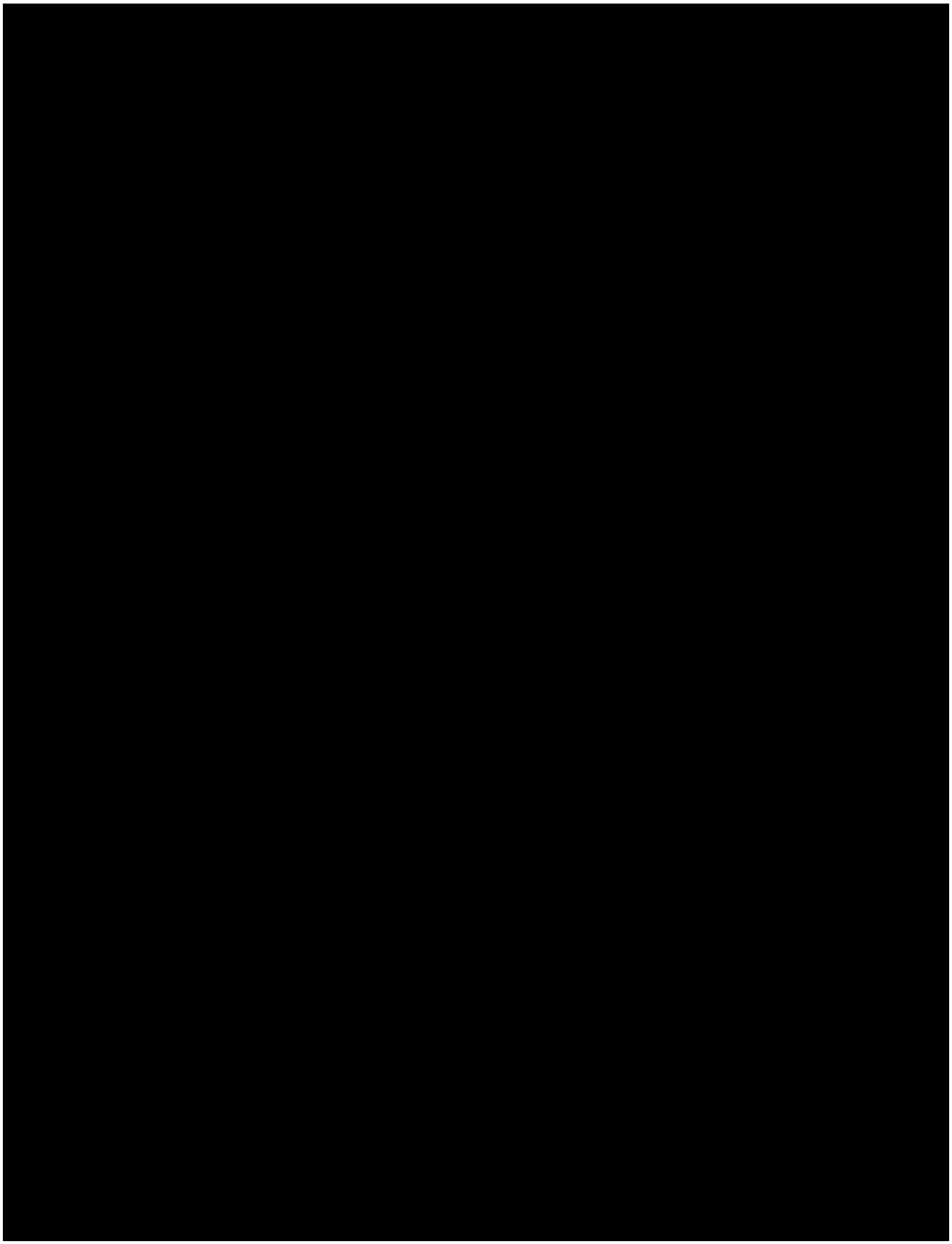


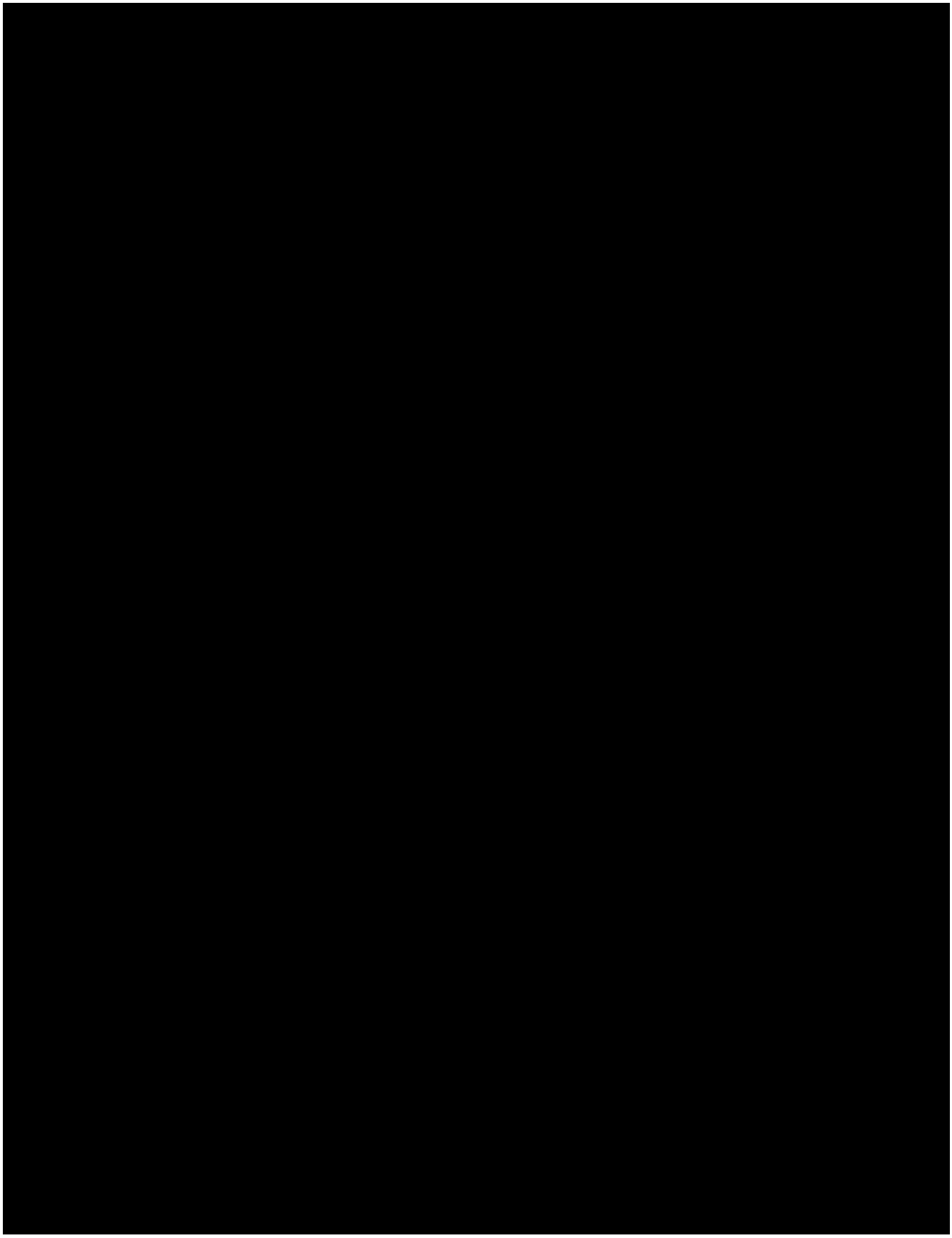




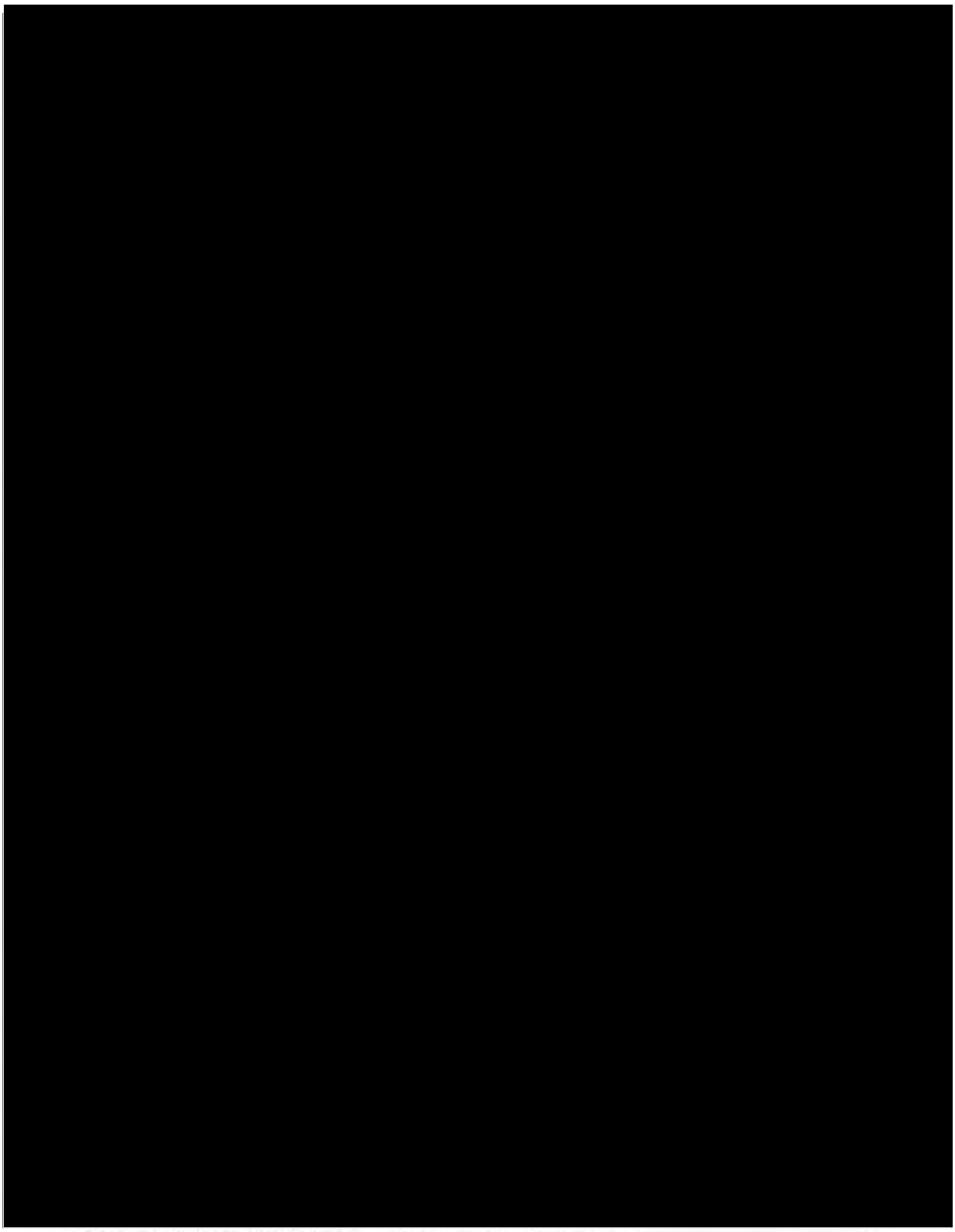








10.19 APPENDIX 19: SNOT-22



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

10.20 APPENDIX 20: CALCULATION OF BRONCHIECTASIS SEVERITY INDEX



MODIFIED MEDICAL RESEARCH COUNCIL BREATHLESSNESS SCORE



10.21 APPENDIX 21: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

10.21.1 Amended protocol 01 (02 January 2024)

This amended protocol 01 is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Revisions were made to the endpoint definition of a pulmonary exacerbation (PE) based upon health authority feedback. 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
1.1 Synopsis 3 Objectives. Endpoints, and Estimands 4.1 Overall design 8.2.1 Disease-specific efficacy measures	The following text: Moderate PE = worsened respiratory symptoms leading to treatment with antibiotics or addition of antibiotic or change in antibiotic. Severe PE = worsened respiratory symptoms resulting in hospitalization or observation for >24 hours in emergency department/urgent care facility or death. Was modified to: All worsening of respiratory symptoms leading to prescription of antibiotics (new, addition or change in) and/or systemic corticosteroids will be captured. An adjudication committee will determine if below criteria for moderate or severe exacerbation are met: *Moderate PE in this study is defined as: A) having 3 or more of the following symptoms for at least 48 hours 1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Haemoptysis AND B) A physician's decision to prescribe antibiotics (or addition of antibiotic or change in antibiotic). *Severe PE is defined as a PE as described above resulting in intravenous antibiotic treatment, or hospitalization or observation for >24 hours in emergency department/urgent care facility, or death.	To align with a health authority request seeking to modify the endpoint definition of a PE.
3. Objectives, Endpoints, and Estimands	The following endpoint was added to the exploratory objectives 'Evaluate the efficacy of itepekimab compared with placebo on occurrence of PEs in NCFB': Annualized rate of all exacerbation (as recorded by Investigator) Annualized rate of all exacerbations leading to prescription with antibiotics Annualized rate of all exacerbations leading to prescription of antibiotics and/or systemic corticosteroids + meeting footnote a Part A criterion of a moderate exacerbation	To align with a health authority request seeking to modify the endpoint definition of a PE.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA) footnote v 5.4 Screen failures 5.2 Exclusion criteria E 04	The following text was added: If the participant experiences a PE (see Section 8.2.1) during the screening period, the screening period may be extended by 4 weeks (up to 9 weeks in total). If the exacerbation has clinically resolved (no symptoms and no treatment for exacerbation) during the extended screening period, screening assessments do not need to be repeated but patient can proceed to Baseline visit and randomization if all other eligibility criteria are still met.	To allow participants with an intercurrent exacerbation to recover prior to randomization
5.1 Inclusion criteria 1.3 Schedule of activities footnote f	The following text was removed from I 02 and SoA: Chest X-ray if CT-scan is not feasible due to local regulations) The following text was added to I 02: AND are mucopurulent sputum producers with a history of chronic expectoration. The following text was added to I 04: In case maintenance antibiotic is used, at least one exacerbation must have occurred while patient was on maintenance antibiotic therapy.	Chest X-ray is not considered a reliable assessment for bronchiectasis Enrich patient population for more inflammation driven bronchiectasis Enrich patient population for patients who are prone to have an exacerbation during the trial
5.2 Exclusion Criteria 6.9 Prior and concomitant therapy	The following text: E 01. Have bronchiectasis due to CF, hypogammaglobulinemia, common variable immunodeficiency, Mannose-binding lectin (MBL) deficiency or pulmonary fibrosis. Was replaced with: E 01. Have bronchiectasis due to CF, hypogammaglobulinemia, common variable immunodeficiency, known active nontuberculous mycobacteria (NTM) lung infection or pulmonary fibrosis. The following text was added to E 17: Anti-TSLP The following text was added to list of prohibited concomitant medication: • Anti-thymic stromal lymphopoietin (TSLP) (Tezepelumab) The following compound was added to list of prohibited concomitant medication related to Anti-IL5 or IL5R mAb: reslizumab	Update to prohibited medical conditions
5.4 Screen failures	The following text: In case of suspicion of misdiagnosis of COPD and/or asthma in the past (eg, no spirometry confirmation or diagnosis of COPD in absence of smoking history and/or smoke exposure), the Investigator can reach out to the sponsor and discuss eligibility. Was replaced with: In case of misdiagnosis of COPD and/or asthma in the past (eg, for COPD no spirometry confirmation or diagnosis of COPD in absence of smoking history and/or smoke exposure, for asthma lack of reliable history of typical variable respiratory symptoms of asthma or confirmation of variable expiratory airflow limitation), the Investigator can document this in the source materials and enroll the patient in the stratum of 'NO COPD and/or asthma'.	Delegate review of misdiagnosis to Investigator.

Section # and Name	Description of Change	Brief Rationale
8.1 Administrative and general/baseline procedures	The following text: • Sputum collection (optional: only in participants able and willing to produce non-induced sputum. Sputum can be collected during the visit, or within 2 hours prior to the visit; date of collection and processing need to be obtained). Was replaced with: • Sputum collection (optional: only in participants able and willing to produce non-induced sputum. Sputum can be collected during the visit, or the morning prior to the visit; date of collection and processing need to be obtained). In case the participant is unable to produce sputum, a morning sputum sample can be brought to the clinic within 1 week after the planned collection date for post randomization visits.	To facilitate use of sputum collected at home in the morning for culture purposes.
8.8 Biomarkers	The following sentence was deleted: "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"	Redundant and conflicting information with Section 10.5 Appendix 5 Genetics.
10.1.5.2 Adjudication committee	The following text was added: A separate confirmatory adjudication will occur for PEs. Adjudicators will adjudicate all reported and suspected exacerbation events leading to prescription of antibiotics (new, addition or change in) in a consistent and unbiased manner throughout the study and check if they meet the protocol definition of a moderate or severe exacerbation (see Section 8.2.1).	Describe process and scope of exacerbation adjudication
10.5 APPENDIX 5: Genetics	In the following sentence: "• The samples will be retained while research on itepekimab and/or study interventions of this class or bronchiectasis continues but no longer than 15 years or other period as per local requirements" the retainment period was updated to 'no longer than 25 years".	Extent retainment period to align with informed consent form information.

10.21.2 Amended protocol 02 (25 April 2024)

This amended protocol 02 is considered to be non-substantial based on the criteria set forth in Article 2(2)(13) of Regulation No 536/2014 of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment addresses the requests of the Member States Concerned of the European Union (EU) during the Clinical Trial Application. It incorporates the recommendation to provide post-trial access after study completion, some updates to Appendix 8 Country-specific/region requirements, and to provide some minor changes or clarifications to the amended protocol 01.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Update of the Sponsor's legal registered address	Administrative change
List of abbreviations 5.3 Lifestyle considerations	Clarification added of abbreviations	Clarification (Health Authority request)
1.1 Synopsis 6.7 Continued access to intervention after the end of the study	Information regarding post-trial access has been added	Provide post-trial access (Health authority request)
6.9 Prior and concomitant therapy	The following therapies were added to the list of prohibited concomitant medication: "other immune-directed biologic therapy such as anti-IL-6 (tocilizumab, sarilumab, siltuximab), anti-IL-17 (bimekizumab, brodalumab, ixekizumab, secukinumab), anti-IL-23 (guselkumab, mirikizumab, risankizumab, tildrakizumab), anti-IL-12/IL-23 (ustekinumab)"	Update the list of monoclonal antibodies that are prohibited (Health authority request)
6.9 Prior and concomitant therapy	Brensocatib was added to the list of prohibited concomitant medications	Update to prohibited concomitant medication to reduce bias
7.1.1 Permanent discontinuation	Added one paragraph to state: "In case of exposure to prohibited concomitant medication such as, but not limited to immunomodulating monoclonal antibodies or immunosuppressants as listed in the prohibited medications from Section 6.9, a decision should be made on the need for temporary or permanent discontinuation of IMP. The decision to resume the treatment with IMP will be made by the Principal Investigator based on the clinical judgment and potential risks of drug interactions."	Update to the permanent discontinuation criteria (Health authority request)
7.1.4 Temporary discontinuation	Use of prohibited medication has been added as a reason for temporary intervention discontinuation	Update to the temporary discontinuation criteria. (Health authority request)
9.4 Sample size determination	Following sentence was added: "Additional detail regarding the methodology to compare efficacy between the two doses will be provided in the SAP."	Update of text (Health authority request)
10.8 Appendix 8: Country-specific/region requirements	<u>Czechia</u> Additional country-specific selection criteria have been added for Czechia (referral to Section 10.8.4 has been added in Section 1.3, Section 5.2 [E 22 and E 24], and Section 8.3.4) <u>European Union</u> The following sentence has been added: "Fatal and life-threatening SUSARs must be reported within 7 calendar days, other SUSARs are to be reported within 15 calendar days."	Update of text (Health authority request)
Throughout the document	Minor editorial, typographical error corrections, and document formatting revisions	Minor, therefore, have not been summarized
Cover page and throughout the document	Document updated to "Amended Clinical Protocol 02" including updated summary of changes, protocol amendment history, and formatting (headers, etc.) related to the protocol amendment	As per Sanofi standards

10.21.3 Amended protocol 03 (15 July 2024)

This amended protocol 03 is considered substantial based on the criteria set forth in Article 2(2)(13) of Regulation No 536/2014 of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment addresses the requests of the Member States Concerned of the European Union (EU) during the Clinical Trial Application. It incorporates the recommendation to provide clarity regarding the availability of post-trial access and to describe in more detail the reasons that can lead to termination of the study. In addition, some minor changes or clarifications to the amended protocol 02 were made.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 6.7 Continued access to intervention after the end of the study	The following sentences: "There are no formal plans to provide post-trial access to itepekimab. However, depending on evidence of the participant's unmet medical need, the non-availability of suitable alternative therapies, and an assessment of what is known about the benefits and risks of itepekimab, Sanofi will only consider providing participants who have successfully completed their participation in this clinical trial with access to itepekimab." "The Investigator/treating physician will determine if access to itepekimab is the best medical option for the participant and will then submit a request to Sanofi." "Sanofi's post-trial access responsibilities will need to be periodically re-evaluated. Based on new information about the investigational product (including adverse reactions), the ongoing health of the individual, and market availability of the product or altrenative therapies, post-trial access may be terminated" Were replaced with: "Depending on evidence of the participant's unmet medical need, the non-availability of suitable alternative therapies, and an assessment of what is known about the benefits and risks of itepekimab, participants who have successfully completed their participation in this clinical trial will be eligible for post-trial access to itepekimab." "The Investigator/treating physician will determine if benefit of continued access to itepekimab can be expected and access to itepekimab is the best medical option for the participant and will then submit a request to Sanofi." "Sanofi's post-trial access responsibilities will need to be periodically re-evaluated. Based on new information about the investigational product (including adverse reactions), the continued health benefit to the individual, and market availability of the product or alternative therapies, post-trial access may be terminated."	Provide clarity regarding the availability of post-trial access (Health Authority request)

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	The following footnote text has been added: "Anabasine Testing Guidelines: in case of negative cotinine test result, do not use anabasine test result for screening/randomization. In case of positive cotinine test result, ask the participant about NRT or non-smoked nicotine use. If the participant is using NRT or non-smoked nicotine and has a positive anabasine test result, exclude the participant. If the participant is using NRT or non-smoked nicotine and has a negative anabasine test result, the participant is eligible as per E 02. If the participant does not claim to smoke nor use NRT/chewing tobacco, exclude the participant."	Clarification
10.1.9 Study and site start and closure	The following sentence: "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." Was replaced with: "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: • For study termination: - Information on the product leads to doubt as to the benefit/risk ratio. - Discontinuation of further study intervention development. - If circumstances beyond the control of the Sponsor make it unreasonable to require the study's continuation."	Describe in more detail the reasons that can lead to termination of the study (Health Authority request)
Throughout the document	Minor editorial, typographical error corrections, and document formatting revisions	Minor, therefore, have not been summarized
Cover page and throughout the document	Document updated to "Amended Clinical Protocol 03" including updated summary of changes, protocol amendment history, and formatting (headers, etc.) related to the protocol amendment	As per Sanofi standards

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