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Sanofi and Regeneron Respiratory Clinical Studies Information Booklet

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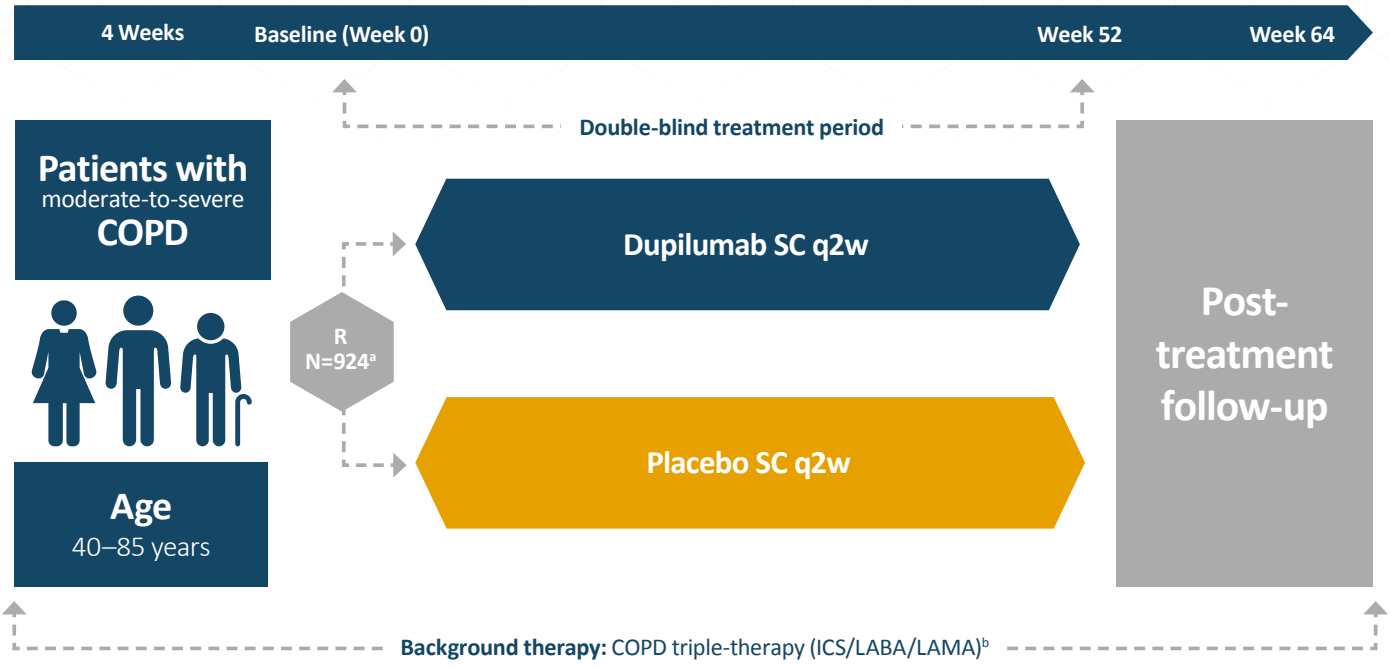
Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate-to-Severe COPD With Type 2 Inflammation (NOTUS)

Primary Objective
To evaluate the efficacy of dupilumab administered every 2 weeks in patients with moderate or severe COPD as measured by annualized rate of AECOPD

NOTUS



[a]Estimated enrollment.

[b]Double therapy with LABA + LAMA is allowed if ICS is contraindicated.

AECOPD, annualized rate of acute moderate or severe COPD exacerbations; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agonist; q2w, every 2 weeks; R, randomization; SC, subcutaneous.

Please refer to https://clinicaltrials.gov/ct2/show/**NCT04456673**, clinical trial number **NCT04456673** for updated information as necessary.

MAT-US-2110349 V5 - P Expiration Date: 10/12/2024

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Eligibility criteria

Key inclusion criteria*

- Physician diagnosis of COPD meeting the following criteria:
  - » Current/former smokers with a smoking history of ≥10 pack-years
  - » Moderate-to-severe COPD†
  - » MRC Dyspnea Scale Grade ≥2
  - » Patient-reported history of signs and symptoms of chronic bronchitis for 3 months in the previous year up to screening in the absence of other known causes of chronic cough
  - » Documented history of high exacerbation risk‡
  - » Background triple-therapy (ICS + LABA + LAMA) for 3 months prior to randomization with a stable dose of medication for ≥1 month prior to Visit 1. Double therapy (LABA + LAMA) allowed if ICS is contraindicated
- Evidence of type 2 inflammation: Patients with blood eosinophils ≥300 cells/µL at Visit 1

Key exclusion criteria*

- COPD diagnosis for <12 months prior to randomization
- Current diagnosis of asthma or history of asthma according to the GINA guidelines or documented history of asthma
- Significant pulmonary disease other than COPD or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts
- Cor pulmonale, evidence of right cardiac failure
- Long-term treatment with oxygen >4.0 L/min OR if a participant requires more than 2.0 L/min in order to maintain oxygen saturation >88%
- Hypercapnia that requires bi-level ventilation
- Diagnosis of α-1 antitrypsin deficiency
- AECOPD as defined in inclusion criteria within 4 weeks prior to screening, or during the screening period
- Respiratory tract infection within 4 weeks of screening, or during screening period
- History of, or planned pneumonectomy or lung volume reduction surgery

What are we looking for?

Primary endpoint

- Annualized rate of moderate or severe COPD exacerbations (AECOPD) over the 52-week treatment period compared to placebo‡

Secondary endpoints

- Change in pre-bronchodilator FEV_1#:
  - » from baseline to Week 12
  - » from baseline to time points up to Week 52
- Change in SGRQ#§
- Improvement in SGRQ§
- Change in post-bronchodilator FEV_1 lung function from baseline to Weeks 2, 4, 8, 12, 24, 36, 52#
- Change in FEF 25–75% from baseline to Weeks 2, 4, 8, 12, 24, 36, 44, and 52
- Annualized rate of severe AECOPD#§
- Time to first AECOPD#§
- AEs/TEAEs through Week 64
- PCSA in laboratory tests from baseline to Week 64
- Anti-drug antibodies from baseline to Week 64

Please talk to your Sanofi or Regeneron Medical Affairs representative if you would like to find out more information or email **Contact-US@sanofi.com**

*Other protocol-defined inclusion/exclusion criteria may apply.

†Post-bronchodilator FEV_1/ forced vital capacity (FVC) ratio <0.70 and post-bronchodilator FEV_1 % predicted >30% and ≤70%.

‡Defined as exacerbation history of ≥2 moderate or ≥1 severe within the year prior to inclusion. At least one exacerbation should have occurred while the patient was taking inhaled corticosteroid (ICS)/long acting beta agonist (LABA)/long acting muscarinic antagonist (LAMA) (or LABA/LAMA if ICS is contraindicated). Moderate exacerbations are recorded by the investigator and defined as AECOPD that require either systemic corticosteroids (intramuscular, intravenous, or oral) and/or antibiotics. One of the two required moderate exacerbations has to require the use of systemic corticosteroids. Severe exacerbations are recorded by the investigator and defined as AECOPD requiring hospitalization or observation >24 hours in emergency department/urgent care facility.

#Compared with placebo.

§From baseline to Week 52.

AE, adverse event; AECOPD, acute exacerbations of COPD; COPD, chronic obstructive pulmonary disease; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; GINA, global initiative for asthma; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MRC, medical research council; PCSA, potentially clinically significant abnormality; SGRQ, St. George's respiratory questionnaire; TEAE, treatment-emergent adverse event.

NOTUS is currently recruiting in Australia, Europe, North America, South Africa, the Russian Federation, Mexico and South America.
These details align with the recruitment status on clinicaltrials.gov as of July 2022

Please refer to https://clinicaltrials.gov/ct2/show/**NCT04456673**, clinical trial number **NCT04456673** for updated information as necessary.

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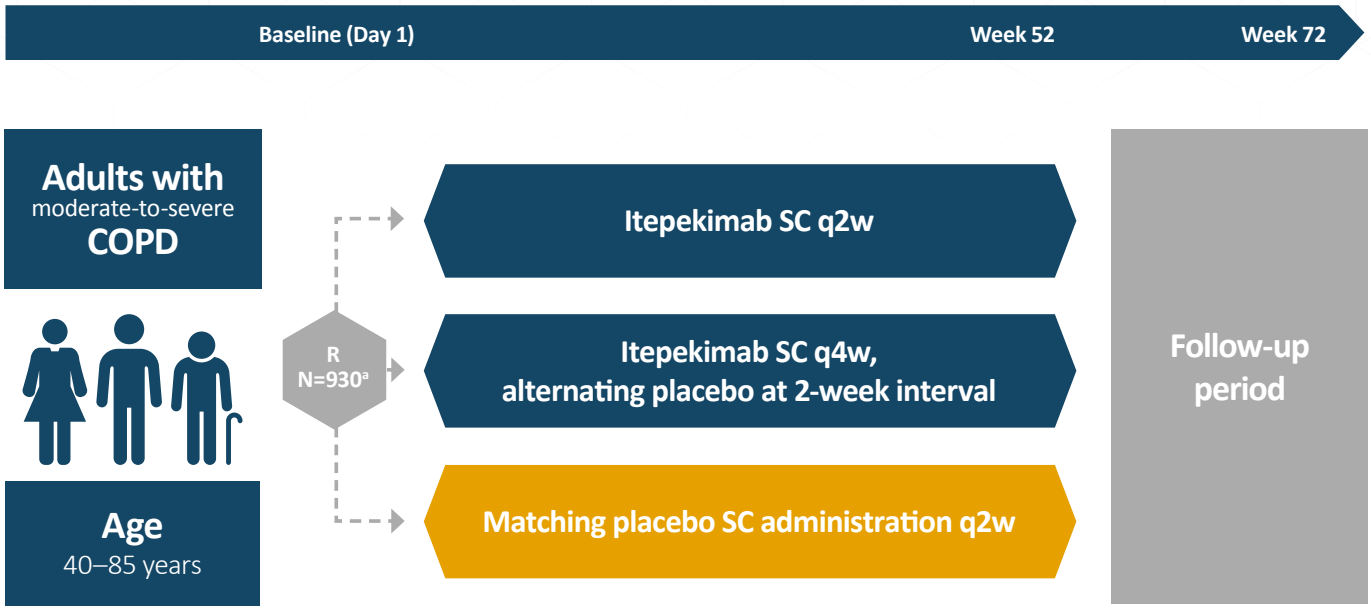
A study to assess the efficacy, safety and tolerability of SAR440340/REGN3500/ Itepekimab in Chronic Obstructive Pulmonary Disease (COPD) (AERIFY-1)

Primary Objective
To evaluate the efficacy of itepekimab compared with placebo on the annualized rate of acute moderate-or-severe COPD exacerbations in former smokers with moderate-to-severe COPD

AERIFY-1



[a]Estimated enrollment.
q2w, every 2 weeks; q4w, every 4 weeks; R, randomization; SC, subcutaneous.

Please refer to https://clinicaltrials.gov/ct2/show/**NCT04701983**, clinical trial number **NCT04701983** for updated information as necessary.

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Eligibility criteria

Key inclusion criteria*

- Age 40–85 inclusive
- Physician diagnosis of COPD for at least 1 year according to GOLD definition
- Smoking history of ≥10 pack-years[†]
- Moderate-to-severe COPD
- History of signs and symptoms of chronic bronchitis
- History of high exacerbation risk[‡]
- Participants with standard of care controller therapy, for ≥3 months prior to screening (visit 1A) and at a stable dose of controller therapy for at least 1 month prior to the screening[#]
- Body mass index (BMI) ≥18.0 kg/m^2
- Female participant who is not pregnant, breastfeeding and with at least one of the following conditions:
  - » Not a woman of child-bearing potential OR
  - » A woman of child-bearing potential who agrees to follow contraceptive guidance during the intervention and for at least 20 weeks after the last dose of study intervention

Key exclusion criteria*

- Current diagnosis of asthma according to the GINA guidelines, or documented history of asthma
- Active smoking or vaping of any products within 6 months prior to screening (visit 1A)
- Clinically significant new abnormal ECG within 6 months prior to or at screening (visit 1A)
- Clinically significant and current pulmonary disease other than COPD
- Diagnosis of cor pulmonale, evidence of right cardiac failure or moderate-to-severe pulmonary hypertension
- Hypercapnia requiring BiPAP
- Moderate or severe exacerbation of COPD (AECOPD) within 4 weeks prior to screening (visit 1A)
- Prior history/planned lung pneumonectomy or lung volume reduction procedures for COPD
- Unstable ischemic heart disease or unstable angina in the 6 months prior to screening (visit 1A)
- Cardiac arrhythmias
- Uncontrolled hypertension
- Participants with active, latent or a history of incompletely treated TB, or suspected extrapulmonary TB infection. Also, those who are at high risk of contracting TB or received BCG vaccination within 12 weeks prior to screening (visit 1A)
- History of HIV infection or positive HIV1/2 serology at screening (visit 1A)
- Suspicion of or confirmed COVID-19 infection or in contact with known exposure to COVID-19 at screening (visit 1A)[§]
- Evidence of acute or chronic infection requiring systemic treatment with anti-bacterial, antiviral, antifungal, antiparasitic or antiprotozoal medications within 4 weeks before screening (visit 1A) or significant viral infections within 4 weeks before screening (visit 1A) that may not have been treated
- Participants with active autoimmune disease or participants using immunosuppressive therapy for autoimmune disease
- History of malignancy within 5 years prior to screening (visit 1A)[‖]
- Previous use of itepekimab

What are we looking for?

Primary endpoint (From baseline up to Week 52)

- Annualized rate of moderate-to-severe acute exacerbation of COPD (AECOPD)

Secondary endpoints

- Change from baseline in pre-BD FEV_1 at Week 24

From baseline up to Week 52:

- Change in pre-BD FEV_1
- Change in post-BD FEV_1
- Time to first moderate or severe AECOPD
- Annualized rate of severe AECOPD
- Time to first severe AECOPD
- Annualized rate of corticosteroid-treated AECOPD
- Change from baseline in E-RS:COPD
- Rate of change in post-BD FEV_1
- Change from baseline in SGRQ total score
- Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score

From baseline up to Week 72:

- Incidence of TEAEs, AESIs, SAEs and AEs leading to permanent treatment discontinuation
- Incidence of potentially clinically significant laboratory test, vital signs, and ECG abnormalities
- Functional itepekimab concentrations in serum
- Incidence of treatment-emergent anti-itepekimab antibody responses

Please talk to your Sanofi or Regeneron Medical Affairs representative if you would like to find out more information or email **Contact-US@sanofi.com**

*Other protocol-defined inclusion/exclusion criteria may apply.
[†]Who are not currently smoking and stopped smoking ≥6 months prior to screening (visit 1A) with an intention to quit permanently.
[‡]Defined as having had ≥2 moderate or ≥1 severe exacerbation within the year prior to screening (visit 1A). At least one exacerbation must have occurred while participants were on their current controller therapy.
[#]Including either inhaled corticosteroid (ICS) + long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA) + LABA or LAMA + LABA + ICS.
[§]Known history of COVID-19 infection within 4 weeks prior to screening (visit 1A); history of requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) secondary to COVID-19 within 3 months prior to screening (visit 1A); participants who have had a COVID-19 infection prior Screening (Visit 1A) who have not yet sufficiently recovered to participate in the procedures of a clinical trial.
[‖]Except for completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.
AE, adverse events; AECOPD, acute exacerbation of COPD; AESIs, adverse event of special interests; BCG, Bacillus Calmette-Guérin; BD, bronchodilator; BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; E-RS:COPD, Evaluating Respiratory Symptoms in COPD; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HIV, human immunodeficiency virus; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; q2w, administered every 2 weeks; q4w, administered every 4 weeks; SAEs, serious adverse events; SC, subcutaneous; SGRQ, St. George''s Respiratory Questionnaire; TB, tuberculosis; TEAEs, treatment-emergent adverse events.

AERIFY-1 is currently recruiting in North America, South America, Mexico, Europe, Russian Federation, Israel and Asia.
These details align with the recruitment status on clinicaltrials.gov as of July 2022

Please refer to https://clinicaltrials.gov/ct2/show/**NCT04701983** , clinical trial number **NCT04701983** for updated information as necessary.

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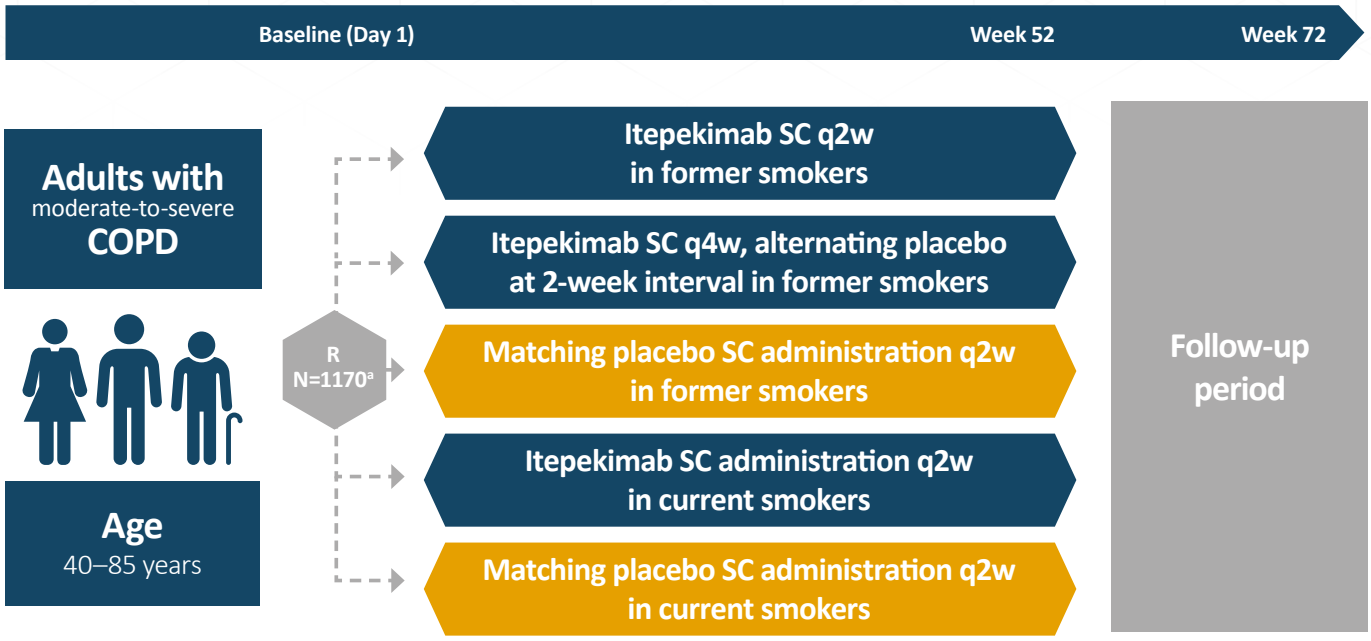
A study to assess the efficacy, safety and tolerability of SAR440340/REGN3500/ Itepekimab in Chronic Obstructive Pulmonary Disease (COPD) (AERIFY-2)

Primary Objective
To evaluate the efficacy of itepekimab compared with placebo on the annualized rate of acute moderate-or-severe COPD exacerbations in former smokers with moderate-to-severe COPD

AERIFY-2



[a]Estimated enrollment.
q2w, every 2 weeks; q4w, every 4 weeks; R, randomization; SC, subcutaneous.

Please refer to https://clinicaltrials.gov/ct2/show/**NCT04751487**, clinical trial number **NCT04751487** for updated information as necessary.

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Eligibility criteria

Key inclusion criteria*

- Age 40–85 inclusive
- Physician diagnosis of COPD for at least 1 year based on GOLD definition
- Smoking history of ≥10 pack-years†
- Moderate-to-severe COPD
- History of signs and symptoms of chronic bronchitis
- History of high exacerbation risk‡
- Participants with standard of care controller therapy for ≥3 months prior to screening (visit 1A) and at a stable dose of controller therapy for at least 1 month prior to the screening#
- Body mass index (BMI) ≥18.0 kg/m²
- Female participant who is not pregnant, not breastfeeding and with at least one of the following conditions:
  - » Not a woman of child-bearing potential OR
  - » A woman of child-bearing potential who agrees to follow contraceptive guidance during the intervention and for at least 20 weeks after the last dose of study intervention

Key exclusion criteria*

- Current diagnosis of asthma according to the GINA guidelines, or documented history of asthma
- Active smoking or vaping of any products (for former smokers) within 6 months prior to screening (visit 1A)
- Vaping within 6 months (for current smokers) prior to screening (visit 1A)
- Clinically significant new abnormal ECG within 6 months prior to, or at screening (visit 1A)
- Clinically significant and current pulmonary disease other than COPD
- Diagnosis of cor pulmonale, evidence of right cardiac failure, or moderate-to-severe pulmonary hypertension
- Hypercapnia requiring BiPAP
- Moderate or severe exacerbation of COPD (AECOPD) within 4 weeks prior to screening (visit 1A)
- Prior history/planned lung pneumonectomy or lung volume reduction procedures for COPD
- Unstable ischemic heart disease within the past year prior to screening or unstable angina in the 6 months prior to screening (visit 1A)
- Cardiac arrhythmias including paroxysomal atrial fibrillation
- Uncontrolled hypertension
- Participants with active, latent or a history of incompletely treated TB, or suspected extrapulmonary TB infection. Also, those who are at high risk of contracting TB or received BCG vaccination within 12 weeks prior to screening (visit 1A)
- History of HIV infection or positive HIV1/2 serology at screening (visit 1A)
- Suspicion of or confirmed COVID-19 infection or in contact with known exposure to COVID-19 at screening (visit 1A)§
- Evidence of acute or chronic infection requiring systemic treatment with anti-bacterial, antiviral, antifungal, antiparasitic or antiprotozoal medications or significant viral infections within 4 weeks before screening (visit 1A) that may not have been treated with antiviral treatment
- Participants with active autoimmune disease or participants using immunosuppressive therapy for autoimmune disease
- History of malignancy within 5 years prior to screening (visit 1A)‖
- Previous use of itepekimab

What are we looking for?

Primary endpoint (From baseline up to Week 52)

- Annualized rate of moderate or severe acute exacerbation of COPD (AECOPD)¶

Secondary endpoints

From baseline to Week 24:

- Change in pre-BD FEV_1 ¶

From baseline up to Week 52:

- Change in pre-BD FEV_1 ¶
- Change in post-BD FEV_1 ¶
- Time to first moderate or severe AECOPD¶
- Annualized rate of severe AECOPD¶
- Time to first severe AECOPD¶
- Annualized rate of corticosteroid treated AECOPD¶
- Change in E-RS:COPD¶
- Rate of change in post-BD FEV_1 ¶
- Change from baseline in SGRQ total score¶
- Proportion of participants with a decrease from baseline of at least 4 points in SGRQ¶
- Annualized rate of moderate or severe AECOPD°
- Change in pre-BD FEV_1 °

From baseline up to Week 72:

- Incidence of TEAEs, AESIs, SAEs and AEs leading to permanent treatment discontinuation¶
- Incidence of potentially clinically significant laboratory test, vital signs, and ECG abnormalities¶
- Functional itepekimab concentrations in serum¶
- Incidence of treatment-emergent anti-itepekimab antibodies responses¶
- Incidence of TEAEs, AESIs, SAEs and AEs leading to permanent treatment discontinuation°
- Functional itepekimab concentrations in serum°
- Incidence of treatment-emergent anti-itepekimab antibodies responses°

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*Other protocol-defined inclusion/exclusion criteria may apply.
†For former smokers: participants who report they're not currently smoking and stopped ≥6 months prior to screening (visit 1A). For current smokers: participants who report they're currently smoking at screening (visit 1A) and who are not participating/planning to initiate a smoking cessation intervention at screening (visit 1A) or during screening.
‡Defined as having ≥2 moderate of ≥1 severe exacerbations within the year prior to screening (visit 1A). At least one exacerbation must have occurred while participants were on their current controller therapy. Moderate exacerbations will be recorded by the Investigator and defined as acute worsening of respiratory symptoms that require systemic corticosteroids and/or antibiotics. Severe exacerbations will be recorded by the Investigator and defined as AECOPD that require hospitalization or observation for >24 hours in the emergency department/urgent care facility.
#Including either inhaled corticosteroid (ICS) + long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA) + LABA or LAMA + LABA + ICS.
§Known history of COVID-19 infection within 4 weeks prior to Screening (Visit 1A); history of requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) secondary to COVID-19 within 3 months prior to Screening (visit 1A); participants who have had a COVID-19 infection prior to Screening (visit 1A) who have not yet sufficiently recovered to participate in the procedures of a clinical trial.
‖Except the completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.
¶In former smokers.
°In current smokers.
AE, adverse events; AECOPD, acute exacerbation of COPD; AESIs, adverse event of special interests; BCG, Bacillus Calmette-Guérin; BD, bronchodilator; BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; E-RS:COPD, Evaluating Respiratory Symptoms in COPD; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HIV, human immunodeficiency virus; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; q2w, administered every 2 weeks; q4w, administered every 4 weeks; SAEs, serious adverse events; SC, subcutaneous; SGRQ, St. George''s Respiratory Questionnaire; TB, tuberculosis; TEAEs, treatment-emergent adverse events.

AERIFY-2 is currently recruiting in North America, South America, Mexico, Europe, Asia, Russian Federation, Israel, Turkey, Puerto Rico and South Africa.
These details align with the recruitment status on clinicaltrials.gov as of July 2022

Please refer to https://clinicaltrials.gov/ct2/show/**NCT04751487**, clinical trial number **NCT04751487** for updated information as necessary.

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