

AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	A Phase 2a, open-label, two-part study to evaluate the mechanism of action of itepekimab (anti-IL-33 mAb) on airway inflammation in patients with chronic obstructive pulmonary disease (COPD)
Protocol number:	PDY16967
Amendment number:	02
Compound number (INN/Trademark):	SAR440340/REGN3500 itepekimab/Not applicable
Brief title:	Mechanistic study of the effect of itepekimab on airway inflammation in patients with COPD
Study phase:	Phase 2
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/ countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	11 September 2024, version 1.0 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	22 September 2022, version 1.0 (electronic 1.0)
Original Protocol		30 June 2021, version 1.0 (electronic 2.0)

Amended protocol 02 (11 September 2024)

This amended protocol 02 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

Enrollment in PDY16967 a mechanistic study has been challenging. The primary purpose of this amendment is to [REDACTED] The overarching goal of the study comparing a cohort of former and current smokers with COPD treated with itepekimab remains the same. [REDACTED]

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
Cover page	NCT number added	Administrative change
1.1 Synopsis	Update of primary, secondary, and exploratory objectives and endpoints and related text	In line with [REDACTED]
1.2 Schema		[REDACTED]
2.1 Study rationale		[REDACTED]
3 Objectives and endpoints		[REDACTED]
4.1 Overall design		
[REDACTED]		
[REDACTED]		
9.3.2 Primary endpoint(s)		
9.3.3 Secondary endpoints		

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis		
1.2 Schema		
4.1 Overall design		
5.4 Screen failures		
9.1 Sample size determination		
1.1 Synopsis	Text added regarding posttrial access to study medication	To provide participants who may have benefited during the study access to study drug
6.6 Continued access to intervention after the end of the study		
1.1 Synopsis	Updated text on the planned statistical analyses	In line with
9.1 Sample size determination		
9.2 Populations for analyses		
9.3 Statistical analyses		
6.8 Prior and concomitant therapy	Additional therapies added to the list of prohibited concomitant medications	In line with new additional available therapies that participants might use
		In line with updated objectives and endpoints
9.3.6.2 Anti-itepekimab antibody variables and analysis	Updated text describing definitions and planned analyses	To align with the definitions and planned analyses across studies in the COPD indication
9.4 Interim analyses	Removal of the planned interim analysis at the end of Part A	
10.1.9 Study and site start and closure	<u>The following sentence:</u> “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” <u>Was replaced with:</u> “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:	To provide more clarity regarding potential Sponsor reasons to terminate the study and site participation

Section # and Name	Description of Change	Brief Rationale
	- 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 continue the study”	
11. References	Following literature reference added (previously unpublished data, now available): Srivatsan S, Asrat S, Nagashima K, Scott G, Lim WK, Birchard D, et al. Interleukin-33 (IL-33) Drives Type 1 and Type 2 Inflammation and Instructs Airway Remodeling (abstract). Am J Respir Crit Care Med. 2023;207:A4473 Removed following literature reference (reference is not valid anymore): Centers for Disease Control and Prevention (CDC). COPD Costs. [Online]. 2018 Feb 21 [cited 2020 Mar 26]. Available from: URL:https://www.cdc.gov/copd/infographics/copd-costs.html.	Update of literature reference list (clarification and correction)
Throughout the document	Updated text to align with Regulation No 536/2014 of the European Parliament and the Council of the European Union (incl. removal of references to the “Directive 2001/20/EC”, addition of information on reporting of serious breaches, data protection, and future use of data and biological samples, etc.)	Administrative change
Throughout the document	Editorial changes to align with current standard protocol template	Administrative change
Throughout the document	Minor editorial changes	Clarification and correction of typographical errors
Throughout the document	Document updated to “Amended Clinical Trial Protocol 02” 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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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2a, open-label, two-part study to evaluate the mechanism of action of itepekimab (anti-IL-33 mAb) on airway inflammation in patients with chronic obstructive pulmonary disease (COPD)

Brief title: Mechanistic study of the effect of itepekimab on airway inflammation in patients with COPD

Rationale:

Chronic obstructive pulmonary disease (COPD) is a serious and life-threatening disease. It is a leading cause of death worldwide and responsible for over 3 million deaths worldwide in 2016 and 160 000 deaths in the United States (US) annually (1, 2, 3). Chronic obstructive pulmonary disease is characterized by progressive decline in lung function and recurrent exacerbations of symptoms. The latter results in rapid disease progression and is associated with increased mortality, particularly following exacerbations that require hospitalization (4). Although smoking cessation in patients with established COPD slows the rate of lung function decline and reduces the risk of hospitalization and mortality, former smokers with COPD are still at high risk for exacerbations, and substantial morbidity and risk of mortality remain (5). Despite currently available therapies, which largely comprise combinations of bronchodilators (BDs) and/or inhaled corticosteroids (ICS), a significant unmet medical need remains, particularly on the key outcomes of reducing the frequency of COPD exacerbations and hospitalization.

Itepekimab (also known as SAR440340 or REGN3500) is a human immunoglobulin (Ig) G4P monoclonal antibody (mAb) that binds interleukin-33 (IL-33) with subnanomolar affinity and thereby inhibits IL-33 signaling. Itepekimab is under development as a potential novel treatment for COPD. Data from the proof-of-concept (PoC) Study ACT15104, in which itepekimab was studied versus placebo in addition to approved standard-of-care (SoC) background therapy, provided preliminary clinical evidence that itepekimab has the potential to confer significant benefit beyond that provided by currently available therapies to patients with moderate-to-severe COPD who are former smokers. Study ACT15104 recruited participants with a smoking history of ≥ 10 pack-years, regardless of smoking status at screening. In a prespecified subgroup analysis by smoking status at screening, itepekimab led to a reduction in the annualized rate of exacerbations and improvement in lung function in former smokers, but no effect on these endpoints was observed in current smokers with COPD. These results suggest that active smoking eliminated the beneficial effects of itepekimab. The biological factors contributing to the differential effects of itepekimab in former and current smokers have not been identified.

Along with two Phase 3 clinical trials of itepekimab in patients with COPD (Study EFC16750 and Study EFC16819), this study is being conducted to help support the development of itepekimab for use in former smokers with moderate-to-severe COPD.

This study will provide insights into the mechanism of action of itepekimab and the differential effect of itepekimab in the airways of former and current smokers with COPD. The primary endpoints of both Part A and Part B of this study are the change in the itepekimab pharmacodynamic normalized enrichment score (NES) in endobronchial biopsies, bronchial and nasal brushings (identified in Part A, former smokers), in current smokers (Part B) with COPD after 12 weeks of treatment with itepekimab.

Objectives and endpoints

Objectives	Endpoints
Primary	
Evaluate the difference in gene expression between former and current smokers with itepekimab treatment	- Change from baseline in itepekimab pharmacodynamic normalized enrichment score (NES) derived from former smokers in endobronchial biopsies in current smokers with COPD at Week 12 - Change from baseline in itepekimab pharmacodynamic NES derived from former smokers in bronchial brushings in current smokers with COPD at Week 12 - Change from baseline in itepekimab pharmacodynamic NES derived from former smokers in nasal brushings in current smokers with COPD at Week 12
Secondary	
- Evaluate the effect of itepekimab treatment on prespecified cell type-associated gene expression signatures in endobronchial biopsies from former and current smokers with COPD - Evaluate the effect of itepekimab on blood eosinophil counts in former and current smokers with COPD - Evaluate the safety and tolerability of itepekimab in former and current smokers with COPD - Evaluate immunogenicity to itepekimab in serum of former and current smokers with COPD - Evaluate the PK profile of itepekimab in serum in former and current smokers with COPD	- Change from baseline in IL-33 treated eosinophil-associated NES in endobronchial biopsies at Week 12 - Change from baseline in IL-33 treated mast cell-associated NES in endobronchial biopsies at Week 12 - Change from baseline in blood eosinophil count at Week 12 - Incidence of TEAEs, AESIs, SAEs, and AEs leading to permanent treatment discontinuation - Incidence of potentially clinically significant abnormalities in clinical laboratory tests, vital signs and ECG abnormalities in the treatment-emergent period - Incidence of treatment-emergent anti-itepekimab antibody responses throughout the study - Functional itepekimab concentrations in serum from baseline to end of study

Abbreviations: AE: adverse event; AESI: adverse event of special interest; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; NES: normalized enrichment score; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Overall design:

This study is an exploratory, two-part, 12-week, Phase 2a study to evaluate the mechanism of action of itepekimab (anti-IL-33-mAb) and its impact on airway inflammation in former and current smokers with COPD.

Brief summary:

The total study duration for each participant is approximately 36 weeks:

- 4-week Screening Period
- 12-week Treatment Period¹
- 20-week Follow-up Period

Additional details of the study duration may be found in the Schedule of Activities (SoA, [Section 1.3](#)).

Part A will consist of up to approximately 25 participants with COPD who are former smokers receiving established background therapy for COPD, including monotherapy (long-acting β 2-agonist [LABA] or long-acting muscarinic antagonist [LAMA]), double therapy (ICS + LABA, LABA + LAMA, or ICS + LAMA), or triple therapy (ICS + LABA + LAMA), while Part B will consist of up to approximately 25 participants who are current smokers with COPD receiving established background monotherapy, double therapy, or triple therapy.

The primary endpoints are the change from baseline in an itepekimab pharmacodynamic NES in endobronchial biopsies, bronchial brushings, and nasal brushings from current smokers with COPD after 12 weeks of treatment with itepekimab, as assessed in participants who complete both the Baseline and Week 12 bronchoscopy with adequate RNA quality (see [Section 9](#) for statistical details). Study treatment will be itepekimab 300 mg Q2W administered SC during the 12-week Treatment Period. Detailed instructions for sample collection and handling are provided in the PDY16967 procedural manual that will be provided to the study sites.

Participants must have been on a SoC controller therapy for COPD for at least 3 months prior to Screening (Visit 1) with stable dose and regimen for controller therapy for ≥ 1 month prior to Screening (Visit 1) and during the Screening Period. Participants must stay on their established controller medications for COPD throughout the duration of the study, with the exception of systemic corticosteroids and/or antibiotics used for acute exacerbation of COPD (AECOPD) (see [Section 6.8](#) for concomitant medications).

Participants in both Part A and Part B are expected to undergo 2 bronchoscopy procedures that will include endobronchial biopsies, bronchial brushings, and (when applicable) bronchoabsorption:

- Bronchoscopy #1: To be conducted at Week 0 (or up to 7 days prior to Week 0)
- Bronchoscopy #2: To be conducted at Week 12 (± 7 days)

¹ If an [REDACTED]

In addition to the bronchoscopy procedures, participants will undergo nasal brushings at Week 0 (Baseline/Visit 2) and Week 12 (End-of-Treatment/Visit 8).

Participants experiencing an AECOPD during the 12-week Treatment Period must wait for 6 weeks after the onset of the exacerbation (defined as initiation of treatment/hospitalization) before undergoing Bronchoscopy #2. [REDACTED]

Number of participants:

A total of up to approximately N=25 former smokers and N=25 current smokers (total up to approximately N=50 participants) are planned to be enrolled in this open-label study to receive itepekimab 300 mg SC Q2W. The goal is to have at least [REDACTED]

[REDACTED] Former smoker participants who might have been enrolled in the Part B former smoker cohort (prior to implementation of this amendment) will be analyzed with former smoker participants enrolled in Part A.

A maximum of 50% of the planned enrollment in each cohort will have a post-bronchodilator [REDACTED] of the predicted value at screening.

Intervention cohorts and duration:

- Part A: Itepekimab 300 mg SC Q2W
- Part B: Itepekimab 300 mg SC Q2W

Participants will be treated for 12 weeks.

Study intervention(s)

Investigational medicinal product(s)

Sterile itepekimab 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.

- Formulation: 2 mL solution for injection (150 mg/mL)
- Route(s) of administration: SC
- Dose regimen: All participants will receive 300 mg Q2W SC

Noninvestigational medicinal products(s)

Participants must continue on their established controller therapy.

- Formulation: Dry powder inhaler (DPI), metered dose inhaler (MDI), or nebulizer
- Route(s) of administration: oral inhalation for LAMA, LABA, ICS + LABA, LABA + LAMA, ICS + LAMA or ICS + LABA + LAMA

- Dose regimen: As per prescribed at the same time of the day during the study

For other information related to COPD controller therapy, including safety precautions, please consult locally approved labels for the products.

Reliever medication

Participants may administer short-acting beta-agonist (SABA) and/or short-acting muscarinic antagonist (SAMA), such as, but not limited to, albuterol/salbutamol, levalbuterol/levosalbutamol, ipratropium, or ipratropium/albuterol as reliever medication as needed during the study.

- Formulation: DPI, MDI, nebulizer
- Route(s) of administration: oral inhalation, nebulization
- Dose regimen: As needed, per prescribed

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

Devices

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

Posttrial 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 may 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.

Statistical considerations:

Proprietary pharmacodynamic gene expression signatures after itepekimab treatment identified in former smokers will be evaluated in endobronchial biopsies, bronchial brushings, and nasal brushings of current smokers. Pre-specified gene expression signatures (eg, from eosinophils, mast cells) will be evaluated in endobronchial biopsy samples of former and current smokers in the secondary endpoints in this exploratory mechanistic study.

The secondary objectives are based on the secondary PD parameters and the evaluation of the safety and tolerability of itepekimab in former and current smokers with COPD.

Safety analyses will focus on the treatment emergent (TE) period defined as the time from the first IMP administration on Day 1 up to the EOS visit (included). The safety analyses (Adverse events [AEs], treatment-emergent AEs [TEAEs], laboratory parameters, vital signs and electrocardiograms [ECGs]) will be based on the review of individual values and descriptive statistics. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, last version at the time of the database lock). Their severity will be graded according to the NCI-CTCAE v5.0 grading. The number (%) of participants experiencing TEAEs will be summarized by primary system organ class, preferred term and by smoker status group ("Former" and "Current" smokers).

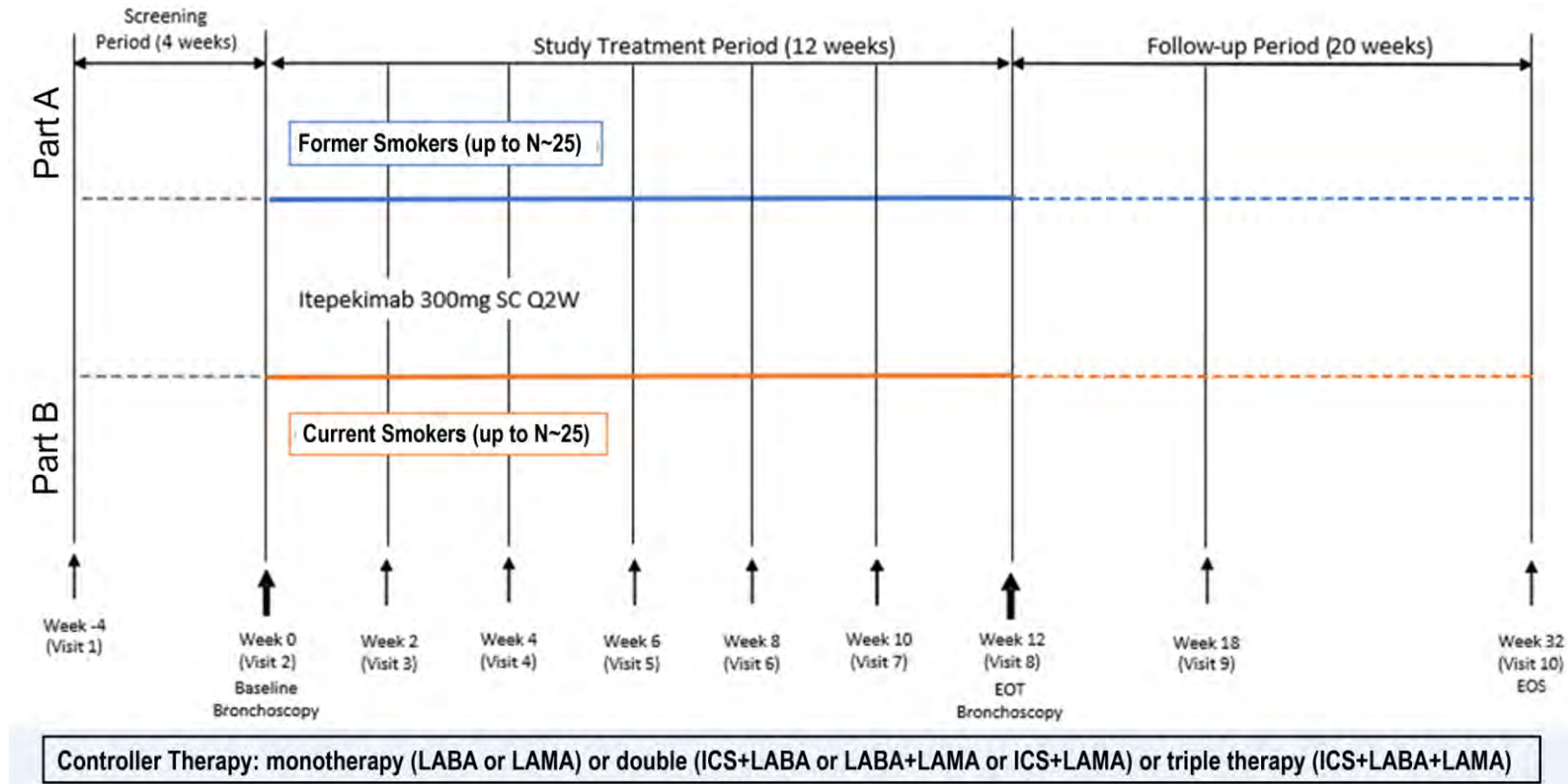
Potentially clinically significant abnormalities (PCSAs) in clinical laboratory test results, vital signs and ECGs will be flagged and summarized by smoker status group.

Summary of ADA at baseline, listing of participants with treatment-emergent and treatment boosted ADA as well as summary table of incidence will be provided for Itepekimab related ADA for each smoker status.

Data Monitoring/Other committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design (Part A+B)



Abbreviations: EOS: end of study; EOT: end of treatment; ICS: inhaled corticosteroids; LABA: long-acting β_2 adrenergic agonists; LAMA: long-acting muscarinic agonists; Q2W: every 2 weeks; SC: subcutaneous(ly)

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure (Part A and Part B)	Screening (4±1 weeks)	Interventional Treatment Period (12 weeks±3 days)							Follow-up Period (20 weeks±5 days)	
		Baseline						EOT/ETD ^{p, r}	Telephone visit	EOS
Visit	1	2	3	4	5	6	7	8	9	10
Week ^a	-4	0	2	4	6 ^a	8	10 ^a	12	18	32
Informed consent	X									
Inclusion and exclusion criteria	X	X ^p								
Demography	X									
Medical and surgical history	X									
Chest X-ray ^b	X									
Spirometry (pre-BD) ^c	X	X		X		X		X		
Spirometry (post-BD) ^c	X							X		
CAT ^d	X									
Smoking status	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Study treatment administration										
Call IRT	X	X	X	X	X	X	X	X	X	X
Enrollment		X								
Itepekimab administration ^e		X	X	X	X	X	X			
Dispense or review of eDiary ^f	X	X		X		X		X		
Safety										
Physical examination ^g	X	X						X		X
Vital signs ^h	X	X		X				X		X

Procedure (Part A and Part B)	Screening (4±1 weeks)	Interventional Treatment Period (12 weeks±3 days)							Follow-up Period (20 weeks±5 days)	
		Baseline						EOT/ETD <i>p, r</i>	Telephone visit	EOS
Visit	1	2	3	4	5	6	7	8	9	10
Week <i>a</i>	-4	0	2	4	6 <i>a</i>	8	10 <i>a</i>	12	18	32
12-lead ECG <i>i</i>	X							X		X
Hematology, biochemistry, coagulation, and urinalysis <i>j</i>	X	X		X				X		X
Hepatitis and HIV serology tests <i>k</i>	X									
TB assessment <i>l</i>	X									
Pregnancy (β-hCG blood) test <i>m</i>	X									
Urine pregnancy test <i>m</i>		X		X		X		X		X
SARS-CoV-2 (COVID-19) test <i>n</i>	X									
AE reporting, including SAEs	←=====→									
Pharmacokinetics and ADA										
Serum PK samples for concentration <i>o</i>		X		X				X		X
Anti-itepekimab antibodies <i>o</i>		X						X		X
Pharmacodynamics										

Procedure (Part A and Part B)	Screening (4±1 weeks)	Interventional Treatment Period (12 weeks±3 days)							Follow-up Period (20 weeks±5 days)	
		Baseline						EOT/ETD ^{p, r}	Telephone visit	EOS
Visit	1	2	3	4	5	6	7	8	9	10
Week ^a	-4	0	2	4	6 ^a	8	10 ^a	12	18	32
Bronchoscopy (biopsy, bronchial brushing, bronchoabsorption [optional at country/site level]) ^{p, q}		X						X ^r		
Nasal brushing		X						X		

Abbreviations: β-HCG, beta human chorionic gonadotropin; AE, adverse event; ADA, antidrug antibody; aPTT, activated partial thromboplastin time; BD, bronchodilator; BP, blood pressure; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; ERS/ATS, European Respiratory Society and the American Thoracic Society; ETD, early treatment discontinuation; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; HCVAb, hepatitis C virus antibody; HIV, human immunodeficiency virus; IgM, immunoglobulin M; ██████████ IMP, investigational medicinal product; IRT, interactive response technology; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; MRI, magnetic resonance imaging; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, tuberculosis

- ^a The Screening Period has duration of 4 weeks (±1 week). The study Treatment Period has duration of 12 weeks. The study safety Follow-up Period has duration of 20 weeks. The study visits should occur on the planned dates (relative to the first injection of the IMP), as scheduled. The visit schedule should be adhered to within ±1 week for the Screening Period, ±3 days for the IMP Treatment Period and ±5 days for the visits during the Follow-up Period, unless otherwise specified. Visit 5 (Week 6) and Visit 7 (Week 10) are telephone visits.
- ^b Chest X-ray to be performed unless a < 6-month-old chest X-ray/chest CT scan/chest MRI scan is available. In case a chest X-ray is not feasible due to local regulations, a chest MRI scan will be performed.
- ^c Spirometry will be performed at clinical sites according to ERS/ATS 2005 guidance. Pre-BD spirometry will be performed during a washout period of bronchodilators according to their duration of action following the guidance of the ERS/ATS 2019 guideline. 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 ultra long-acting LABA (eg, vilanterol) or the last dose of LAMA should be withheld for at least 36 hours before spirometry is performed. The timing of washout 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. Spirometry results will be centrally read (refer to [Section 8.1.2.1](#)). No alcohol or caffeine should be consumed 8 hours prior to spirometry; 1 hour prior to spirometry the current smoker participant should refrain from smoking (refer to [Section 5.3.2](#)).
- ^d Inclusion criteria will be based on the CAT score (refer to Appendix 10; [Section 10.10](#)).
- ^e Home injection may be performed at Visit 5 (Week 6) and Visit 7 (Week 10). 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.
- ^f An eDiary will be used to record participant's answers to the Self-Reported Use of Cigarette (Current Smokers Only) and Controller Medication/Reliever Medications. This device will be dispensed at Screening (Visit 1) (including instructions for use) and recorded information will be downloaded from this device on indicated days. At the EOT Visit the eDiary data will be downloaded and the device will be returned to the site.

- g* Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Height (cm) will be measured and recorded at Screening (Visit 1) only. Body weight (kg) will be measured and recorded at Screening (Visit 1), Baseline (Visit 2), and the EOT and EOS Visits.
- h* Vital signs, including systolic and diastolic BP (mmHg), pulse rate (beats per minute), body temperature (°C), oxygen saturation level, and respiratory rate (breaths per minute) will be measured.
- i* Single 12-lead ECGs will be collected and centrally read. ECGs to be preferably performed prior to laboratory assessments and spirometry measurements in order to prevent the potential effect of albuterol/salbutamol or levalbuterol/levosalbutamol administration on ECG parameters.
- j* Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count with differential (including neutrophils and eosinophils), and complete red blood cell count. Serum biochemistry will include creatinine, blood urea nitrogen, glucose (fasting), lactate dehydrogenase, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, bicarbonate), CRP, and creatine phosphokinase. Coagulation panel will include INR, aPTT, and PT. Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen, and bilirubin; [REDACTED] If any urinalysis parameter on the dipstick test is abnormal, a urine sample must be sent to the central laboratory for quantitative measurement. If a urinalysis sample is abnormal for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory.
- k* 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 enrollment 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.
- l* TB assessment per local guidelines, or if not available, a blood sample for QuantiFERON® testing should be sent to the central laboratory.
- m* 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 Screening (Visit 1) and enrollment (Visit 2). In case of a positive urine test at any subsequent visits during the Treatment Period, 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.
- n* SARS-CoV-2 testing for active infection per local guidelines. If no local guidelines exist, then nasopharyngeal swabs and a reverse transcriptase polymerase chain reaction (RT-PCR) test should be performed to detect SARS-CoV-2 infection.
- o* Blood samples for measurement of PK, ADA, and [REDACTED] will be collected before the administration of IMP, when applicable. In the event of suspected treatment-related serious adverse events (SAEs), such as anaphylaxis or hypersensitivity, additional PK and ADA samples may be collected at or near the onset when possible.
- p* Bronchoscopy at Visit 2 (Week 0) should be performed prior to the first injection of IMP, and it may be performed up to 7 days prior to the first dose of IMP. In case bronchoscopy #1 is scheduled prior to Visit 2 (Week 0), prior to conducting the bronchoscopy #1 procedure in and exclusion criteria should be re-checked. Bronchoscopy at Week 12 may be performed 7 to 21 days after the last dose of IMP (Week 10), so between Week 11 and Week 13. The bronchoscopy procedure will collect endobronchial biopsies, bronchial brushings, and (when applicable) bronchoabsorption. The location of the biopsy should be annotated on the samples. Additional details will be provided in the procedural manual. [REDACTED]
[REDACTED]
[REDACTED]
- q* Nasal brushing should be performed on the same day as bronchoscopy, prior to the procedure. If unable to perform prior to bronchoscopy, use nostril opposite to one used for bronchoscopic approach.
- r* Patients who discontinue prematurely from the study (ie, early treatment discontinuation [ETD]), prior to completing the 12-week IMP treatment (eg, due to an adverse event or due to other reasons), will be evaluated as soon as possible at the individual participants' EOT/ETD Visit, using procedures as planned for the EOT/ETD Visit at Week 12 (Visit 8). If ETD occurs at Week 8 or later, the participant is encouraged to undergo a bronchoscopy at the ETD visit. If ETD occurs prior to Week 8, a bronchoscopy is not required. After the ETD visit, participants will proceed immediately to the 20 weeks Follow-up Period. See [Section 7.1](#) for more details.

2 INTRODUCTION

Itepekimab (also known as REGN3500 or SAR440340) is a human Ig G4P mAb that binds IL-33 with subnanomolar affinity and thereby inhibits IL-33 signaling. Itepekimab is under development as a potential novel treatment for COPD. A PoC study (ACT15104) in patients with moderate-to-severe COPD on controller therapy of LAMA, LABA, and/or ICS therapy demonstrated a clinically important and nominally significant effect in former smokers on the annualized rate of COPD exacerbations and improvement in pre-BD forced expiratory volume in 1 second (FEV1), but did not demonstrate efficacy in current smokers. The aim of this Phase 2a study is to evaluate the effect of itepekimab on airway gene expression in patients with COPD who are former and current smokers to establish a mechanistic rationale for this observed differential efficacy.

2.1 STUDY RATIONALE

Chronic obstructive pulmonary disease is a serious and life-threatening disease. It is a leading cause of death worldwide and responsible for over 3 million deaths worldwide in 2016 and 160 000 deaths in the US annually (1, 2, 3). Chronic obstructive pulmonary disease is characterized by progressive decline in lung function and recurrent exacerbations of symptoms. The latter results in rapid disease progression and is associated with increased mortality, particularly following exacerbations that require hospitalization (4). Although smoking cessation in patients with established COPD slows the rate of lung function decline and reduces the risk of hospitalization and mortality, former smokers with COPD are still at high risk for exacerbations, and substantial morbidity and the risk of mortality remain (5). Despite currently available therapies, which largely comprise bronchodilators with or without ICS, a significant unmet medical need remains, particularly on the key outcome of reducing the frequency of COPD exacerbations and hospitalization.

Interleukin-33 is a proinflammatory cytokine localized to the nuclei of a variety of cell types, including epithelial cells, endothelial cells, and fibroblasts (6). When epithelial cells are damaged by exposure to airborne allergens, viruses, cigarette smoke, or air pollutants, IL-33 is released locally and has been proposed to both initiate and to amplify innate and adaptive inflammatory pathways (7). Interleukin-33 binds to its cognate receptor, suppression of tumorigenicity 2 (ST2), and subsequently engages the interleukin-1 receptor accessory protein (IL-1RAcP) as a coreceptor to initiate signaling and activation of downstream inflammatory pathways characteristic of both type 1 and type 2 inflammation. Based on the proximal position of IL-33 to external inflammatory insults (ie, IL-33 is stored in epithelial cells), IL-33 may be a common inflammatory mediator in diseases featuring epithelial inflammation.

Accumulating clinical and nonclinical data implicate IL-33 in the pathogenesis of COPD. Interleukin-33 protein expression is increased in bronchial epithelial cells of patients with COPD compared with non-COPD controls and correlates with excess airway mucus production and mucin gene expression (8). Interleukin-33 protein expression in lung homogenates from patients with COPD correlates with COPD severity and is negatively correlated with FEV1 (9). Interleukin-33 levels in exhaled breath condensate, sputum, and serum of patients with COPD are

elevated compared with those from healthy nonsmokers and healthy smoker controls (10). Plasma IL-33 levels in patients with stable COPD are elevated compared to healthy controls and are associated with higher blood eosinophil counts and a higher prevalence of the chronic bronchitis phenotype (11).

Chronic exposure to cigarette smoke, pollutants, and airborne contaminants are the major drivers of the pathogenesis of COPD. Pharmacology studies have evaluated the impact of cigarette smoke on the IL-33 pathway. Cigarette smoke induces IL-33 protein expression in bronchial epithelial cells in mice (9) and humans (12). Pharmacology models have demonstrated that IL-33 expression in the lungs of mice exposed to house dust mite (HDM) extract remains elevated, even when allergen exposure is stopped for prolonged periods of time (13). These chronic in vivo models suggest that chronic insults to the lung induce IL-33 expression, and that this cytokine can persist even in the absence of the initial trigger. However, the role of IL-33 in patients with COPD and the modifying effect of cigarette smoking on this pathway in COPD are not understood.

Human genetic association studies to test the hypothesis that genetic variants in the IL-33 pathway were associated with COPD were recently performed (14). Data were analyzed from 2 independent studies (~100 000 subjects in the Geisinger Health System [GHS], including ~11 000 with COPD, and ~450 000 subjects in the UK Biobank, including ~11 000 with COPD). A rare IL-33 loss-of-function (LOF) variant, rs146597587, was associated with a reduced risk of COPD. Two common gain-of-function variants of IL-33 and its receptor, interleukin 1 receptor-like 1 (IL1RL1), were associated with an increased risk of COPD (15). These findings suggest a causal role for the IL-33 pathway in COPD pathogenesis.

Data from the PoC Study ACT15104, in which itepekimab was studied versus placebo in addition to approved SoC background therapy, provided preliminary clinical evidence that itepekimab has the potential to confer significant benefit beyond that provided by currently available therapies to patients with moderate-to-severe COPD who are former smokers. Study ACT15104 recruited participants with a smoking history of ≥ 10 pack-years, regardless of smoking status at screening. In the overall study population (including both former and current smokers), itepekimab reduced the risk of experiencing moderate-to-severe AECOPD compared to placebo by 19.2% over a Treatment Period of 24 to 52 weeks, although the difference did not reach statistical significance (rate ratio [RR]: 0.808, 95% confidence interval [CI] 0.613 to 1.065; $p=0.1296$). One of the prespecified subgroup analyses conducted in this study was by smoking status, where a clear effect was seen in former smokers.

This effect was consistent across a number of subgroups within the former smoker population, including subgroups by controller therapy (triple [ICS + LABA + LAMA] therapy or double [ICS + LABA, ICS + LAMA, or LABA + LAMA] therapy) and regardless of blood eosinophil level or COPD Assessment Test (CAT) score at baseline. Improvement in pre-BD FEV1 was also seen in former smokers overall and in the subgroup with baseline blood eosinophil counts ≥ 250 cells/ μL at baseline. These results contrast with the results in the current smoker population, where itepekimab did not demonstrate efficacy for any endpoint, including the rate of moderate-to-severe AECOPD

The objectives of the current study are to understand the biological effects of itepekimab in the airways of patients with COPD and to identify differences in the effects of itepekimab between former and current smokers. In order to evaluate this, the primary endpoint is the change in the itepekimab pharmacodynamics normalized enrichment score (NES) in endobronchial biopsies, bronchial brushings, and nasal brushings after treatment with itepekimab 300 mg Q2W SC from Baseline to Week 12.

2.2 BACKGROUND

Chronic obstructive pulmonary disease is a common, progressive lung disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities associated with an abnormal inflammatory immune response in the lung to noxious particles and gases (16). Chronic inflammation causes structural changes, narrowing of the small airways, destruction of the lung parenchyma, and reduced lung elastic recoil, resulting in progressive airflow obstruction. The main cause of COPD in the US is tobacco smoke exposure, but additional causes, such as air pollution, exposure to biomass fuel combustion, occupational exposures, and genetic susceptibility, contribute to the risk of COPD. Although significant heterogeneity exists in COPD, individual risk factors (apart from alpha-1 antitrypsin deficiency) have not been correlated with unique COPD phenotypes. The most common respiratory symptoms include chronic dyspnea, cough, and sputum production. Chronic obstructive pulmonary disease is characterized by exacerbations, which are typically caused by either viral or bacterial infections of the lungs that trigger an inflammatory response and tissue destruction. An increased exacerbation frequency has been associated with more rapid disease progression (measured by the rate of lung function decline over time). Exacerbations are associated with increased mortality, particularly following severe exacerbations (those that require hospitalization) (4). Medical comorbidities, such as cardiovascular disease, diabetes, lung cancer, skeletal muscle dysfunction, osteoporosis, mental health disorders, and metabolic syndrome, are common among patients with COPD and occur across the spectrum of disease severity (17).

The prevalence of COPD is projected to grow rapidly over the coming decades due to past and/or continued exposure to risk factors and an aging population, increasing the substantial economic and social burden of COPD (16, 18, 19). Based on the Burden of Obstructive Lung Diseases (BOLD) study and other epidemiological studies, it is estimated that there were 384 million cases of COPD globally in 2010 (16). In the US alone, there are approximately 16 million patients with COPD (2), of whom more than 38% are current smokers (20). Healthcare costs attributable to COPD increase with increasing disease severity; the annual costs attributable to COPD were \$32.1 billion in 2010 and were projected to increase to \$49 billion in 2020 (19, 21). Although smoking cessation in patients with established COPD slows the rate of decline of lung function and reduces the risks of hospitalization and mortality, former smokers with COPD are still at high risk for exacerbations, and substantial morbidity and the risk of mortality remain (5). In one study, former smokers had an exacerbation rate of 22.8 per 1000 person-years, as compared with 27.4 per 1000 person-years among current smokers (21). In addition, the results from the PoC study performed with itepekimab (ACT15104, presented herein) show a similar rate of exacerbations between former and current smokers who received placebo. This indicates a remaining high unmet need for additional therapies that reduce exacerbations, improve lung function, and improve symptoms in patients with COPD who are former smokers.

The greater efficacy of itepekimab in patients who are former smokers compared with that in current smokers observed in Study ACT15104 is not without precedent. Inhaled corticosteroid therapy has shown improved efficacy in the subset of patients with COPD who are former smokers compared with that of current smokers (22, 23, 24, 25). For example, the addition of ICS to LAMA + LABA was associated with a 30% reduction in exacerbations in former smokers compared with a 14% reduction in current smokers in the IMPACT study (22). The SUMMIT study found that ICS + LABA reduced exacerbations by 36% compared to placebo among former smokers and by only 19% compared to placebo among current smokers (24). A similar difference in the effect of ICS on FEV1 was also found in the SUMMIT study.

The lower efficacy of ICS in current smokers may be due to a blunting of the anti-inflammatory effects of ICS by cigarette smoke. For example, cigarette smoking has been shown to lead to corticosteroid resistance due to reduction of histone deacetylase 2 (HDAC2), an essential cofactor for glucocorticoid binding to their receptor (26, 27). These results are consistent with the fact that cigarette smoking is well known to lead to corticosteroid resistance in asthma and COPD (23, 26, 27). Alternatively, a more specific impact of cigarette smoke on IL-33 or IL-33 pathway gene transcription (eg, epigenetic modification) and/or on IL-33 protein activity, for example, through oxidation-driven inactivation, may be responsible (28). A definitive mechanistic understanding of the observed differential effect in current versus former smokers is lacking.

Previous studies with azithromycin have demonstrated efficacy in former smokers with COPD, but not in current smokers with COPD, and a recommendation for the use of azithromycin only in former smokers is included in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment guidelines (16, 29, 30). A secondary analysis of data from a large randomized long-term trial of macrolide therapy was conducted to identify subgroups that most effectively respond to long-term treatment with azithromycin; the reduction in exacerbation risk with azithromycin was strongest in former smokers, and azithromycin had relatively little effect in current smokers (29). The mechanisms underlying this finding are not well understood (31).

The intention of this study is to contribute to the understanding of the effect of itepekimab on airway inflammation in former smokers with COPD, and to assess differences in the effect of itepekimab on gene expression between former and current smokers with COPD.

2.3 BENEFIT/RISK ASSESSMENT

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

While there are no important identified risks, there are several important potential risks for those participants who will receive itepekimab (Table 1). In addition to these important potential risks, all participants in this study will undergo 2 bronchoscopy procedures that are beyond SoC procedures typically employed in the management of COPD. These procedures carry potential risks to participants enrolled in this study. However, these procedures are intended to provide biological samples that will be used to elucidate the mechanism of action of itepekimab, a first-in-class potential therapy for COPD. This information may help inform an understanding of the mechanism of action of itepekimab and may contribute to understanding differential clinical

results among subgroups. The sites chosen to conduct this study have previously conducted research-based bronchoscopy studies and will have both the technical experience and established safety protocols to safely conduct this study. Furthermore, bronchoscopy has been safely conducted in COPD patients (32). The Sponsor considers the benefit/risk for participants in this study to be acceptable for continued investigation.

2.3.1 Risk assessment

Itepekimab has been well tolerated in completed studies conducted thus far, including Phase 2 studies in patients with COPD, asthma, and atopic dermatitis. While there are no important identified risks, there are several important potential risks. In general, the administration of mAbs is associated with the important potential risk of systemic hypersensitivity reactions (including immunogenicity). Based upon the mechanism of action of itepekimab as an antagonist of IL-33, an epithelial cytokine that triggers downstream inflammatory pathways in the setting of epithelial damage, serious infections including opportunistic infections are considered an important potential risk. Potential risks for itepekimab will be managed in this clinical study through careful participant selection, close monitoring, and early recognition and treatment of AEs (Table 1).

Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of itepekimab on the fetus and newborn are unknown. Monoclonal antibodies can cross the placenta and may cause harm to the fetus. In cynomolgus monkeys, there were no effects on microscopic findings in male and female reproductive organs after 26 weeks of treatment with itepekimab and no effects on surrogate parameters of fertility. Risk minimization measures are in place within the study. Female participants who are lactating, breastfeeding or who are pregnant are excluded from the study. Women of childbearing potential (WOCBP; premenopausal female participants biologically capable of becoming pregnant) are only eligible for inclusion in the study if they employ one of the acceptable forms of highly effective contraception methods specified in this protocol (see Inclusion Criterion I 11).

Male contraception is not required in the study. Extremely low levels of itepekimab are expected to reach the fetus via seminal fluid. Monoclonal antibodies have physicochemical characteristics that limit their passive transmission through biological membranes. In order to reach the fetus, any therapeutic antibody present in seminal fluid would need to undergo vaginal absorption, which presents a significant barrier. Using the dose of itepekimab being tested in this study (300 mg Q2W SC), applying conservative assumptions (33, 34), and assuming that 100% of maternal exposure is transferred to the fetus, the highest potential exposure to a fetus of itepekimab through seminal transfer would be approximately [REDACTED]. This value is approximately [REDACTED] than the pharmacologically active concentration measured in vitro.

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

In Study ACT15102, which was a Phase 2A PoC study in asthma, itepekimab 300 mg SC Q2W monotherapy or coadministered with dupilumab 300 mg Q2W for 16 weeks was well tolerated in patients with moderate-to-severe asthma; the percentage of participants with at least 1 TEAE was well balanced across treatment groups (35). In Study ACT15104, which was a Phase 2A PoC study in COPD, itepekimab 300 mg SC Q2W for 24 to 52 weeks was well tolerated in similar population of patients with moderate-to-severe COPD; the percentage of participants with at least 1 treatment-emergent SAE was balanced across treatment groups: 29 (16.9%) participants in the itepekimab group and 36 (21.1%) participants in the placebo group. In Study R3500-AD-1798, itepekimab 300 mg SC Q2W monotherapy or coadministered with dupilumab 300 mg Q2W for up to 16 weeks was well tolerated in patients with moderate-to-severe atopic dermatitis; the percentage of participants with at least 1 TEAE was well balanced across treatment groups. In Study R3500-AD-1805, itepekimab 300 mg SC Q2W or 300 mg SC 4QW, or 100 mg SC Q4W, or 30 mg SC Q8W monotherapy for up to 16 weeks was well tolerated in patients with moderate-to-severe atopic dermatitis; the percentage of participants with at least 1 TEAE was well balanced across treatment groups. There was no itepekimab treatment-emergent antidrug antibody (ADA) response in any of the studies. The safety data and potential risks for itepekimab are also summarized in the IB.

Risk Assessment of Bronchoscopy

Although fiberoptic bronchoscopy with moderate sedation and analgesia (conscious sedation) is generally a safe procedure, there are risks to the patient undergoing bronchoscopy. The overall complication rate in adults undergoing bronchoscopy ranges between 0.8% to 2.2% (36, 37, 38). In a large retrospective study of about 20,000 patients, the rate of serious complications was 1.1% (39). In COPD patients, a study found that the incidence of complications requiring hospitalization was 2.0% (32). When complications occur, mild or minor complications occur more often. Sedative and analgesic medications can cause side effects, such as transient hypotension, hypoxemia, hypoventilation, nausea, and vomiting, which are largely dose related. Topical anesthetics applied to the oral and/or nasal cavity, larynx, and tracheobronchial tree can rarely cause seizures, arrhythmias, or methemoglobinemia if absorbed systemically after excessive topical dosing. Bronchoscopy can cause nasal discomfort and sore throat, and postprocedural low-grade fever and transient hypoxemia are common. Less common complications include bronchospasm, AECOPD, syncope, laryngeal edema or injury, airway injury, fractured equipment, pneumonia, and bacteremia. Endobronchial biopsy can lead to bleeding. Almost all bleeding episodes are mild and resolve spontaneously. Death related to bronchoscopy is rare (0.01 to 0.02%) (39, 40). The risks of bronchoscopy will be minimized by careful selection of participants, monitoring of participants during and after the procedure, judicious use of medications, selection of experienced bronchoscopists and research centers, and ensuring that safety equipment is available and safety protocols are followed. In addition, higher risk procedures, such as transbronchial biopsy and bronchoalveolar lavage, will not be performed as part of the study. The risks associated with bronchoabsorption (optional at site/country level) and bronchial brushing are considered low, since these assessments are not invasive.

The program will have an independent Data Monitoring Committee (DMC) that will review the benefit/risk for participants based on all the safety data from all studies on a regular basis. Risk minimization, monitoring, and management plans are in place and are outlined in the IB.

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s): Itepekimab		
Systemic hypersensitivity reactions, including events associated with immunogenicity	There were no preclinical findings suggestive of systemic hypersensitivity reactions. The occurrence of immunogenicity to itepekimab was low in preclinical models, 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 that received the 100 mg/kg IV dose (out of 48 monkeys that received itepekimab) 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 Study ACT15102, the incidence of systemic hypersensitivity AESIs was slightly higher in the itepekimab and itepekimab + dupilumab groups compared with that in the 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). Two PTs for systemic hypersensitivity which were considered by the Investigator as related to the IMP and therefore led to permanent treatment discontinuation as per-protocol requirement were rash pruritic in the itepekimab+dupilumab group and urticaria in the placebo group. These two participants recovered with permanent discontinuation of IMP and corrective treatment. All cases of systemic hypersensitivity AEs were mild or moderate in intensity and none were serious. All participants with systemic hypersensitivity AEs recovered. In Study ACT15104, the incidence of systemic hypersensitivity AESIs was [REDACTED] [REDACTED] [REDACTED] [REDACTED] All cases of systemic hypersensitivity AEs were moderate in intensity and none were serious. No PTs for hypersensitivity were considered by the Investigator as related to the IMP in ACT15104. None required discontinuation of IMP. All participants with systemic hypersensitivity AEs recovered.	Protocol exclusion criteria: Participants with a history of a systemic hypersensitivity reaction to a mAb or to itepekimab excipients. Monitoring: [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Serious infections, including opportunistic infections	There were no preclinical findings suggestive of infections. In Study ACT15102, SAEs of infection were similar between the 4 groups: 0 events in placebo, 1 event in 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 Study ACT15104, 19 participants with SAEs of infection were reported during the study: 10 in the placebo arm and 9 in the itepekimab arm. █ participant in the placebo arm and █ participants in the itepekimab arm experienced an opportunistic infection of herpes zoster. All cases were of mild-to-moderate intensity and led to protocol predefined permanent treatment discontinuation. Neither case was considered serious or related to IMP by the Investigator. Both events were resolved at the time of data cut-off. It is not yet known whether itepekimab will pose an additional risk for participants in the context of the current COVID-19 pandemic. There were no identified cases suggestive of SARS-CoV-2 infections in the ACT15104 study as the treatment period was completed prior to the onset of the COVID-19 pandemic. For the overall susceptibility for serious and/or opportunistic infection, refer to the relevant section in this table.	Protocol exclusion criteria: Participants with recent bacterial, protozoal, viral, or parasite infection requiring systemic treatment. Participants with active or latent TB, or participants with a history of TB or systemic fungal diseases. Participants will be screened for TB. Participants with HIV infection or HIV seropositivity at Screening (Visit 1). Participants with a positive hepatitis B surface antigen, surface antibody, or core antibody or hepatitis C antibody at Screening (Visit 1). Protocol exclusion criteria: Suspicion of, or confirmed, COVID-19 infection or in contact with a known exposure to COVID-19 at Screening (Visit 1) or during the Screening Period; known history of COVID-19 infection within 6 weeks before Screening (Visit 1); history of requiring mechanical ventilation or ECMO secondary to COVID-19 within 12 months before Screening (Visit 1); participants who have had a COVID-19 infection before Screening (Visit 1) who have not yet sufficiently recovered to participate in the rigors of a clinical trial. Monitoring and management: Inclusion only of participants who have received appropriate vaccination against SARS-CoV-2 according to local recommendations, administered a minimum of 1 week prior to Screening (Visit 1) (refer to Inclusion Criterion I 09) Participants will be monitored for any signs or symptoms of a SARS-CoV-2 infection and tested/treated as per local/international guidelines. Itepekimab <u>can</u> temporarily be withheld after a confirmed <u>symptomatic</u> SARS-CoV-2 infection based upon <u>clinical judgement</u>, and guidelines for resumption of

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		therapy must be followed as per clinical protocol. Participants must fully clinically recover from symptomatic SARS-CoV-2 infection before resumption of itepekimab (refer Exclusion Criterion E 21). Similar to all participants with COPD, it is important to minimize the risk of exposure of participants to SARS-CoV-2 at the site and, follow prevention and mitigation guidelines.
Study procedures		
Bronchoscopy	Bronchoscopy will be performed prior to treatment initiation and at the EOT to allow assessment of the effects of itepekimab within the lung and provide a mechanistic understanding of the response to itepekimab in patients with COPD. The risks of bronchoscopy include discomfort and coughing (which will be reduced through local anesthetics), wheezing (which can be reduced by premedication with a beta-agonist), low oxyhemoglobin saturation (which will be monitored and treated as needed during the procedure), minor bleeding, infection, and fever. COPD exacerbations may also be a complication of bronchoscopy.	Protocol exclusion criteria Comorbid disease that might interfere with the evaluation of IMP or conduct of study procedures (eg, bronchoscopy) or history of moderate or severe complications following bronchoscopy, as determined by the Investigator. Monitoring and management Bronchoscopies will be performed at experienced research centers with established standard operating procedures. Prior to the procedure, the Investigator will confirm patient suitability by evaluating the patient's current lung function (eg, FEV1), oxygen saturation and COPD disease control. In addition, prior to the procedure, the Investigator will perform assessments, such as coagulation tests and platelet counts, to confirm suitability, as well as any other assessments, such as a chest X-ray, at the Investigator's discretion. Patients will be monitored after the procedure for at least 1 hour to allow detection and treatment of any complications.
Other		
None		

Abbreviations: ADA, antidrug antibody; AESI, adverse event of special interest; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in 1 second; HIV, human immunodeficiency virus; IMP, investigational medicinal product; IV, intravenous; PT, preferred term; Q2W, every 2 weeks; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, tuberculosis

2.3.2 Benefit assessment

In Study ACT15104, in the overall population of patients with moderate-to-severe COPD, itepekimab 300 mg Q2W reduced the risk of experiencing moderate-to-severe AECOPD compared to placebo by 19.2% over a Treatment Period of 24 to 52 weeks, although the finding did not reach statistical significance (RR: 0.808, 95% CI 0.613 to 1.065; p=0.1296). One of the prespecified subgroup analyses conducted in this study was by smoking status, where a clear

effect was seen in former smokers. Itepekimab demonstrated an RRR in former smokers compared to placebo in moderate-to-severe AECOPD [REDACTED]

[REDACTED] This effect was consistent across a number of subgroups within the former smoker population, including subgroups by controller therapy (triple [ICS + LABA + LAMA] or double [ICS + LABA, ICS + LAMA, or LABA + LAMA] therapy) and regardless of blood eosinophil level or CAT score at baseline. Improvement in pre-BD FEV1 was also seen in former smokers overall and in the subgroup with a baseline blood eosinophil count ≥ 250 cells/ μ L. These results contrast with the results in the current smoker population, where itepekimab did not demonstrate efficacy for any endpoints, including the rate of moderate-to-severe AECOPD [REDACTED]

[REDACTED] The results of Study ACT15104 support continued evaluation of itepekimab as a potential agent for treatment of moderate-to-severe COPD in patients who are former smokers.

Two Phase 3 clinical trials in former smokers with COPD (Study EFC16750 and Study EFC16819) with 2 dose regimens of itepekimab (300 mg SC Q2W and 300 mg every 4 weeks [Q4W]), with the aim of confirming the PoC study results, are ongoing.

This mechanistic study with a single-dose regimen of itepekimab 300 mg SC Q2W provides an opportunity to evaluate the biological effects and safety of the investigational medicinal product (IMP) in former and current smokers with COPD.

2.3.3 Overall benefit: risk conclusion

Itepekimab is generally well tolerated based on the available clinical data, mechanism of action, and supportive nonclinical studies. Taken together, the data, along with the risk minimization and monitoring activities for all important potential risks established to date, indicate that the overall risk-benefit ratio is acceptable in this study aimed at understanding the biological effects of itepekimab in the airways of patients with COPD.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
Evaluate the difference in gene expression between former and current smokers with itepekimab treatment	- Change from baseline in itepekimab pharmacodynamic normalized enrichment score (NES) derived from former smokers in endobronchial biopsies in current smokers with COPD at Week 12 - Change from baseline in itepekimab pharmacodynamic NES derived from former smokers in bronchial brushings in current smokers with COPD at Week 12 - Change from baseline in itepekimab pharmacodynamic NES derived from former smokers in nasal brushings in current smokers with COPD at Week 12
Secondary	
- Evaluate the effect of itepekimab treatment on prespecified cell type-associated gene expression signatures in endobronchial biopsies from former and current smokers with COPD - Evaluate the effect of itepekimab on blood eosinophil counts in former and current smokers with COPD - Evaluate the safety and tolerability of itepekimab in former and current smokers with COPD - Evaluate immunogenicity to itepekimab in serum of former and current smokers with COPD - Evaluate the PK profile of itepekimab in serum in former and current smokers with COPD	- Change from baseline in IL-33 treated eosinophil-associated NES in endobronchial biopsies at Week 12 - Change from baseline in IL-33 treated mast cell-associated NES in endobronchial biopsies at Week 12 - Change from baseline in blood eosinophil count at Week 12 - Incidence of TEAEs, AESIs, SAEs, and AEs leading to permanent treatment discontinuation - Incidence of potentially clinically significant abnormalities in clinical laboratory tests, vital signs and ECG abnormalities in the treatment-emergent period - Incidence of treatment-emergent anti-itepekimab antibody responses throughout the study - Functional itepekimab concentrations in serum from baseline to end of study
Exploratory	
██ ██ ██ ████████	██ ██ ██ ██ ██ ██

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Abbreviations: AE: adverse event; AESI: adverse event of special interest; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; FEV1: forced expiratory volume in 1 second; IL-33: interleukin-33; MUC5AC: mucin 5AC; NES: normalized enrichment score; NK cells: natural killer cells; PK: pharmacokinetics; RNA: ribonucleic acid; SAE: serious adverse event; ST2: suppression of tumorigenicity 2; TEAE: treatment-emergent adverse event; TSLP: thymic stromal lymphopoietin

Each of the PD and safety assessments chosen for use in this study are considered well established and relevant for gene expression studies. In this study, gene expression analyses will be performed through RNA sequencing (RNA-Seq). RNA-Seq allows for evaluation of the entire transcriptome and the development of a gene expression signature.

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4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is an exploratory, two-part, 12-week, Phase 2a study to evaluate the mechanism of action of itepekimab (anti-IL-33-mAb) and its impact on airway inflammation in participants with COPD. The study will include participants with COPD who are former and current smokers, aged 40 to 70 years.

The total study duration for each part (Part A and Part B) is approximately 36 weeks:

- 4-week Screening Period
- 12-week Treatment Period²
- 20-week Follow-up Period

Additional details of the study duration may be found in the SoA ([Section 1.3](#)). Part A and Part B represent analysis cohorts, but enrollment in either participant cohort is planned as concurrent.

Part A will consist of up to approximately 25 participants with COPD who are former smokers receiving established background monotherapy (LAMA or LABA), double therapy (ICS+LABA, ICS+LAMA, or LAMA+LABA), or triple therapy (ICS + LABA + LAMA), while Part B will consist of up to approximately 25 participants who are current smokers with COPD receiving established background monotherapy, double therapy, or triple therapy.

For Part A and Part B, the primary endpoints are the change from baseline in itepekimab treatment NES in endobronchial biopsies, bronchial brushings, and nasal brushings from former and current smokers with COPD after 12 weeks of treatment with itepekimab, as assessed in participants who complete both the Baseline and Week 12 bronchoscopy with adequate RNA quality (see [Section 9](#) for statistical details). Study treatment for both Part A and Part B will be itepekimab 300 mg Q2W administered SC during the 12-week Treatment Period. Detailed instructions for sample collection and handling are provided in the PDY16967 procedural manual that will be provided to the study sites.

Participants must have been on a SoC controller therapy for COPD for at least 3 months prior to Screening (Visit 1) with stable dose and regimen of controller therapy for ≥ 1 month prior to Screening (Visit 1) and during the Screening Period. Participants must stay on their established controller medications for COPD throughout the duration of the study, with the exception of systemic corticosteroids and/or antibiotics used for AECOPD (see [Section 6.8](#) for concomitant medications).

Participants in both Part A and Part B are expected to undergo 2 bronchoscopy procedures that will include endobronchial biopsies, bronchial brushings, and (when applicable) bronchoabsorption:

- Bronchoscopy #1: To be conducted at Week 0 (or up to 7 days prior to Week 0)
- Bronchoscopy #2: To be conducted at Week 12 (± 7 days)

In addition to the bronchoscopy procedures, participants will undergo nasal brushings at Week 0 (Baseline/Visit 2) and Week 12 (End-of-Treatment/Visit 8).

Participants experiencing an [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Based on the results of ACT15104, itepekimab is proposed to reduce the annualized rate of AECOPD and increase pre-BD FEV1 in former smoker participants with COPD by inhibiting the IL-33 signaling pathway. This cytokine is hypothesized to have a role in COPD based primarily on the observation that IL-33 levels are elevated in serum, sputum and bronchial biopsies of participants with COPD (8, 9, 41, 42, 43). Furthermore, tobacco smoke has been reported to promote intracellular accumulation of IL-33, although smoking is not an active inducer of IL-33 release (9). Gene expression differences in COPD compared to healthy volunteers have been reported to be impacted by smoking or smoking status (44) and so have differences in IL-33 expression (43).

In this study, gene expression analyses will be performed through RNA-Seq. A signature of the effect of itepekimab on the airway of former smokers participants with COPD will be developed from these analyses. This population of former smokers with COPD was chosen for the development of the signature due to the substantial clinical response to itepekimab treatment in ACT15104 (Section 2.3.2). As COPD is a heterogeneous syndrome with multiple phenotypes and evolving endotypes (16), developing a gene expression signature may be important in understanding and predicting the differential clinical effect of itepekimab in various COPD participant subpopulations. In the case of this study, an analysis of gene expression differences will be performed on the contrasting subpopulations of former smokers and current smokers.

The objective of developing a gene expression signature will be achieved using endobronchial biopsies collected during bronchoscopy. This compartment is highly relevant in COPD and, as stated above, studies have shown increased IL-33 expression in these tissues. To build upon the understanding of the mechanism of action of itepekimab in participants with COPD, we will also assess gene expression changes by bronchial brushings, nasal brushings, and in peripheral blood. This evaluation of gene expression across compartments can reveal common and differential

pathways (45). Furthermore, simultaneous evaluation of bronchial and nasal brushings may provide insights as to whether nasal brushings can be used as a proxy for invasive procedures in the future. The correlation of nasal and bronchial brushings has been previously studied in the context of smoking-related gene expression in non-COPD studies participants (46). Ultimately, the findings of the correlation between these two compartments will help to advance the identification of itepekimab-responsive populations using non-invasive methods.

4.2.1 Participant input into design

A participant input meeting took place in May 2021. During these interactions, the design and endpoints were discussed with a group of patients from the US COPD Foundation. Participants at the meeting advocated for a higher upper age limit at inclusion. This has been taken into consideration but eventually the upper age limit at inclusion was not changed due to the higher risk of comorbidities associated with advanced age and higher risk of complications during bronchoscopy, which both might negatively affect the benefit-risk ratio of the 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 patients with moderate-to-severe asthma (Study ACT15102 [35]; itepekimab 300 mg Q2W [N=73], itepekimab Q2W + dupilumab Q2W [N=74]) and for 24 to 52 weeks in patients with moderate-to-severe COPD (Study ACT15104; N=172 [14]). Itepekimab dose regimens of 300 mg SC Q2W and Q4W are being studied in ongoing Phase 3 studies (EFC16750 and EFC16819) of patients with moderate-to-severe COPD who are former smokers, the primary population; one ongoing Phase 3 study (EFC16819) also includes a secondary population of current smokers receiving itepekimab 300 mg SC Q2W.

The itepekimab PK profile in healthy subjects, participants with asthma, and participants with COPD is described by a 2-compartment population 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] 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, a dosing regimen of itepekimab 300 mg Q2W was selected for evaluation in Phase 2 and 3 studies. In Study ACT15104, itepekimab 300 mg SC Q2W provided substantial efficacy in patients with COPD who were former smokers but not current smokers. Use of the 300 mg SC Q2W regimen in this study is intended to confirm these previous results and provide further mechanistic insight into differential effects in these populations.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last scheduled procedure shown in the SoA ([Section 1.3](#)) for the last participant in the trial globally.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit/last contact (EOS/Visit 10), withdrawn from the study, or is lost to Follow-up (ie, the study patient can no longer be contacted by the Investigator).

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 40 to 70 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

- I 02. Participants with a physician diagnosis of COPD for at least 1 year (based on the GOLD definition [16]).
- I 03. Participants with a smoking history of ≥ 10 pack-years
- For former smokers: Participants who report that they are not currently smoking, and smoking cessation must have occurred ≥ 6 months prior to Screening (Visit 1) with an intention to quit permanently. Note: [REDACTED]. Please see E 02.
 - For current smokers (not eligible for Part A): Participants who report that they are currently smoking tobacco (participant smoked at least 5 cigarettes per day on average during the past 7 days) at Screening (Visit 1) and at Baseline, and who are not currently participating in, or planning to initiate, a smoking cessation intervention at Screening (Visit 1) or during the Screening Period.
- [REDACTED]
- [REDACTED]
- [REDACTED]

- I 06. Participant-reported history of signs and symptoms of chronic bronchitis (chronic productive cough for at least 3 months in the year before screening in a participant in whom other causes of chronic cough [eg, inadequately treated gastroesophageal reflux or chronic rhinosinusitis; or clinical diagnosis of bronchiectasis] have been excluded).
- I 07. Participants with a documented or self-reported history of exacerbation having had ≥ 1 moderate or severe exacerbation within the 5 years prior to Screening (Visit 1), with at least 1 exacerbation treated with systemic corticosteroids:
- Moderate exacerbations are defined as an acute worsening of respiratory symptoms that requires either systemic corticosteroids (intramuscular [IM], intravenous [IV], or oral) and/or antibiotics.

- Severe exacerbations are defined as AECOPD that require hospitalization or observation for >24 hours in emergency department/urgent care facility.
- I 08. Participants treated with SoC controller therapy for ≥ 3 months before Screening (Visit 1) and at a stable dose and regimen of controller therapy for at least 1 month before the Screening (Visit 1) AND during the Screening Period, including either:
- Triple therapy: LAMA + LABA + ICS
OR
 - Double therapy: ICS + LABA or LABA + LAMA or ICS + LAMA.
OR
 - Monotherapy: LABA or LAMA
- I 09. Participants who have received appropriate vaccination according to local recommendations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), administered a minimum of 1 week prior to Screening (Visit 1) (see Concomitant Therapy, [Section 6.8](#)).

Weight

- I 10. Body mass index (BMI) $\geq 18 \text{ kg/m}^2$

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

- I 11. All participants

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

a) Male participants

No contraceptive measures required for this study.

b) Female participants

Contraceptive use by WOCBP should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP

OR

- A WOCBP who agrees to follow the contraceptive guidance during the intervention period and for at least 20 weeks after the last dose of study intervention.

Informed Consent

- I 12. Provides signed informed consent as described in the protocol, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

- E 01. Participants with a current diagnosis or previously confirmed diagnosis of asthma according to the Global Initiative for Asthma (GINA) guidelines (47) unless asthma resolved before 18 years of age and has not recurred.
- E 02. For former smokers (Part A): Active smoking or vaping of any products (eg, nicotine, tetrahydrocannabinol [THC]) within 6 months prior to Screening (Visit 1) or during the Screening Period. [REDACTED]

For current smokers (Part B): vaping of any products (eg, nicotine, THC) within 6 months prior to Screening (Visit 1) or during the screening period.

- E 03. Participants who are expected to be regularly exposed to environmental (ie, “second hand”) tobacco smoke in an indoor setting during the Screening or Treatment Periods.
- E 04. Participants with a clinically significant new abnormal electrocardiogram (ECG) within 6 months before or at Screening (Visit 1) that may affect the participant’s participation in the study in the judgment of the Investigator.
- E 05. Participants with clinically significant and current pulmonary disease other than COPD, eg, sarcoidosis, interstitial lung disease, bronchiectasis (clinical diagnosis), diagnosis of α -1 anti-trypsin deficiency, or another diagnosed pulmonary disease.
- E 06. Participants with a diagnosis of cor pulmonale, evidence of right cardiac failure, or moderate-to-severe pulmonary hypertension.
- E 07. Participants who require more than 2 L/min of long-term treatment with oxygen at rest. Participants who use up to 4L/min of supplemental oxygen during exercise may enroll. Oxygen during sleep is allowed.
- E 08. Participants with hypercapnia that requires bi-level positive airway pressure (BiPAP).

- E 09. Participants with moderate or severe exacerbation of COPD (AECOPD, as defined in I 07) within 8 weeks prior to Screening (Visit 1) or during the Screening Period.
- E 10. Participants with a prior history of pneumonectomy, lobectomy, segmentectomy, or therapeutic bronchoscopy procedure (including bronchoscopic volume reduction).
Note: Prior history of surgical lung biopsy or wedge resection are not exclusion criteria.
- E 11. Participants with any surgery or major procedures (including those requiring conscious sedation) planned to occur during the study. Minor skin procedures are allowed.
- E 12. Participants with a history of clinically significant renal, hepatic, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, or other significant medical illness or disorder, which in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. A specific example includes, but is not limited to, poorly controlled insulin-dependent diabetes.
- E 13. Participants with unstable ischemic heart disease, including acute myocardial infarction within 1 year before Screening (Visit 1), or unstable angina within 6 months before Screening (Visit 1) or during the Screening Period.
- E 14. Participants with cardiac arrhythmias, including paroxysmal (eg, intermittent) atrial fibrillation, are excluded. Participants with isolated premature ventricular contractions (PVCs) or premature atrial contractions (PACs) may be considered for inclusion.
- E 15. Participants with cardiomyopathy, as defined by Stage III-IV (New York Heart Association) cardiac failure, or other relevant cardiovascular disorder that may affect the participant's participation in the study in the judgment of the Investigator.
- E 16. Participants with any underlying disease requiring the use of prophylaxis for endocarditis.
- E 17. Participants with uncontrolled hypertension (ie, systolic blood pressure [BP] >180 mm Hg or diastolic BP >110 mm Hg with or without use of antihypertensive therapy).
- E 18. Participants with active tuberculosis (TB), latent TB, a history of incompletely treated TB, suspected extrapulmonary TB infection (TBI), or who are at high risk of contracting TB (such as close contact with individuals with active or latent TB) or received Bacillus Calmette Guérin (BCG)-vaccination within 12 weeks before Screening (Visit 1).

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

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

AND

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

AND

- For whom review and approval for eligibility have been granted by the Sponsor

- E 19. Participants with a history of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at Screening (Visit 1).

[REDACTED]

- E 21. Participants with a suspicion of, or confirmed, coronavirus disease 2019 (COVID-19) infection or contact with known exposure to COVID-19 at Screening (Visit 1) or during the Screening Period; known history of COVID-19 infection within 6 weeks before Screening (Visit 1); history of requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) secondary to COVID-19 within 12 months before Screening (Visit 1); participants who have had a COVID-19 infection before Screening (Visit 1) who have not yet sufficiently recovered to participate in the procedures of a clinical trial.

[REDACTED]

- E 23. Participants with evidence of acute or chronic infection requiring systemic treatment with antibacterial, antiviral, antifungal, antiparasitic, or antiprotozoal medications within 6 weeks before Screening (Visit 1) or during the Screening Period, significant viral infections within 6 weeks before Screening (Visit 1) or during the Screening Period that may not have been treated with antiviral treatment (eg, influenza receiving only symptomatic treatment).

- E 24. Participants with active autoimmune disease or participants taking immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis).

- E 25. Participants with a 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.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- E 29. Current unstable liver or biliary disease per Investigator assessment defined, eg, by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.
NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria.

- E 30. Symptomatic herpes zoster within 3 months prior to screening

Prior/concomitant therapy

- E 31. Participants with previous use of itepekimab.
- E 32. Participants who have received live attenuated vaccine(s) within 4 weeks before Screening (Visit 1) or plans to receive such vaccines during the study are excluded (see Appendix 14 [[Section 10.14](#)]).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Prior/concurrent clinical study experience

E 38. Active participation in another interventional study or previous enrollment in this study.

Diagnostic assessments

E 39. Participants with comorbid disease that might interfere with the evaluation of IMP or conduct of study procedures (eg, bronchoscopy) or history of moderate or severe complications following bronchoscopy, as determined by the Investigator.

Other exclusions

E 40. Participants who are accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 41. Any country-related specific regulation that would prevent the participant from entering the study - see the protocol (country-specific requirements; Appendix 8 [[Section 10.8](#)]).

E 42. Participants not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 43. Participants who are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation [ICH]-Good Clinical Practice [GCP] Ordinance E6).

- E 44. Participants with any specific situation during study implementation/course that may raise ethics considerations.
- E 45. Participants with a 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 46. Known history of alcohol or substance abuse, that in the opinion of the Investigator, would pose a risk to the patient or the study.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.3.1 Meals and dietary restrictions

Not applicable.

5.3.2 Caffeine, alcohol, and tobacco

[REDACTED]

Current smokers are participants who report that they are actively smoking tobacco (participant smoked at least 5 cigarette per day on average during the past 7 days) at Screening (Visit 1) and at Baseline, and who are not currently participating in, or planning, to initiate a smoking cessation intervention at Screening (Visit 1) or during the Screening Period. One hour prior to spirometry the current smoker participant should refrain from smoking. Current smokers will also be asked to refrain from smoking 6 hours prior to bronchoscopy.

For all study participants, vaping is not allowed from 6 months prior to Screening (Visit 1) or during the study.

Use of alcohol and caffeine is allowed. However, 8 hours prior to spirometry, no alcohol or caffeine should be consumed (for details, refer to [Section 8.1.2.1](#)).

5.3.3 Activity

Not applicable.

5.4 SCREEN FAILURES

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

Participants who are eligible for rescreening may be rescreened once for any reason except for failing to meet I 04 (spirometry), which will lead to screen failure. Participants who fail any of the other inclusion or meet any exclusion criteria may be rescreened during the open Screening Period of the study; a different participant identification number will be issued. There is no requirement for a waiting period between the screen failure date and the rescreen.

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

If certain dynamic laboratory tests do not meet the inclusion criteria at Screening (Visit 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 (Visit 2). There is no need to screen fail such participants if the test finally meets the inclusion criteria.

Part A will consist of up to approximately 25 participants who are former smokers with COPD. Part B will consist of up to approximately 25 participants who are current smokers with COPD. A maximum of 50% of the planned enrollment in each cohort (Part A former smokers and Part B current smokers) will have a post-bronchodilator [REDACTED] of the predicted value at screening.

In addition to the spirometry, [REDACTED] and controller therapy requirements, participants are required to have appropriate vaccination according to local recommendations against SARS-CoV-2 at least 1 week prior to Screening (Visit 1). Participants completing vaccination regimen in less than 1 week prior to Screening (Visit 1) will be screen failed. All the tests out of the protocol window should be repeated and entered to the appropriate eCRF pages.

5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING OR ENROLLMENT/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9): should be considered for screening/enrollment/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

All study participants will receive itepekimab 300 mg Q2W SC. The IMP is to be administered every 14 ± 3 days (Q2W) (up to 6 doses) during the 12-week Treatment Period ([Table 3](#)). Administration will start at Baseline/Visit 2 and will continue every 14 ± 3 days until Visit 7/Week 10. Each prefilled syringe contains a deliverable volume of 2 mL with an itepekimab concentration of 150 mg/mL.

The IMP will be administered by the Investigator/health care professional or designee following clinic procedures and blood collection. [REDACTED]

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

[REDACTED]

[REDACTED] 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, a paper diary will be provided to record information related to the injections. The diary will be kept as source data in the participant's study file. For home injections with scheduled telephone contacts as per the SoA ([Section 1.3](#)), the site should verify the IMP compliance/administrations with the participant and at next on-site visit check the completed diary.

Table 3 - Overview of study interventions administered

Intervention label	Itepekimab 300 mg SC Q2W
Intervention name	Itepekimab
Type	Drug
Dose formulation	Prefilled syringe
Unit dose strength(s)	150 mg/mL
Dosage level(s)	300 mg Q2W
Route of administration	SC Injection
Use	experimental
IMP or NIMP	IMP
Packaging and labeling	Study intervention will be provided in prefilled syringes. Each prefilled syringe will be labeled as required per country requirement.
Current/Former name(s)	Itepekimab/ SAR440340/REGN3500

Abbreviations: IMP, investigational medicinal product; NIMP, non-investigational medicinal product; Q2W, every 2 weeks; SC, subcutaneous

The IMP may be supplied at the site or from the PI/site/Sponsor to the participant 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](#)).

Non-investigational medicinal products(s)

Participants must continue their established controller therapy. The Sponsor will not supply such controller and reliever medications during this trial. Participants must continue the controller therapy regimen and continue to use the same dose (see [Section 6.5.1](#)).

- Formulation: DPI, MDI, nebulizer
- Route(s) of administration: oral inhalation for LAMA, LABA, ICS + LABA, ICS + LAMA, LABA + LAMA or ICS + LABA + LAMA
- Dose regimen: As per prescribed at the same time of the day during the study

For other information related to COPD controller therapy, including safety precautions, please consult locally approved labels for the products.

Reliever medication

Participants may administer SABA and/or SAMA, such as, but not limited to, albuterol/salbutamol, levalbuterol/levosalbutamol, ipratropium, or ipratropium/albuterol, as reliever medication as needed during the study.

- Formulation: DPI, MDI, nebulizer
- Route(s) of administration: oral inhalation, nebulization

- Dose regimen: As needed, per prescribed

For other information related to COPD reliever medications, including safety precautions, please consult the prescription labels for the products. The Sponsor will not supply reliever medications during this trial.

6.1.1 Devices

Medical devices for therapeutic interventions will not be supplied for this study. Medical devices for diagnostic interventions (eg, spirometry, ECG, biopsy forceps) are not considered as “medical devices” 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 may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

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

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient [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. For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 ([Section 10.9](#)).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open-label study. There is no randomization or blinding.

6.4 STUDY INTERVENTION COMPLIANCE

The specific intervention to be taken by a participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the enrollment status on the applicable case report form, if required. 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 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 administering the study intervention. During scheduled telephone contacts as per SoA, the site should verify the IMP compliance/administrations with the participant and at next on-site visit check the completed eCRF.

6.5 DOSE MODIFICATION

No dose modification or interval modification is allowed for IMP. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.5.1 Reliever medicine

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

Participants may administer SABA or SAMA, such as, but not limited to, albuterol/salbutamol, levalbuterol/levosalbutamol, ipratropium, or ipratropium/albuterol as reliever medication as needed during the study.

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

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

Table 4 - Conversion of [REDACTED]

[REDACTED]

[illegible]

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.

6.7 TREATMENT OF OVERDOSE

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

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

1. Contact the Sponsor immediately
2. Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 20 weeks after last dose)
4. 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 (determined on a case-by-case basis)
5. Document appropriately in the case report form (CRF)

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.

6.8 PRIOR AND CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the following details:

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

The following treatments are not permitted during the Screening and Treatment Periods:

██

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will have an early treatment discontinuation (ETD) visit with all assessments planned for the Week 12/EOT Visit and enter the 20-week Follow-up Period. See the SoA ([Section 1.3](#)) 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. Participants with early treatment discontinuation at Week 8 or later are encouraged to undergo bronchoscopy. Participants discontinuing prior to Week 8 will not be required to undergo bronchoscopy. After the ETD visit, the patient will proceed immediately to the 20 weeks Follow-up Period.

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 13 [[Section 10.13](#)]).
- Diagnosis of a malignancy during study, excluding squamous or basal cell carcinoma of the skin

- Any situation that meets definitive discontinuation rule as outlined in Appendix 6 ([Section 10.6](#)).
- Any opportunistic infection, [REDACTED]
- Serum alanine aminotransferase (ALT) $>3 \times$ ULN and total bilirubin >2 ULN (see Appendix 6 [[Section 10.6](#)]).
- Serum ALT $>5 \times$ ULN if baseline ALT $\leq 2 \times$ ULN or ALT $>8 \times$ ULN if baseline ALT $>2 \times$ ULN (see Appendix 6 [[Section 10.6](#)]).

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

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

Handling of participants after permanent intervention discontinuation

Participants will have an early treatment discontinuation visit with all assessments planned for the Week 12/EOT Visit and then immediately enter the 20-week Follow-up Period 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.

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

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic and participate in Follow-up assessments according to the visit schedule described in the Follow-up Period. The Follow-up Period will start at Week 12 for patients who complete the IMP Treatment Period and may start earlier than Week 12 for patients who discontinue IMP prior to 12 weeks of treatment.

7.1.2 Liver chemistry stopping criteria

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

7.1.3 Temporary discontinuation

Temporary intervention 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 or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9]). For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.4 Rechallenge

Reinitiation of intervention with the IMP after a potential allergic reaction will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1.1 and Appendix 13 [Section 10.13]).

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

7.1.4.1 Study intervention restart or rechallenge after liver stopping criteria met

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

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted with all assessments planned for the Week 12/EOT Visit, as shown in the SoA (Section 1.3). 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 for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will have an early treatment discontinuation visit with all assessments planned for the Week 12/EOT Visit and enter the 20-week Follow-up Period.

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

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

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

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

7.3 LOST TO FOLLOW UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- If a participant continues to be unreachable and has been withdrawn from the study, the site should continue to try to obtain a vital status update (death) via available resources, if possible

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

[REDACTED]

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

[REDACTED]

[REDACTED]

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 ([Section 10.9](#)).

8.1 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]
[REDACTED]

[REDACTED]

Table 7 - [REDACTED]

[REDACTED]

8.1.1 Other biomarker research

Collection of samples for other biomarker research is also part of this study.

- Total IL-33 will be measured with a quantitative immunoassay.

An optional collection of serum/plasma samples that will be archived for other biomarker research is also part of this study.

- The archived samples may be used for research purposes related to respiratory diseases such as COPD or inflammatory diseases (eg, exploratory biomarkers of disease or drug effect), IL-33 and pathway biology, additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol.

[REDACTED]

- Samples may be stored for a maximum of 25 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis.

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

8.1.2 Disease-specific measures

8.1.2.1 Spirometry

Spirometry at clinical site visits should be performed in accordance with the European Respiratory Society/American Thoracic Society (ERS/ATS) 2005 guidelines and prior to administration of investigational product (48).

[REDACTED] spirometry will be performed after a washout period of BDs according to their action duration following the guidance of the ERS/ATS 2019 guideline (51). 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 (E 02) and resuming smoking is strongly discouraged

- Consuming intoxicants within 8 hours before testing (to avoid problems with coordination, comprehension, and physical ability)
- Performing vigorous exercise within 1 hour before testing (to avoid potential exercise induced bronchoconstriction)
- Wearing clothing that substantially restricts full chest and abdominal expansion (to avoid external restrictions on lung function)
- At least 3 measurements fulfilling the ERS/ATS acceptability and repeatability criteria should be obtained at every visit, if possible. In very rare cases it can happen that a participant is already enrolled into the study after immediate results of spirometry, and later an alert notification is received mentioning that the inclusion criteria on [REDACTED] was not met (after manual central reading by a vendor registered respiratory therapist). In that case, these participants do not have to be withdrawn from the study and do not have to stop study treatment.

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

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in [Section 8.3](#).

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

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the skin, nasal cavities, eyes, ears, cardiovascular, respiratory, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses and pay special attention to signs or symptoms of infection or malignancy.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

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

8.2.3 Electrocardiograms

- Single 12-lead ECG 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 meets the definition of an AE ([Section 8.2.5](#)) the Investigator will continue to monitor the participant with additional ECGs until the ECG findings return to baseline ECG findings or the Investigator determines that follow-up is no longer necessary.
- Any clinically significant ECG related to a pre-existing condition at Screening (Visit 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.
- In addition, all ECGs will be reviewed by a central reader (cardiologist). In case of potential conflicts with regard to eligibility, or safety concerns, the site and the Sponsor will be notified.
- Further details related to ECG, including alert criteria, will be provided in a separate Manual, which will be provided by the vendor.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 ([Section 10.2](#)) for the list of clinical laboratory tests to be performed and to the SoA ([Section 1.3](#)) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 20 weeks 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.
- 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 samples 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 8](#).

Table 8 - 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	Test for HBV DNA
(with or without HBsAb positive)	If HBV DNA Positive: Excluded

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; IgM, immunoglobulin M

8.2.5 Pregnancy testing

Pregnancy testing will be performed in all WOCBP at screening with a blood test using a central laboratory, and at all subsequent clinic visits using Sponsor-provided urine tests. Pregnancy urine test will be performed at the visits specified in SoA ([Section 1.3](#)). The outcome will be recorded. In case of a positive urine test at any subsequent visits during the Treatment Period, the study treatment will be withheld and a serum pregnancy test performed as soon as possible to confirm the pregnancy.

- At the screening and baseline, the Investigator is responsible for review of medical history, menstrual history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an early undetected pregnancy.
- Pregnancy testing (urine [baseline] or serum [screening]) should be conducted at the planned day of the screening and baseline (prior to itepekimab administration) visit.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3 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 8.3.8](#).

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

AE 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 all AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention and procedure (see [Section 7](#)).

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](#)).

8.3.1 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 Follow-up visit at the time points 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 he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs, and AEs of special interest (as defined in [Section 8.3.8](#)), will be followed until resolution, stabilization, the

event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 7.3](#)). Further information on Follow-up procedures is provided in Appendix 3 ([Section 10.3](#)).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of 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.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 20 weeks after last dose of IMP.
- If a pregnancy is reported, the Investigator 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 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 8.3.4](#). While the Investigator is not obligated to actively seek this information in former study participants/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.

8.3.6 Death events

The program will have an independent DMC that will review all death events during the study. The independent DMC will review benefit/risk for participants based on all the safety data from all studies on a regular basis. Risk minimization, monitoring, and management plans are in place and are outlined in the IB.

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

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

Any COPD exacerbations are disease-related events that are common in participants with moderate-to-severe COPD and they will not be reported according to the standard process for reporting of AEs unless the event meets the definition of a SAE. NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a disease-related event):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

Once the Investigator has become aware of any COPD exacerbation events, they will record details of the events on the corresponding exacerbation page in the eCRF only if the events meet AECOPD definition of moderate-or-severe AECOPD.

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

8.3.8 Adverse event of special interest

Adverse event 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 of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP;
 - 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 (NIMP)
 - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose during an interval of <8 days.
 - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the maximum prescribed daily dose, within the intended therapeutic interval.
- Significant ALT elevation
 - $ALT > 3 \times \text{the ULN}$ associated with total bilirubin $> 2 \times \text{ULN}$;
OR
 - $ALT > 5 \times \text{the ULN}$ if baseline $ALT \leq 2 \times \text{ULN}$;
 - $ALT > 8 \times \text{ULN}$ if baseline $ALT > 2 \times \text{ULN}$
- 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

- Malignancy
- Other project specific AESI(s)
 - Anaphylactic reactions or systemic allergic reactions that require treatment (see Appendix 13 [[Section 10.13](#)])
 - 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: AE intensity should be reported as “severe” if ISR is reported as “severe ISR AESI”

8.3.9 Guidelines for reporting product complaints

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

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

8.4 PHARMACOKINETICS

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

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

Table 9 - Summary of bioanalytical methods for PK samples

Analyte	PK (itepekimab)
Matrix	
Analytical technique	
Site of bioanalysis	

PK: pharmacokinetic(s).

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

An unscheduled systemic drug concentration page in the eCRF must be completed as well.

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

8.5 PHARMACOGENETICS/PHARMACOGENOMICS

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

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

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

8.6 BIOMARKERS

Collection of samples for other biomarker research is also part of this study. Refer to [Section 8.1](#) for detailed information about biomarker assessments and type of samples to be collected. Samples for biomarker research will be collected from all participants in this study as specified in the SoA ([Section 1.3](#)).

8.7 IMMUNOGENICITY ASSESSMENTS

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

The bioanalytical method for ADA is summarized in [Table 10](#).

Table 10 - Summary of bioanalytical methods for ADAs

Analyte	ADA
Matrix	
Analytical technique	
Site of bioanalysis	

ADA = antidrug antibody; [REDACTED]

Note: If an SAE or AESI (anaphylaxis, systemic hypersensitivity reaction, and severe ISR lasting more than 24 hours) occurs in a participant, additional blood samples may be collected for ADA assessment at or near the onset of the occurrence of the event. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled page in the eCRF must be completed as well.

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

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics OR medical resource utilization and health economics parameters are not evaluated in this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

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

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

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

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

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.

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

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

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 12 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Exposed	All screened participants who took at least 1 dose of study intervention.
Enrolled	All participants from the screened population who have been allocated to a study intervention by IRT regardless of whether the study intervention was received or not.
Biomarker (BM)	All enrolled and treated participants (safety population) having at least one post-baseline biomarker value.
Per-protocol (PP)	All enrolled and treated participants (safety population) who completed 12 weeks of study intervention, and either 2 bronchoscopies or 2 nasal brushings with adequate RNA quality, who have maintained the same smoking status since baseline.
Pharmacodynamic (PD)	All enrolled and treated participants (safety population) having at least one post-baseline PD disease-specific clinical value (related to spirometry measurements)
Safety	All enrolled participants who took at least 1 dose of study intervention.
Pharmacokinetic (PK)	All enrolled and treated participants (safety population) with adequate blood samples enabling determination of itepekimab concentrations.
ADA	All enrolled participants treated with itepekimab with at least one post-baseline ADA result (positive, negative, or inconclusive)

Abbreviations: ADA, antidrug antibody; ICF, informed consent form; IRT, interactive response technology; RNA, ribonucleic acid

Participants will be analyzed according to the intervention they received.

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

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

9.3 STATISTICAL ANALYSES

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

9.3.1 General considerations

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

The baseline value is defined as the last available value before the first dose of IMP.

The statistical analyses to be conducted on the safety data as well as on the other baseline characteristics (including disease characteristics at baseline) and the concomitant medications will be performed on the safety population.

The statistical analyses to be conducted on pharmacodynamic biomarker endpoints will be performed on the per-protocol (PP) population. If there is a relevant difference between the PP and biomarker (BM) populations, these statistical analyses will also be provided on the BM population.

The statistical analyses to be conducted on pharmacodynamic disease-specific clinical endpoints (spirometry), will be performed on the PP population. If there is a relevant difference between the PP and pharmacodynamic (PD) populations, these statistical analyses will also be provided on the PD population.

The statistical analyses to be conducted on pharmacokinetics (PK) and antidrug antibodies (ADA) data will be performed on the PK and ADA populations, respectively.

Observation period

The observation period will be divided into 3 periods:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **treatment-emergent period** is defined as the period from the first IMP administration up to the EOS Visit (inclusive).
- The **post-treatment** period is defined as the period after the EOS Visit.

9.3.2 Primary endpoint(s)

9.3.2.1 Definition of endpoints

The primary endpoints are:

- Change from baseline in itepekimab treatment normalized enrichment score (NES) derived from former smokers in endobronchial biopsies in current smokers with COPD at Week 12
- Change from baseline in itepekimab treatment NES derived from former smokers in bronchial brushings in current smokers with COPD at Week 12
- Change from baseline in itepekimab treatment NES derived from former smokers in nasal brushings in current smokers with COPD at Week 12

9.3.2.2 Main analytical approach

[REDACTED]

NES calculation

Normalized Enrichment Scores are mathematical methods for evaluating the overall differences in gene expression for a predefined list of genes as an overall molecular phenotype, rather than one gene at a time. The NES reflects the degree to which the activity level of a set of transcripts is overrepresented at the extremes (top or bottom) of the entire ranked list of transcripts by expression level (as measured by number of Transcripts Per Million [TPM]) within a sample and is normalized by accounting for the number of transcripts in the set (48, 49).

The NES will be calculated to provide an indication of the difference in gene expression levels for a particular individual before and after treatment for a defined set of genes. The NES change calculated for the itepekimab treatment effects in former smokers reflect the expression at Week 12 relative to baseline of a gene set that is differentially expressed in endobronchial biopsies, bronchial brushings, and nasal brushings. The NES in current smokers, at baseline and at Week 12, will be calculated based on the gene signatures of former smokers.

NES endpoint

To determine if there is a significant difference between the NES score derived from former smokers in current smokers, a Wilcoxon signed-rank test will be performed, which can account for the paired (ie, pre-post) nature of the analysis.

Covariates (such as eg, region, eosinophils count, plate) may be considered.

9.3.2.3 Sensitivity analyses

If any, sensitivity analyses will be described in the SAP.

9.3.2.4 Supplementary analyses

If any, supplementary analyses will be described in the SAP.

9.3.3 Secondary endpoints

The secondary endpoints detailed in this section are those related to NES scores and blood eosinophils count. Other secondary endpoints analyses are defined in [Section 9.3.5.1](#) (Adverse events), [Section 9.3.5.2](#) (Laboratory variables, vital signs and ECG), and [Section 9.3.6.1](#) (Anti-itepekimab antibody variables and analysis), and will be further described in the SAP.

9.3.3.1 Secondary endpoints related to NES

NES scores will be computed for prespecified gene expression signatures which have been derived from eosinophils and mast cells that have been exposed to IL-33 in vitro.

9.3.3.2 Blood eosinophil counts

Raw and change from baseline of blood eosinophil counts will be summarized by visit and smoker status group (former or current smokers), using descriptive statistics.

Blood eosinophil count change from baseline at Week 12 will also be analyzed using an analysis of covariance (ANCOVA) model [REDACTED]

[REDACTED] Estimates and two-sided 95% CI for the mean of each smoker status and the mean difference between smoker status (former versus current smokers) will be provided within the model framework.

9.3.4 Exploratory endpoint(s)

Details of exploratory endpoints analyses will be provided in the SAP, which will be finalized before database lock.

9.3.5 Safety analysis

9.3.5.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

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

Analysis of all adverse events

Adverse event incidence table will be provided by smoker status for all types of TEAEs: all TEAEs, all treatment-emergent AESI (defined with a PT or a prespecified grouping), all treatment-emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

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

Deaths will also be analyzed.

9.3.5.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

For laboratory variables, vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided by smoker status and time. Summary statistics will include the number of participants, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

Analyses according to Potentially Clinically Significant Abnormality (PCSA)

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

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

For vital signs and ECG variables, the incidence of participants with at least 1 PCSA during the treatment-emergent period will be summarized by smoker status regardless of the baseline level.

For laboratory variables, the incidence of participants with at least 1 PCSA during the treatment-emergent period will be summarized by smoker status regardless of the baseline level and according to the following baseline status categories:

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

9.3.6 Other analysis

9.3.6.1 PK analyses

Details of PK analyses will be provided in the SAP.

9.3.6.2 Anti-itepekimab antibody variables and analysis

In case of low ADA incidence for itepekimab, a listing of individual data will only be provided.

Otherwise:

Incidence of positivity in the anti-itepekimab ADA assay will be assessed as absolute occurrence (n) and percent of patients (%), presented by smoker status. Plots of concentrations of itepekimab may be examined and the potential influence of ADA on individual concentration-time profiles may be evaluated.

The ADA variables include ADA status (positive or negative in the ADA assay) and titer as follows:

- Number (%) of participants negative in the ADA assay at all times
- Number (%) of participants with pre-existing immunoreactivity
- Number (%) of participants with treatment-boosted ADAs
- Number (%) of participants with treatment-emergent ADA response

Definitions:

- Pre-existing immunoreactivity: defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than [REDACTED], over baseline titer levels.
- Treatment-boosted ADA: defined as a positive response in the ADA assay post first dose that is greater than or equal to [REDACTED] over baseline titer levels, when baseline results are positive.
- Treatment-emergent ADA: defined as a positive response in the ADA assay post first dose when baseline results are negative or missing.

Summary of ADA at baseline, listing of participants with treatment-emergent ADA and treatment-boosted ADA, and summary table of incidence will be provided for itepekimab related ADA variables for each smoker status.

Listings of all ADA peak titer levels will be provided for treatment-emergent and treatment-boosted ADA response participants.

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

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

9.4 INTERIM ANALYSES

No interim analysis has been planned.

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 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.
 - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator Brochure, [IDFU] 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:
 - 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
 - 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 reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to requirements of the Regulation No 536/2014 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 48 hours 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 Investigator or his/her representative will explain the nature of the study to the participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In addition to “main” protocol ICF required for study participation, the participant can consent to the following optional assessments:
 - Pharmacogenomic DNA assessments
 - Future use of samples
 - Home nursing visits
 - Direct-to-Patient services
- 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 or their legally authorized representative, where applicable.

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 addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section “Optional tests/procedures” and

future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research 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.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 ([Section 10.9](#)).

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 and 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 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 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 US Food and Drug Administration (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.
- The participant must be informed that his/her 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.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- 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 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](https://www.sanofi.com)).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
 - Personnel within Sanofi or partners or service providers involved in the study
 - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
 - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
 - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to 25 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 - 46 Avenue de la Grande Armée - 75017 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

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

10.1.6 Dissemination of clinical study data

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.

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

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available 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 may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the “European Federation of Pharmaceutical Industries and Associations (EFPIA) Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations”.

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion instruction.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of

noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- 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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification 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 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 continue the study
- 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 13](#) will be performed by the central laboratories.
- 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.

Table 13 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit <u>White blood cell (WBC) count with differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry ^a	Blood urea nitrogen (BUN) Creatinine [REDACTED] Glucose (fasting) Potassium Sodium Calcium Bicarbonate Creatinine phosphokinase Albumin Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase ^b Uric acid Lactate dehydrogenase Total bilirubin (case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin) Total protein Total Cholesterol
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)

Laboratory tests	Parameters
Pregnancy testing	For women of childbearing potential: Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test at Screening (Visit 1) and urine pregnancy tests at all mandatory clinic visits during the Treatment and Follow-Up Periods. A negative result must be obtained at Visit 1 and Visit 2 (Week 0) prior to IMP administration. 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. The result will be recorded. Participant will be instructed in case of suspected/confirmed pregnancy and contact the site. ^c
Other screening tests	- Coagulation panel and panel and related tests - 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 enrollment 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) - Tuberculosis testing according to local guidelines (local laboratory) or if not available, in central laboratory (QuantiFERON® test) at Screening (Visit 1) - Nasopharyngeal swabs and a quantitative polymerase- chain- reaction tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes coronavirus disease 2019 [COVID-19]) at Screening (Visit 1)

NOTES:

- a Details of liver chemistry stopping criteria and required actions and follow-up are given in [Section 7.1.2](#) (Liver Chemistry Stopping Criteria) and Appendix 6 ([Section 10.6](#)). All events which may indicate severe liver injury (possible Hy's Law) must be reported to Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
- b If alkaline phosphatase is elevated, consider fractionating.
- c 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

10.3.1 Definition of AE

AE definition

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

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event 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, or 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 participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
 - Symptomatic and/or
 - Requiring either corrective treatment or consultation, and/or
 - Leading to IMP discontinuation or modification of dosing, and/or
 - Fulfilling a seriousness criterion, and/or
 - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

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

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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.
- Note: 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
 - $ALT > 3 \times ULN$ + total bilirubin $> 2 \times ULN$ or asymptomatic ALT increase $> 10 \times ULN$
 - Suicide attempt or any event suggestive of suicidality
 - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
 - Bullous cutaneous eruptions

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

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- 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 1 of the following categories:

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

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

Assessment of causality

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

10.3.4 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 off-line 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 off-line, 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 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 time frames.
- Contacts for SAE reporting can be found in the Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.

- 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 hormonal replacement therapy (HRT).
- 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.

Permanent sterilization methods include:

- 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, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

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

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

10.4.2 Contraception guidance

If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:

Highly effective methods^b that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*

Implantable progestogen-only hormone contraception associated with inhibition of ovulation^c

Intrauterine device (IUD)

Intrauterine hormone-releasing system (IUS)^c

Bilateral tubal occlusion

Azoospermic partner (vasectomized or due to a medical cause)

Azoospermia 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.

Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly effective methods^b that are user dependent *(failure rate of <1% per year when used consistently and correctly)*

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 from friction).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

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

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

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

Female participants who become pregnant

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

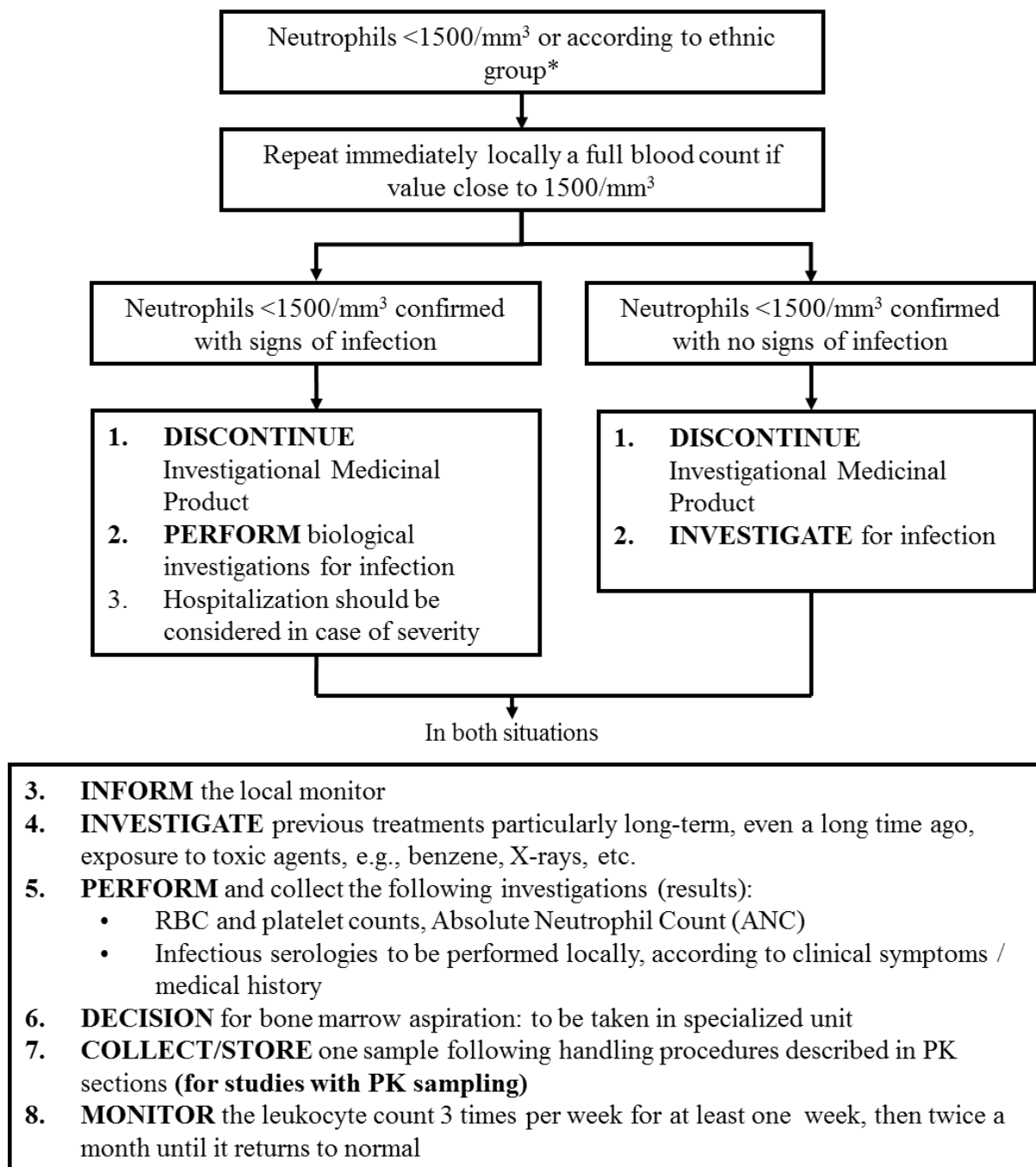
10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA

- 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.
- DNA samples will be used for research related to itepekimab or COPD and related diseases. They may also be used to develop tests/assays including diagnostic tests related to itepekimab or related drugs and other pulmonary diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to itepekimab or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses will not be reported in the clinical study report (CSR), but may be presented in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on itepekimab or study interventions of this class or indication continues but no longer than 25 years or other period as per local requirements.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: ACTIONS AND FOLLOW-UP ASSESSMENTS AND STUDY INTERVENTION RECHALLENGE GUIDELINES

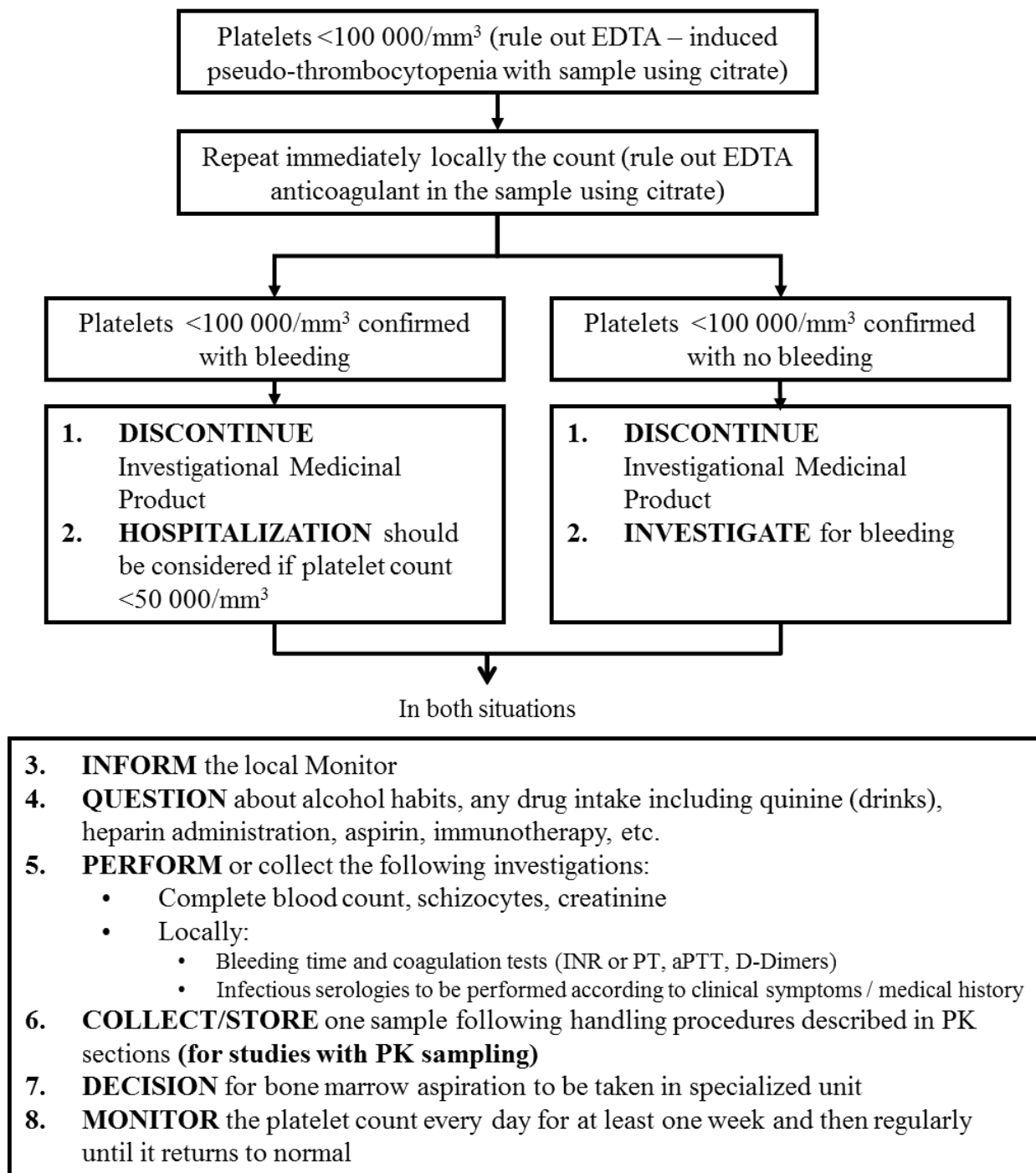
NEUTROPENIA



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

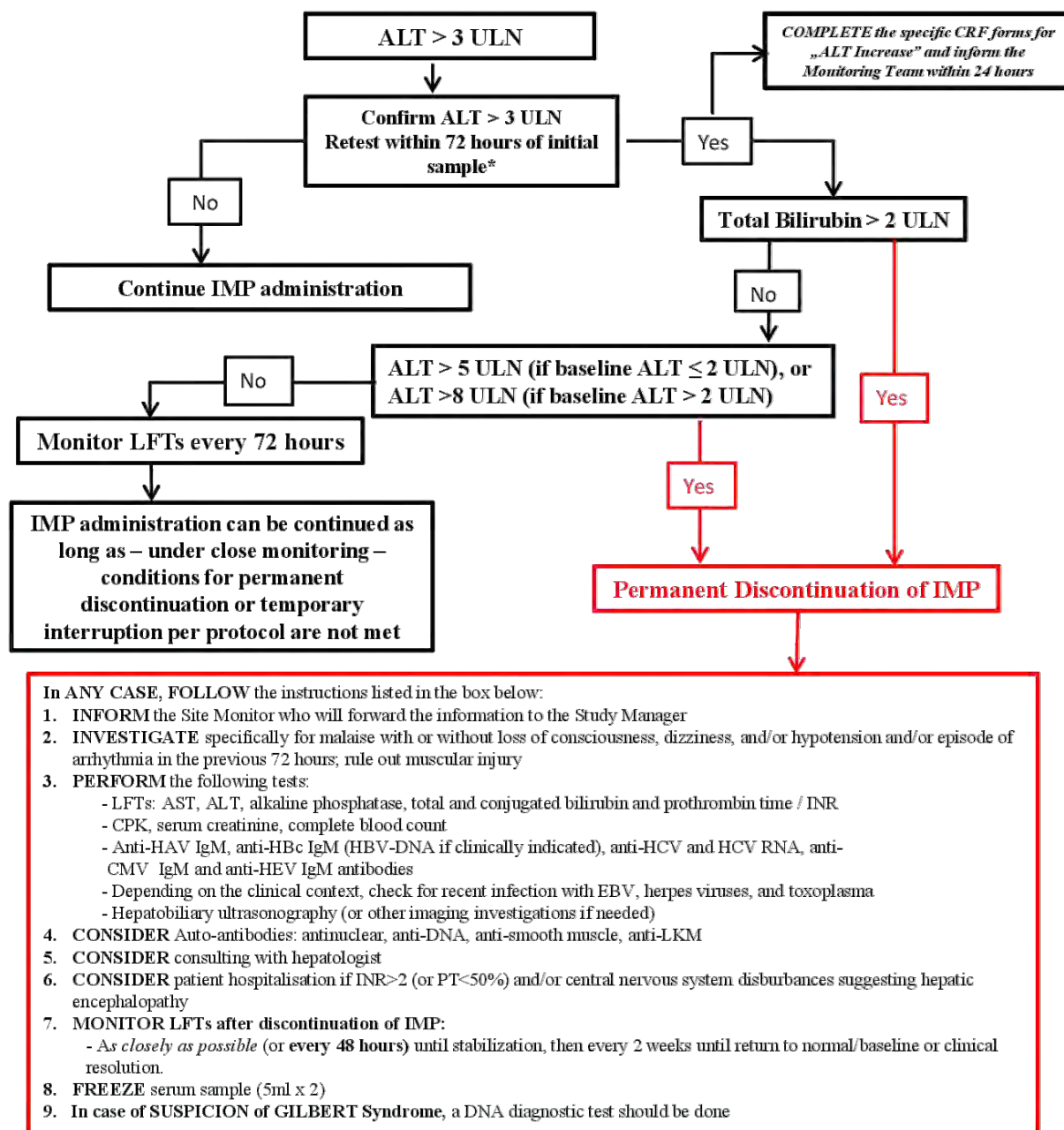
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in [Section 10.3.1](#) is met.

THROMBOCYTOPENIA



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 [Section 10.3.1](#) is met.

INCREASE IN ALT



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

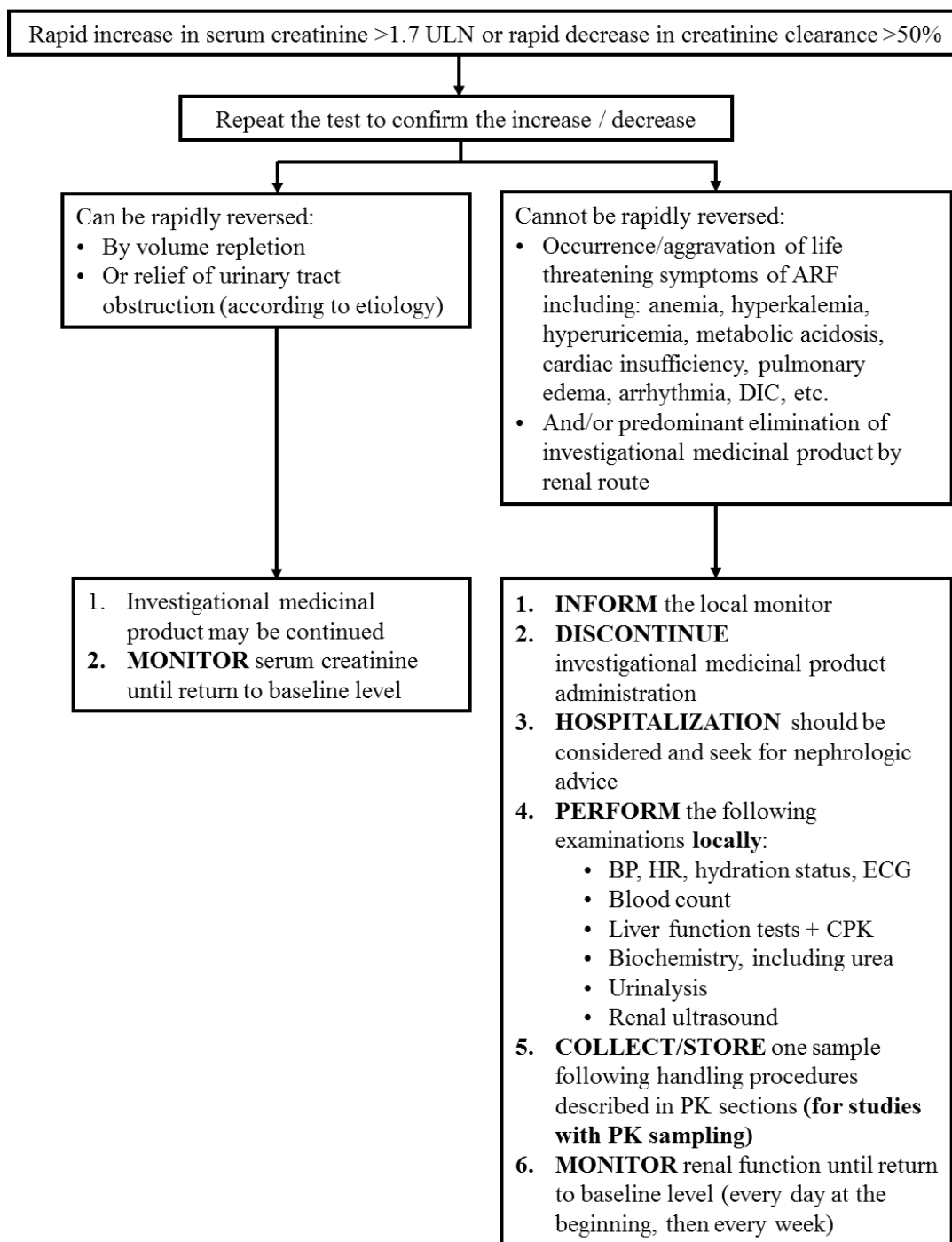
Note:

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

See [Section 10.3.1](#) for guidance on safety reporting.

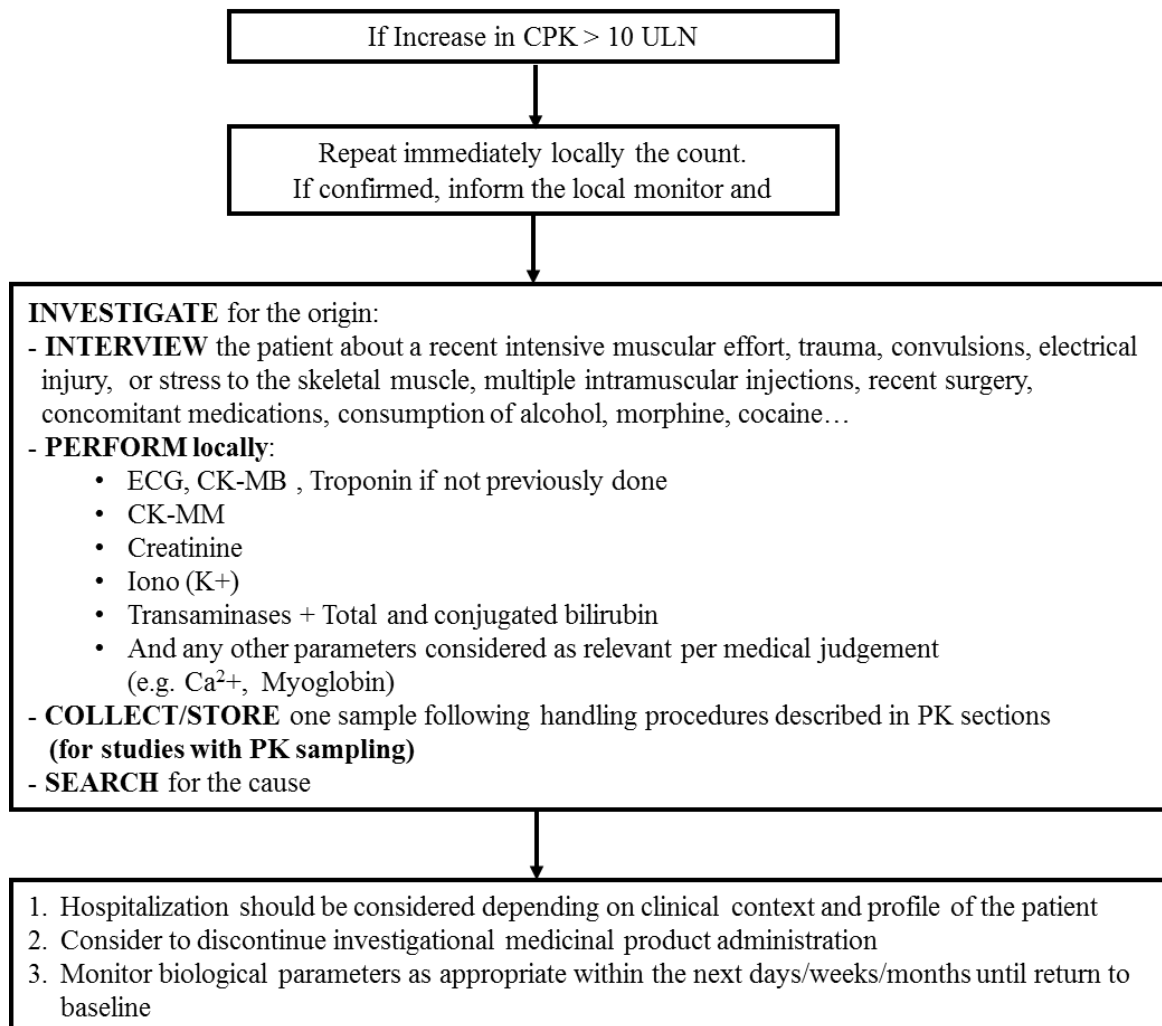
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

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



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 [Section 10.3.1](#) is met.

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



Increase in creatine phosphokinase 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 10.3.1](#) is met.

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

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

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.8.1 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 7.1.1](#), [Section 8.3](#), [Section 10.1.3](#) and [Section 10.9](#).

10.8.2 European Union

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.

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 proposed, 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 -4]) 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

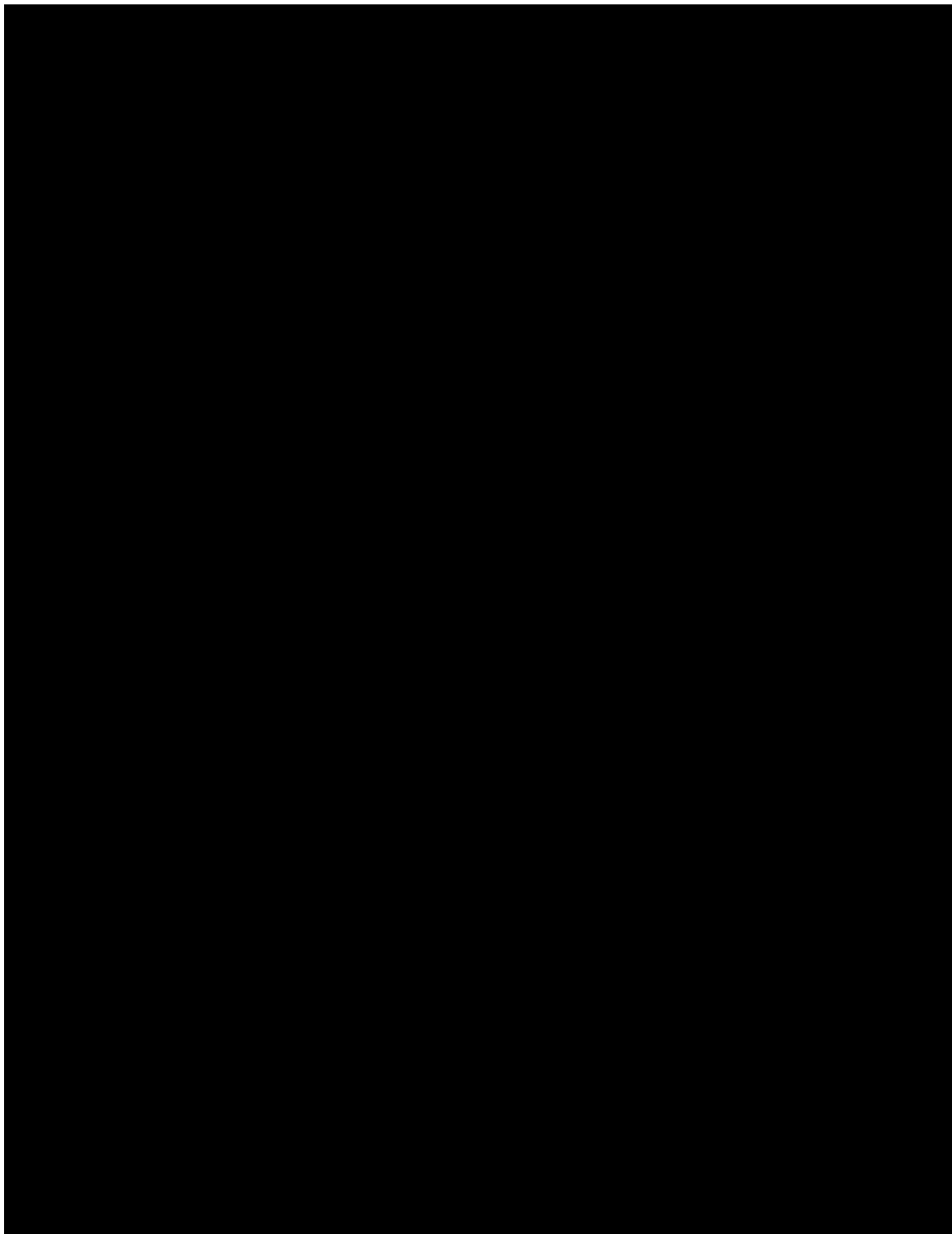
10.10.1 Compliance with Member State application rules for the collection, storage and future use of human biological samples (Article 7.1h)

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: COPD ASSESSMENT TEST (CAT) SCORE



10.12 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

10.13 APPENDIX 13: DEFINITION OF ANAPHYLAXIS

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (Adapted from Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7).

Clinical criteria for diagnosing anaphylaxis:

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a <u>likely</u> 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 <u>known</u> allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
PEF, Peak expiratory flow; BP, blood pressure. *Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.14 APPENDIX 14: LIST OF PROHIBITED LIVE ATTENUATED VACCINES

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

This list is indicative and not exhaustive.

10.15 APPENDIX 15: ABBREVIATIONS

ADA:	antidrug antibody
AE:	adverse event
AECOPD:	acute exacerbation of chronic obstructive pulmonary disease
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BD:	bronchodilator
BM:	biomarker
BMI:	body mass index
BP:	blood pressure
CAT:	COPD assessment test
CI:	confidence interval
COPD:	chronic obstructive pulmonary disease
COVID-19:	coronavirus disease 2019
CV:	coefficient of variation
DMC:	Data Monitoring Committee
DPI:	dry powder inhaler
DTP:	direct-to-patient
ECG:	electrocardiogram
ECMO:	extracorporeal membrane oxygenation
EOS:	end of study
EOT:	end of treatment
ERS/ATS:	European Respiratory Society and American Thoracic Society
ETD:	early treatment discontinuation
FDA:	US Food and Drug Administration
FEV1:	forced expiratory volume in 1 second
FSH:	follicle-stimulating hormone
FVC:	forced vital capacity
GCP:	Good Clinical Practice
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
HBcAb:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus total antibody
HDAC2:	histone deacetylase 2
HIV:	human immunodeficiency virus
HRT:	hormonal replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
ICS:	inhaled corticosteroids
IEC:	Independent Ethics Committees

Ig:	immunoglobulin
IL-33:	interleukin-33
IM:	intramuscular
IMP:	investigational medicinal product
IRB:	Institutional Review Boards
ISR:	injection site reaction
IV:	intravenous
JAK:	Janus kinase
LABA:	long-acting β 2-agonist
LAMA:	long-acting muscarinic antagonist
mAb:	monoclonal antibody
MDI:	metered dose inhaler
NES:	normalized enrichment score
NIMP:	non-investigational medicinal product
NRT:	nicotine replacement therapy
PCSA:	potentially clinical significant abnormality
PDE-4:	phosphodiesterase type 4
PK:	pharmacokinetic(s)
PoC:	proof-of-concept
PP:	per-protocol
Q2W:	every 2 weeks
Q4W:	every 4 weeks
RNA:	ribonucleic acid
RNA-Seq:	RNA sequencing
RR:	rate ratio
RRR:	relative risk reduction
SABA:	short-acting beta-agonist
SAE:	serious adverse event
SAMA:	short-acting muscarinic antagonist
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
SC:	subcutaneous(ly)
SD:	standard deviation
SoA:	schedule of activities
SoC:	standard of care
ST2:	suppression of tumorigenicity 2
SUSAR:	suspected unexpected serious adverse reaction
TB:	tuberculosis
TBI:	tuberculosis infection
THC:	tetrahydrocannabinol
TNF:	tumor necrosis factor
ULN:	upper limit of normal
US:	United States
WOCBP:	women of childbearing potential

10.16 APPENDIX 16: PROTOCOL AMENDMENT HISTORY

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

10.16.1 Amended Protocol 01 (22 September 2022)

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

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is being amended to ensure the enrolled patient population reflects the broad population of patients with COPD in whom IL-33 may be a driver of disease.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 SYNOPSIS	The following text:	Text changed in order to reflect changes to inclusion criterion I 08 (see below)
4.1 OVERALL DESIGN	‘Part A will consist of approximately 20 participants with COPD who are former smokers receiving established background triple (ICS + long-acting β2-agonist [LABA] + long-acting muscarinic antagonist [LAMA]) or double (ICS + LABA) controller therapy.’ And ‘Part B will consist of approximately 20 participants who are former smokers with COPD and approximately 20 participants who are current smokers with COPD receiving established background triple (ICS + LABA + LAMA) or double controller therapy (ICS + LABA).’ Was replaced by: ‘Part A will consist of up to approximately 20 participants with COPD who are former smokers receiving established background therapy for COPD, including monotherapy (long-acting β2-agonist [LABA] or long-acting muscarinic antagonist [LAMA]), double therapy (ICS + LABA, LABA + LAMA or ICS + LAMA), or triple therapy (ICS + LABA + LAMA).’ And ‘Part B will consist of up to approximately 20 participants who are former smokers with COPD and up to approximately 20 participants who are current smokers with COPD receiving established background monotherapy, double therapy, or triple therapy.’	

Section # and Name	Description of Change	Brief Rationale
	The following sentence was added: 'Recruitment of current smoker participants in Part B will be monitored and may be paused temporarily to allow recruitment of a similar number of former smoker participants.'	Language added to control equal number of former and current smoker participants in Part B
1.1 SYNOPSIS	The following sentence was deleted: [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] The following sentence was deleted: [REDACTED] [REDACTED]	Introduce more flexibility related to recruitment by applying fewer binding rules. [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
1.1 SYNOPSIS 6.1 STUDY INTERVENTION(S) ADMINISTERED 6.5.1 RELIEVER MEDICINE	The following modifications were made: 'Participants may administer short-acting beta-agonist (SABA) and/or short-acting muscarinic antagonist (SAMA), <u>such as, but not limited to</u>, albuterol/salbutamol, levalbuterol/levosalbutamol, ipratropium, or ipratropium/albuterol, as reliever medication as needed during the study.'	Allow broader use of short acting reliever medication during the study.
1.1 SYNOPSIS 9.1 SAMPLE SIZE DETERMINATION	[REDACTED]	[REDACTED]
THROUGHOUT THE PROTOCOL	Text was amended to indicate bronchoabsorption is an optional assessment at country/site level.	In some limited geographical areas bronchoabsorption is considered an investigational procedure due to local regulations and is therefore an optional procedure for these geographical regions.
1.3 SCHEDULE OF ACTIVITIES (SOA) 3. OBJECTIVES AND ENDPOINTS	The following text in the SoA: 'Circulating cytokines (plasma)' [REDACTED] [REDACTED] [REDACTED] [REDACTED]	To allow for measurement of non-cytokine biomarkers

VV-CLIN-0635335 2.0

Section # and Name	Description of Change	Brief Rationale
	I 07 Changed 'within the 2 years' to 'within the 5 years.'	Allow recruitment of patients with lower baseline risk of exacerbations. Less risk of interference of intercurrent exacerbations and associated rescue treatment with primary endpoint.
	I 08 Changed 'Double therapy: ICS + LABA' to 'Double therapy: ICS + LABA or LABA + LAMA or ICS + LAMA.' Added 'OR Mono therapy: LABA or LAMA'	Allow recruitment of patients on double therapy containing LABA + LAMA or ICS + LAMA and allow recruitment of patients on monotherapy LABA or LAMA to permit examination of the pathobiological role of IL-33 in a population of patients with COPD receiving a range of background therapies.
	I09 the following text: 'Participants who have completed the vaccination regimen against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), administered a minimum of 6 weeks prior to Screening (Visit 1) (see Concomitant Therapy, Section 6.8).'	Text was adapted to fit different vaccination strategies in participating countries, and more flexible since now booster vaccinations are no longer considered as prohibited medication.
	Was replaced by: 'Participants who have received appropriate vaccination according to local recommendations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), administered a minimum of 1 week prior to Screening (Visit 1) (see Concomitant Therapy, Section 6.8).'	
5.2 EXCLUSION CRITERIA	The following text was added to exclusion criterion 01: 'unless asthma resolved before 18 years of age and has not recurred.'	To ensure the enrolled patient population reflects the broad target population of patients with COPD, since childhood asthma is a risk factor for COPD.
	The following text: 'E 07. Participants who receive long-term treatment with oxygen or an oxygen saturation on room air <94% at rest.'	To allow enrollment of patients receiving supplemental oxygen meeting specific conditions
	Was changed to: 'E 07. Participants who require more than 2 L/min of long-term treatment with oxygen at rest. Participants who use up to 4L/min of supplemental oxygen during exercise may enroll. Oxygen during sleep is allowed.'	
	The following text in exclusion criterion E 21: 'known history of COVID 19 infection within 6 months before Screening (Visit 1)'	To allow quicker (re)screening of patients with uncomplicated COVID-19 infection.
	Was changed to: 'known history of COVID 19 infection within 6 weeks before Screening (Visit 1)'	

VV-CLIN-0635335 2.0

[illegible]

Section # and Name	Description of Change	Brief Rationale
10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY	Section updated to state that the Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).	Aligned with Sanofi procedures.
THROUGHOUT THE PROTOCOL	Minor editorial/formatting changes.	Correction of minor editorial/formatting issues

11 REFERENCES

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