

STATISTICAL ANALYSIS PLAN

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

Compound number (INN/Trademark): SAR440340/REGN3500 (itepekimab/Not applicable)

Study phase: Phase 2

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

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Date of issue: 12-Aug-2025

Regulatory agency identifier number(s):

IND:	134401
EU trial number:	2024-512007-39
NCT:	NCT05326412
WHO	U1111-1255-5322

Total number of pages: 32

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for Study PDY16967 (version 1) is based on the protocol amended version 2, dated 11-September-2024. The original version of the protocol was approved on 30-June-2021 and the protocol was firstly amended on 22-September-2022 and secondly amended on 11 September 2024.

This section summarizes the major changes in the statistical analyses’ features mentioned in the SAP compared to those initially planned in the protocol amended version 2.

Table 1 - Major changes in Statistical Analysis Plan

SAP Version	Approval Date	Changes	Rationale
1	10-Apr-2025	Secondary endpoint: Statistical analysis changed from ANCOVA model to MMRM model for blood eosinophil count change from baseline at Week 12.	To take into consideration the repeated measurements
2	12-Aug-2025	Analysis populations: updated definitions for biomarker and pharmacodynamic populations	
		General considerations	
Other analyses – PK: minor details have been added			To specify details of data handling

This SAP is approved before the availability of major biomarkers data and the database lock.

1 INTRODUCTION

1.1 STUDY DESIGN

This study is an exploratory, multi-center, two-part, 12-week repeated dose, Phase 2a study to evaluate the mechanism of action of itepekimab (anti-IL-33 mAb) and its impact on airway inflammation in participants with Chronic Obstructive Pulmonary Disease (COPD).

The study will include participants with COPD who are former and current smokers, aged 40 to 70 years.

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 (inhaled corticosteroids [ICS] + LABA, ICS+LAMA or LABA+LAMA), or triple therapy (ICS+LAMA+LABA).

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.

Study intervention for both former (Part A) and current (Part B) smokers will be itepekimab 300 mg every 2 weeks (Q2W) (up to 6 doses) administered subcutaneously (SC) during the 12-week Treatment Period.

Former and current smoker participants may administer a 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. Moreover, if a former smoker participant resumes smoking or if a current smoker participant ceases smoking, this should be reported in the eCRF, but it does not necessitate the study intervention discontinuation. In addition, 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.

During the study, former and current smoker participants are expected to undergo 2 bronchoscopy procedures that will include endobronchial biopsies, bronchial brushings, and (when applicable) bronchial lining fluid using broncho absorption device:

- 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, former and current smoker participants will undergo nasal brushings at Week 0 (Baseline/Visit 2) and Week 12 (End-of-Treatment/Visit 8). Blood samples collection for biomarkers analyses will be done at the same time; an additional blood sample collection is done at Week 4 for Total IL-33 assessment.

If throughout the 12-week treatment period some participants experience an acute exacerbation of COPD (AECOPD), they must wait for 6 weeks after the onset of the exacerbation (defined as initiation of treatment/hospitalization) before undergoing Bronchoscopy #2. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

1.2 OBJECTIVE AND ENDPOINTS

Primary, secondary, as well as tertiary/exploratory objectives and endpoints are summarized in [Table 2](#).

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.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF
Enrolled	All participants from the screened population who have been allocated to a study intervention by interactive response technology (IRT) regardless of whether the study intervention was received or not.
Biomarker (BM)	All enrolled and treated participants (safety population) having at least one biomarker datapoint, and who have maintained the same smoking status since baseline up to Week 12.
Per-protocol (PP) ^a	All enrolled and treated participants (safety population) who completed 12 weeks of study intervention and either 2 bronchoscopies ^b or 2 nasal brushings with adequate RNA quality and who have maintained the same smoking status since baseline up to Week 12.
Pharmacodynamic (PD) ^c	All enrolled and treated participants (safety population) with at least one baseline and post-baseline spirometry measurements, and who have maintained the same smoking status since baseline up to Week 12.
ADA	All enrolled participants treated with itepekimab with at least one post-baseline ADA result (positive or negative).
Pharmacokinetic (PK)	All enrolled and treated participants (safety population) with at least one non-missing result for functional itepekimab concentration in serum after first dose of the study intervention.
Safety	All enrolled participants who take at least 1 dose of study intervention.

Note:

^a The compliance with the smoking status as entered in IRT/RAVE will be checked during the treatment period

^b Bronchoscopy procedures include endobronchial biopsies, bronchial brushings and (when applicable) bronchoabsorption

^c PD data: Primary or secondary or tertiary/exploratory pharmacodynamic endpoints.

Participants exposed to study intervention before or without being enrolled 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.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, unless otherwise specified, continuous data will be summarized using the number of observations available, mean, standard deviation [SD], standard error of the mean [SEM] (for pharmacodynamics parameters (biomarkers as well as spirometry data)), median, interquartile range (Q1;Q3) (for ADA only and if relevant), minimum, and maximum (including also, geometric mean (for itepekimab serum concentrations and if relevant for PD parameters as well) and coefficient of variation [CV] for itepekimab serum concentrations).

Categorical and ordinal data will be summarized using the count and percentage of participants, as appropriate.

Except for ECG data, the baseline value is defined at Week 0 as the last available value before the first dose of IMP. However, in case of missing values at Week 0, the screening value could be considered.

For ECG data, the baseline will be defined at Screening as per protocol, no assessments being planned at Week 0.

Smoking status

Planned smoking status:

Smoking status as entered at screening in IRT will be considered as the planned smoking status.

Actual smoking status:

- For former smokers, the actual smoking status will be stated at baseline, derived from data collected both at screening and at baseline according to the definitions below.
- For current smokers, the actual smoking status at baseline will be the same as the planned.

The whole statistical analyses will be done according to the actual smoking status as stated at baseline.

Change in smoking status during the treatment period (From baseline (Week 0) up to Week 12):

For former smoker participants with COPD, the use of tobacco products will not be allowed from 6 months prior to screening visit until after the final follow-up visit. If abstinence is difficult for the participants, they may seek medical help and receive supportive treatment with nicotine replacement therapy (NRT).

The smoking status will be checked during the treatment period (from Week 0 up to Week 12)

Current smoker participants with COPD are participants who report that they are actively smoking tobacco **at screening and at baseline** (at least 5 cigarettes per day on average during the past 7 days) and who are not currently participating in, or planning, to initiate a smoking cessation intervention at screening 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 current smokers, the smoking status as stated at screening will be considered maintained during the whole treatment period if at Week 12, the number of smoked cigarettes since last visit is reported to be at least 5 cigarettes per day or if cotinine test is positive.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to the first investigational medicinal product (IMP) administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration up to the end-of-study (EOS) visit (included). The treatment-emergent period includes the following 2 periods:
 - The on-treatment period defined as the period from the first IMP administration to the last administration of the IMP + 14 days (planned time between 2 IMP administrations).
 - The residual treatment period defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the TE period.

The reporting of the safety statistical analyses will be programmed following the recommendations and templates of the operational guideline “Conventions for analyzing and reporting standard Early Development clinical trial data (except oncology)” version 1.0 dated 25-Oct-2023 and “Standard Statistical Outputs Templates” version 1.0 dated on 29-Sep-2023.

The whole 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 the primary and secondary pharmacodynamics biomarker endpoints will be performed on the per-protocol population. If there is a relevant difference between the PP and BM populations, this kind of statistical analysis will also be provided on the BM population.

The statistical analyses to be conducted on the exploratory pharmacodynamics biomarker endpoints will be performed on the BM population.

The statistical analyses to be conducted on spirometry data will be performed on the PP population. If there is a relevant difference between the PP and PD populations, this kind of statistical analysis 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.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The statistical analyses to be performed on [Section 3.3.2](#) (Blood eosinophils counts) for secondary PD endpoints, for the whole safety data ([Section 3.6](#)) including the analyses described in appendix 2 (Demographics and baseline characteristics, prior or concomitant medications) as well as descriptive analyses for data related to pharmacokinetic (itepekimab serum concentrations,

[Section 3.7.1.1](#)), immunogenicity ([Section 3.7.1.2](#)), smoker profile ([Section 3.7.1.3](#)) and spirometry data ([Section 3.7.1.4](#)) will be conducted under the responsibility of Early Clinical Biostatisticians (ECB) at Sanofi.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The primary objective is to evaluate the pharmacodynamic (PD) effects of itepekimab in current smokers by assessing changes in normalized enrichment scores (NES) using gene expression signatures derived from former smokers with COPD. The analysis measures changes in NES values in current smokers at baseline and after 12 weeks of treatment with itepekimab.

The statistical analyses will be performed on the complete cases of the PP population. If relevant, these statistical analyses may also be performed on the BM population.

3.2.1 Definition of endpoint(s)

The primary endpoints are defined as the change from baseline at Week 12 in NES values for three airway sample types (endobronchial biopsies, bronchial brushings, and nasal brushings) of current smokers with COPD.

- Change from baseline in itepekimab pharmacodynamic 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.

3.2.2 Main analytical approach

[REDACTED]

NES calculation

Normalized Enrichment Scores (NES) 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 ([1](#), [2](#)).

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 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 between endobronchial biopsies, bronchial brushings and nasal brushings from former smokers with COPD compared to baseline. The NES in current smokers, at baseline and at Week 12, will be calculated based on the gene signatures of former smokers.

Technical details on NES calculation will be provided in a separate programming document.

NES endpoint

To determine if there is a significant difference between the NES score derived from former smokers at baseline and Week 12 in current smokers, a Wilcoxon signed-rank test will be performed, which can account for the paired (ie, pre-post) nature of the analysis.

The two-sided statistical significance level will be set at 0.05. A p-value and adjusted p-values (3) will be reported to indicate a statistically significant change in NES from baseline at Week 12. In addition, the Hodges-Lehmann estimate, and its 95% confidence interval will be provided.

A box plot and/or a line plot, in addition to tabulated results (descriptive statistics), will be provided for each smoker status group illustrating the distribution of NES values at baseline and Week 12 across different sample types (endobronchial biopsies, bronchial brushings, and nasal brushings).

3.2.3 Sensitivity analysis

Non-parametric test (rank ANCOVA) accounting for covariates (such as eg, region, blood eosinophils count at baseline, plate) may be considered as sensitivity analysis.

3.2.4 Supplementary analyses

Not applicable.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

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

The secondary endpoints detailed in this section are those related to evaluating pre-specified gene signatures ([Section 3.3.1](#)) and blood eosinophil counts ([Section 3.3.2](#)).

Other secondary endpoint analyses are defined in [Section 3.6.2](#) (AE, SAE), [Section 3.6.3](#) (Additional safety assessments), [Section 3.7.1.1](#) (PK analyses) and [Section 3.7.1.2](#) (Immunogenicity analyses).

The statistical analyses of secondary PD biomarker endpoints will be performed by smoker status group on the complete cases of the PP population. This statistical analysis may also be conducted on the BM population, if relevant, only.

3.3.1 Evaluation of prespecified gene signature

The effect of itepekimab treatment on pre-specified cell type-associated gene expression signatures will be evaluated in endobronchial biopsies of both former and current smokers with COPD. This analysis focuses specifically on in vitro derived gene expression signatures associated with eosinophils and mast cells treated with IL-33.

For each participant, the normalized enrichment score will be calculated using the pre-defined gene signatures at two time points: baseline and Week 12.

The endpoints are the following:

- 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.

To assess changes in NES values over time, the difference between baseline and Week 12 will be tested for each gene signature type (eosinophil-associated and mast cell-associated). [REDACTED]

A boxplot and/or a line plot will be provided in addition to tabulated results, illustrating the distribution of NES values at baseline and Week 12.

3.3.2 Blood eosinophils 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.

The blood eosinophil count change from baseline at Week 12 will be analyzed using a mixed model with repeated measurements (MMRM). [REDACTED]

Statistical inferences on smoking status comparisons for the change from baseline in blood eosinophil count at Week 12 will be derived from the mixed-effect model. Least Square (LS) estimates and their corresponding standard error (SE) for each smoking status group will be provided at each visit. Difference in LS mean change from baseline and the corresponding 95% CI will be provided for comparison between smoking status group (former versus current smokers) at Week 12.

No imputation will be performed for missing values in this analysis; the missing data will be handled using the MMRM model which assumes that missing data are missing at random (MAR).

Other statistical models could be tested in case of deviation to normality (for example, log-transformation of data).

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

3.5 MULTIPLICITY ISSUES

The p-values for the primary endpoints for each sample type (bronchial biopsies, bronchial brushings, and nasal brushings), will be adjusted using Hochberg step-up (3) correction.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population on each smoker status group (former or current smokers) using the following common rules:

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

3.6.1 Extent of exposure

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

Duration of IMP exposure

Duration of IMP exposure expressed in weeks is defined, regardless of unplanned intermittent discontinuations using the following formula:

$$(\text{Last IMP administration date} - \text{first IMP administration date} + 14 \text{ days})/7.$$

If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively and categorically: 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the total volume of the syringe.

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

Treatment compliance will be summarized quantitatively and categorically: [$<80\%$, $\geq 80\%$].

A listing of participants not compliant to background controller therapy across the study course, will also be provided.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class

(SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be classified into predefined standard categories according to chronological criteria:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period;
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the TE period;
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

The primary focus of AE reporting will be on TEAEs.

Analysis of all adverse events

The following TEAEs summaries will be presented:

- Overview of TEAEs: Number (%) of participants with:
 - Any TEAE
 - Any severe TEAE
 - Any treatment emergent serious AE (SAE)
 - Any TEAE leading to death (if any occurred)
 - Any TEAE leading to permanent study intervention discontinuation
 - Any TEAE leading to permanent study discontinuation
 - Any treatment emergent AE of special interest (AESI)
- Summary of TEAEs will be generated with number (%) of participants experiencing at least one event together with the number of occurrences by primary SOC and PT sorted by SOC internationally agreed order and by decreasing frequency of PTs in the current smoker status group.

All adverse events, any deaths, serious and other significant AEs as well as any AEs leading to permanent study intervention/study discontinuation and any AESI will be listed by participant, and by date and time of occurrence of each AE within participant.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following variables will be analyzed. They will be converted into standard international units.

- Laboratory variables (see section 8.2.4 of the protocol): hematology, clinical chemistry, urinalysis variables (pH):

- Vital signs (see section 8.2.2 of the protocol): heart rate, systolic and diastolic blood pressure according to position (sitting), body temperature, body weight, oxygen saturation level and respiratory rate (breaths per minute);
- ECG variables (see section 8.2.3 of the protocol): heart rate, PR, QRS, QT, and corrected QT (QTc) (according to both Fridericia and Bazett formula).

Quantitative analyses

For vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each planned visit and time during the study period. These analyses will be performed using central measurements only (when available) ECG variables.

Analyses according to PCSA

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

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

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

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

For vital signs and ECG variables above, the incidence of participants with at least one PCSA during the TE period will be summarized regardless of the baseline level.

Additional analyses for potential drug-induced liver injury

An intext listing of liver function tests data for participants with potential drug-induced liver injury (“ALT >3 ULN and Total bilirubin >2 ULN” or “Direct bilirubin >35% of Total bilirubin and Total bilirubin >1.5 ULN”) will be provided.

Additionally, listing of ALT increase documentation (including specific medical history, alcohol habits, associated signs and symptoms, trigger factors...) will also be provided for participants with one or more ALT increases greater than or equal to 3 ULN.

Listing of participants with QTc >480 msec and/or change from baseline QTc >60 msec

An intext listing of participants with QTc >480 msec and/or change from baseline QTc >60 msec will be provided.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

The concentrations for Itepekimab in serum will be summarized by visit/nominal timepoint and smoker status group on the PK population, using descriptive statistics and then, listed. If date and/or time of the drug injection and/or sampling is missing, the concentration will not be taken into account.

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

3.7.1.2 Immunogenicity analyses

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

Definitions:

The ADA status of each participant may be classified as one of the following:

- Positive: see details below
- 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.
- Negative: If all samples are found to be negative in the ADA assay.

The ADA category of each positive participant will be further classified as:

- Treatment-boosted response: 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 response: defined as a positive response in the ADA assay post first dose when baseline results are negative or missing.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Statistical analyses:

The incidence of positive ADA response for itepekimab will be assessed as absolute occurrence (n) and percent of participants (%), presented by smoker status group.

Summary of ADA at baseline, listing of participants with negative, positive (treatment-emergent and treatment-boosted responses), and pre-existing immunoreactivity, and summary table of incidence will be provided by nominal timepoint and smoker status group for itepekimab related ADA variables.

The following summaries will be provided:

Baseline summary:

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

Post-baseline summary:

- Number (%) of participants with pre-existing immunoreactivity
- Number (%) of participants with ADA negative responses at all time points
- Number (%) of ADA positive participants
- Number (%) of participants with treatment-emergent ADA response
 - Descriptive statistics of the peak post-baseline titer for treatment-emergent ADA-positive participants
- Number (%) of participants with treatment-boosted ADA response
 - Descriptive statistics of the peak post-baseline titer for treatment-boosted ADA-positive participants

Listing of all ADA 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.

3.7.1.3 Smokers profile analyses

The following variables observed over the time between baseline and Week 12 will be summarized using descriptive statistics on the PP population, for each smoker status group (when relevant):

- Number of cigarettes per day for current smokers,
- Number of cigarettes per day for former smokers who resume smoking,
- Number and percentage of participants who changed their type of background controller therapy (mono, double, triple),

- Number and percentage of participants who used systemic corticosteroids,
- Number and percentage of participants who used antibiotics,
- Number and percentage of participants who used reliever medication intake (SABA, SAMA),
- Number and percentage of participants who have been hospitalized for COPD worsening,
- Number and percentage of participants who visited an emergency room or urgent care facility for worsening of COPD symptoms.

If there is a relevant difference between the PD and PP populations, this kind of statistical analysis will also be provided on the PD population.

3.7.1.4 Spirometry analyses

A summary of descriptive statistics will be done on change from baseline in spirometry parameters

These statistical analyses will be performed by smoker status group on the PP population. This statistical analysis may also be conducted on the PD population, if relevant, only.

3.7.2 Subgroup analyses

If relevant only, descriptive statistics to be conducted on primary analysis as well as on PD parameters could be provided by the following subgroups defined at baseline, within each smoker status group:

No formal interim analysis has been planned. For exploratory purposes or unexpected safety concerns, statistical analyses may be performed on safety, pharmacokinetic or/and pharmacodynamics/biomarker data during the course of the study.

This section summarizes major changes to the protocol statistical section since the original version of the protocol.

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Age Group	Percentage Vaccinated
18-24	75%
25-34	95%
35-44	90%
45-54	85%
55-64	80%
65-74	75%
75-84	70%
85+	65%

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5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	AntiDrug Antibody
AE:	Adverse Event
AECOPD:	Acute Exacerbation of COPD
AESI:	Adverse Event of Special Interest
ALT:	ALanine aminoTransferase
BD:	Bronchodilator
BMI:	Body Mass Index
BS:	Biomarker Statistician
CV:	Coefficient of Variation
ECB:	Early Clinical Biostatistician
eCRF:	electronic Case Report Form
EOS:	End Of Study
EOT:	End of Treatment
HLGT:	High-Level Group Term
HLT:	High Level Term
ICF:	Informed Consent Form
ICS:	Inhaled Corticosteroids
IMP:	Investigational Medicinal Product
LABA:	Long-Acting β 2-Agonist
LAMA:	Long-Acting Muscarinic Antagonist
LLT:	Lower-Level Term
MedDRA:	Medical Dictionary for Regulatory Activities
NRT:	Nicotine Replacement Therapy
PCSA:	Potentially Clinically Significant Abnormality
PD:	Pharmacodynamic
PK:	Pharmacokinetic
PP:	Per Protocol
PT:	Preferred Term
Q2W:	Once every 2 weeks
QTc:	QT corrected
RNA:	RiboNucleic Acid
SABA:	Short-Acting Beta-Agonist
SAE:	Serious Adverse Event
SAMA:	Short-Acting Muscarinic Antagonist
SAP:	Statistical Analysis Plan
SC:	Subcutaneous(ly)
SD:	Standard Deviation
SEM:	Standard Error of the Mean

SOC:	System Organ Class
TE:	Treatment-Emergent
TEAE:	Treatment-Emergent Adverse Event
ULN:	Upper Limit of Normality
WBC:	White Blood Cells
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the safety population for each smoker status group (former or current smokers).

Demographic and baseline characteristics:

- age in [years] as quantitative variable and in categories (40 to <50, 50 to <60, 60 to 70)
- age in [years] according to EudraCT categories (18 to 64, 65 to 84 years)
- gender (Male, Female)
- race (eg, White, Black or African American...)
- ethnicity (eg, Hispanic or Latino, not Hispanic or Latino)
- body weight group (<50, 50 to <100, ≥100 kg)
- body mass index (BMI, kg/m²)
- BMI group (<18.5, 18.5 to <25, ≥25-<30, ≥30 kg/m²)

Baseline safety, and PD parameters (biomarkers as well as spirometry data) will be presented along with the safety and pharmacodynamics summaries.

All medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock. All medical history will be summarized by primary SOC and PT using a frequency table (number and % of participants).

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by smoker status group (former or current smokers) on the safety population:

- Age at diagnosis of COPD (years) calculated as the year of COPD diagnosis minus the year of birth.
- Time since diagnosis of COPD at enrollment (years) calculated as the year of the study intervention allocation by IRT minus the year of COPD diagnosis.

- Time since last COPD exacerbation at enrollment (months) calculated as:

$\frac{(\text{Date of study intervention allocation by IRT} - \text{date of last COPD exacerbation} + 1 \text{ day})}{30.4375}$

The rule for handling missing/partial dates as described in [Section 3.5](#) of this SAP will be applied.

- Background controller therapy groups (Controller medication^(*)) at baseline:

-
- Number and percentage of participants with mono, double or triple therapies:
 - Monotherapy: LABA or LAMA.
 - Double therapy: ICS+LABA, ICS+LAMA or LABA+LAMA.
 - Triple therapy: ICS+LABA+LAMA.
 - Number and percentage of participants who used reliever medication up to baseline (SABA, SAMA).

The other controller and reliever medications will be considered as “Other” in the summary tables.

- History of COPD as well as COPD exacerbations within up to 5 years before screening visit.
- Number of moderate COPD exacerbations experienced within 2 years before screening visit.
- Number of severe COPD exacerbations experienced within 2 years before screening visit.
- Time since cessation of smoking (months) calculated as:

$\frac{(\text{Date of study intervention allocation by IRT} - \text{date of cessation of smoking} + 1 \text{ day})}{30.4375}$

The rule for handling missing/partial dates as described in [Section 5.3](#) of this SAP will be applied.

- Smoking quantity in pack-years^(**) at enrollment for former smokers.
- Smoking quantity in pack-years^(**) for current smokers.

*(**) Smoking quantity in pack-years will be defined as follows with reference of one standard pack of 20 cigarettes:*

$\frac{(\text{Number of cigarettes smoked per day}) \times (\text{Number of smoking years})}{20}$

- Alcohol habits: frequency of alcohol drinking, number of standard alcohol glasses.
- Baseline spirometry data

- Baseline COPD Assessment Test (CAT) score.
- Baseline blood eosinophil count [REDACTED]).

Prior or concomitant medications

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

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during study intervention period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the on-treatment period (see definition in [Section 3.1](#)).
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.

A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The concomitant medications will be summarized for the safety population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. The counting will be done by smoker status group (former or current smokers).

Participants disposition

The number (%) of participants included in the analysis populations listed in [Table 3](#) will be summarized.

Screen failures are defined as participants who have signed the informed consent form (ICF) and failed to be eligible for the study or have retired his consent. The number (%) of screen failures with inclusion criteria not met and/or exclusion criteria met will be provided in the screened population.

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

- Enrolled participants.
- Enrolled and exposed participants.
- Participants who completed the study treatment period as per protocol.
- Participants who did not complete the study treatment period as per protocol and main reason for permanent study intervention discontinuation.
- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

The exposed and not enrolled participants will be listed. In addition, the number (%) of participants screened, screened-failed, enrolled, enrolled and exposed, with permanent study intervention discontinuation and with premature end of study will be provided by country and site.

Listings of participants with permanent study intervention discontinuation and/or with premature end of study (ie, who did not complete the study period as per protocol) will be provided (if there is at least one case) with the main reason of discontinuations.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized.

If any and relevant, this summary could be done according to the status of critical and major deviations.

5.3 APPENDIX 3 DATA HANDLING CONVENTIONS

In the statistical appendices and in-text tables, the following study intervention group labels will be used:

- Former smokers
- Current smokers

“Itepekimab 300 mg SC Q2W” will be indicated as footnote.

For parameters with evaluations before administration and in cases of rechecked value(s) for one participant, only the last observation will be used as baseline in descriptive statistics and derivations of other parameter values.

After baseline, only observations planned in the protocol will be used in descriptive statistics.

For clinical laboratory parameters with nonnumeric values, the imputed values used for the descriptive statistics and/or the flags will be determined by considering the following rules:

- If database value is ‘<X’, the value used will be X/2.
- If database value is ‘>X’, the value used will be X.
- If database value is a range (eg, ‘X – Y’), the values used will be (Y + X)/2.

Pharmacokinetic analyses

For ease of presentation, mean values will be arithmetic mean unless specified. Concentration values below the [REDACTED] assay limit will be treated as zero in calculating mean values. Mean values below LLOQ will be reported as LLOQ in the tables and not plotted in the figures if after C_{max}. Mean calculations and their associated statistics will be generated from unrounded numbers and may differ slightly from those values that would be determined using the rounded numbers

displayed in the tables. Values expressed in all tables will be for ease of presentation and will not be meant to imply accuracy to more than 3 significant figures.

[REDACTED]

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

Handling missing data for adverse events

In case of missing or inconsistent information, an adverse event will be counted as a TEAE, unless it can clearly be ruled out that it is not a treatment emergent adverse event (eg, by partial dates or other information).

If the start date (or time) of an AE is incomplete or missing, it will be counted as TEAE except if an incomplete date (or time) or comment indicates that it is a pre- or post-treatment event.

If relationship to study medication is missing, the AE will be assessed as unrelated if it started before administration of study intervention; in all other cases it will be assumed to be related.

If the severity is missing for an AE, the severity will be left as missing.

PCSAs and multiraces participants

In case a participant is considered “Black and White” (multiraces), for white blood cells (WBC) and Neutrophils, the PCSA rule for Non-Black will be applied (worst case scenario).

Handling missing/partial dates

For the disease characteristics at baseline, the following rules will be applied regarding missing/partial dates:

- If the day is missing, it will be imputed by the first day of the month.
- If the month is missing, it will be imputed by the first month of the year.
- If the date is completely missing, no imputation will be performed.

6 REFERENCES

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

3. Hochberg Y. A sharper bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-2.

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