AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A randomized, double-blind, placebo-controlled, parallel-group, dose ranging study to assess the efficacy, safety, and tolerability of subcutaneous amlitelimab in adult participants with moderate-to-severe asthma**
Protocol number:	**DRI17509**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR445229 amlitelimab/Not applicable**
Brief title:	**Dose ranging study of amlitelimab in adult participants with moderate-to-severe asthma**
Acronym:	**TIDE-asthma**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette, 91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	

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Other:	Not applicable

Date: 14-Dec-2023 Total number of pages: 144

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	All	14 December 2023, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	South Korea	03 April 2023, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	23 November 2022, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	17 June 2022, version 1 (electronic 1.0)
Original Protocol		09 March 2022, version 1 (electronic 3.0)

Amended protocol 04 (14 December 2023)

This amended protocol (amendment 04) is considered to be non-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 because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is amended to modify the type of interim analysis.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk assessment	[redacted]	Risk assessment description of this case in the context of the study.
1.1 Synopsis 4.1 Overall design 6.1 Study intervention(s) administered	Sentence added for non-IMPs: "The class of reliever medication should not change during the study."	Background therapy should remain stable throughout the study, clarification added for reliever medications.
6.8.4 Prohibited concomitant medication	Systemic steroids use allowed for up to 7 consecutive days.	Systemic steroids for treatment of conditions other than asthma are allowed for up to 7 consecutive days.
7.2 Participant discontinuation/withdrawal from the study	A note has been added: "Safety follow-up (EOS, end-of-study) visit should be performed after [redacted] after the last IMP."	Clarification.

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
1.1 Synopsis and 9.2.2 Primary endpoint(s) analysis	Primary endpoint supplementary analysis of intercurrent events was detailed.	Clarification.
1.1 Synopsis and 9.2.3 Secondary endpoint(s) analysis	Modification of “supportive” analyses of intercurrent events to “supplementary” analysis.	Harmonization.
[redacted]	[redacted]	[redacted]
10.2 Appendix 2: Clinical Laboratory tests	Addition of the following tests to the list: uric acid, total cholesterol, albumin, lactate dehydrogenase, chloride, bicarbonate.	List of the study central laboratory tests was incomplete.
10.6 Appendix 6: Liver and other safety: suggested actions and follow-up assessments	Update of the management of increase in ALT as per Sanofi standard.	Clarification.
Section 10.12 Appendix 12: Protocol amendment history	The text of summary of changes for Protocol amendment 03 is added.	Appendix 12 is updated to reflect the document history of previous amendment.
Throughout the document	Small changes (editorial) have been made.	Clarification.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A randomized, double-blind, placebo-controlled, parallel-group, dose ranging study to assess the efficacy, safety, and tolerability of subcutaneous amlitelimab in adult participants with moderate-to-severe asthma

Brief title:

Dose ranging study of amlitelimab in adult participants with moderate-to-severe asthma

Rationale:

Amlitelimab (also known as SAR445229 or KY1005), a human anti-OX40 ligand (OX40L, CD252) monoclonal antibody (mAb) (subclass IgG4PE kappa) that binds OX40L to block the interaction with its receptor, OX40 (CD134), is an investigational drug being developed for the treatment of immune-mediated diseases. This study will explore the efficacy and safety of amlitelimab in adult participants with moderate-to-severe asthma.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of different doses of amlitelimab compared to placebo in participants with moderate-to-severe, uncontrolled asthma.	• Annualized rate of severe exacerbation events over 48 weeks, defined as: - Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of oral corticosteroids (OCS) for the treatment of asthma, a doubling of the dose for 3 or more days; or - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids
Secondary	
• To evaluate the effects of amlitelimab compared to placebo on lung function as measured by forced expiratory volume in 1 second (FEV1)	• Change from baseline in pre-bronchodilator (BD) FEV1 at Week 48 (**key secondary endpoint**) • Change from baseline in post-BD FEV1 at Week 48 • The absolute change in the percent predicted FEV1 from baseline to Week 48 (pre-BD and post-BD)
• To evaluate the effects of amlitelimab on Asthma Control Questionnaire 5 (ACQ-5)	• Change from baseline in ACQ-5 score at Week 48 (**key secondary endpoint**) • Change from baseline in ACQ-5 score at Weeks 2, 4, 8, 12, 24, 36, and 60

Objectives	Endpoints
• To evaluate the effects of amlitelimab on time to first severe exacerbation event	• Time to first severe exacerbation event
• To evaluate the effects of amlitelimab on other spirometry assessments	• Change from baseline in pre-BD and post-BD FEV1 and other lung function measurements (peak expiratory flow [PEF], forced vital capacity [FVC], and forced expiratory flow [FEF] 25-75%) at each spirometry endpoint
• To evaluate the effects of amlitelimab on fraction of exhaled nitric oxide (FeNO)	• Change from baseline in FeNO at Weeks 2, 4, 8, 12, 16, 24, 36, 48 and 60
• To evaluate the effects of amlitelimab compared to placebo on reducing the incidence of "loss of asthma control" (LOAC) events	• Annualized rate of LOAC events, during 48 weeks of treatment, defined by one or several of the following criteria: - A 30% or greater reduction from baseline in morning PEF on 2 consecutive days. - ≥6 additional reliever puffs of short-acting beta 2-agonists (SABA) OR ≥4 additional puffs of low-dose ICS/formoterol in a 24-hour period (compared to baseline) on 2 consecutive days - Increase in ICS ≥4 times than the Visit 2 dose - Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of OCS for the treatment of asthma, a doubling of the dose for 3 or more days - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids severe exacerbation event
• To evaluate the effects of amlitelimab on time to first LOAC event	• Time to first LOAC event
• To evaluate the effects of amlitelimab on asthma symptoms	• Change from baseline in the Asthma Daytime Symptom Diary (ADSD) 6-item daily morning score and in the Asthma Nighttime Symptom Diary (ANSD) 6-item daily evening scores at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
• To evaluate the effects of amlitelimab on reducing the incidence of severe asthma exacerbations requiring hospitalization or emergency room or urgent care visit	• Annualized rate of severe asthma exacerbations requiring hospitalization or emergency room or urgent care visit during 48 weeks of treatment
• Assess the effect of amlitelimab on BD therapy	• Change from baseline in the numbers of inhalations/day of SABA or low-dose ICS/formoterol for symptom relief at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
• To evaluate the pharmacokinetics (PK) of amlitelimab and anti-drug antibodies to amlitelimab in participants with asthma	• Serum amlitelimab concentrations measured throughout the study • Incidence of anti-amlitelimab antibody positive response

Objectives	Endpoints
• To evaluate the safety of amlitelimab in participants with asthma	• Percentage of participants with treatment-emergent adverse events (TEAEs), including local reactions, adverse events of special interest (AESIs), serious adverse events (SAEs) • Incidence of potentially clinically significant laboratory test, vital signs, and ECG abnormalities in the treatment period
• To evaluate the effects of amlitelimab on participant reported outcomes (PROs)	• Change from baseline in Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered Score at Week 48 **(key secondary endpoint)** • AQLQ (S) Self-Administered Score at Weeks 2, 4, 8, 12, 24, 36, and 60 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Weeks 2, 4, 8, 12, 24, 36, 48, and 60 • Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 48
• To evaluate the effects of amlitelimab on ACQ-6 and ACQ-7	• Change from baseline in ACQ-6 score and ACQ-7 at Weeks 2, 4, 8, 12, 24, 36, 48, and 60

Overall design:

This is a Phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of add-on therapy with subcutaneous (SC) amlitelimab in adult participants (aged 18-75 years, inclusive) with moderate-to-severe asthma. All eligible participants will be randomized into (2:2:1:2) ratio and treated for 60 weeks, receiving a SC administration of amlitelimab every 4 weeks (Q4W) for the first 6 doses and every 12 weeks (Q12W) thereafter or matching placebo according to one of the following doses:

- Amlitelimab 250 mg with 500 mg loading dose on Day 1
- Amlitelimab 125 mg with 250 mg loading dose on Day 1
- Amlitelimab 62.5 mg with 125 mg loading dose on Day 1
- Matching placebo

Randomization will be stratified by Screening Visit 1 eosinophil count (<300 cells/μL and ≥300 cells/μL), number of severe asthma exacerbations (as defined above in the 'objectives and endpoints' table) in the previous 12 months (=1 exacerbation or >1 exacerbations) and by region.

To avoid recruiting a skewed population due to competing studies, alerts will be built into the interactive voice/web response system (IVRS/IWRS) to limit enrolling participants in the following 2 stratification groups:

- Only 1 severe asthma exacerbation in the previous 12 months: not more than approximately 50% of participants (210 participants).
- Eosinophils <300 eosinophils/µL: not more than approximately 50% of participants (210 participants).

Amlitelimab will be administered as add-on therapy to inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], methylxanthines, long-acting muscarinic antagonist [LAMA]) with or without oral prednisone for the maintenance treatment of asthma. Participants requiring a third controller are allowed to participate in this study (please see Section 5.1), which consists of three periods:

- Screening period (up to 4 weeks) to determine whether participants meet entry criteria and to establish the level of asthma control before randomization
- Randomized treatment period (approximately 60 weeks)
- Follow-up period (approximately 12 weeks) to monitor participants after treatment
  - Eligible participants who complete the treatment period will be offered the opportunity to participate in the long term safety (LTS) study with amlitelimab. Participants subsequently enrolled in the LTS study will not participate in the follow-up period of this trial but will have a follow up period after the LTS study.

Brief summary:

This is a parallel, Phase 2, global, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, four-arms study for treatment.

The purpose of this study is to assess the efficacy, safety, and tolerability of add-on therapy with amlitelimab in adult participants with moderate-to-severe asthma.

Study details include:

- The study duration (per participant) will be up to approximately 76 weeks for participants not going into LTS study and will be up to approximately 64 weeks for participants going into LTS study.
- The randomized treatment duration will be up to approximately 60 weeks.
- The scheduled number of visits will be 13.

Number of participants:

Approximately 420 participants will be randomized to study intervention.

Note: Randomized participants are all participants from screened participants who have been allocated to an intervention by IVRS/IWRS regardless of whether the intervention was received or not.

Intervention groups and duration:

All participants will receive SC administration of amlitelimab 250 mg with 500 mg loading dose on Day 1, or 125 mg with 250 mg loading dose on Day 1, or 62.5 mg with 125 mg loading dose on Day 1 or matching placebo, Q4W for the first 6 doses and Q12W thereafter until Week 48 for all arms.

Study intervention(s)

Amlitelimab and placebo matching amlitelimab are supplied as solutions in vials that are visually indistinguishable.

Investigational medicinal product(s)

- Formulation:
  - Amlitelimab: a 125 mg/mL amlitelimab solution in a vial to deliver up to 125 mg of amlitelimab in a 1 mL injection.
  - Placebo matching amlitelimab: identical formulation to the active amlitelimab formulation without amlitelimab, in a vial to deliver placebo in a up to 1 mL injection.
- Route(s) of administration: SC injection, to abdomen or outer thigh. IMP should not be administered at the exact site of a recent injection or in areas which in the Investigator's opinion are not suitable (eg, tender, bruised, red or hard).
- Dose regimen:
  - Amlitelimab 250 mg with 500 mg loading dose treatment group: one initial loading dose of 500 mg of amlitelimab (two 2 mL injections of 250 mg of amlitelimab) on Day 1, followed by one 2 mL injection of 250 mg of amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.
  - Amlitelimab 125 mg with 250 mg loading dose treatment group: one initial loading dose of 250 mg of amlitelimab (two 2 mL injection of 125 mg of amlitelimab) on Day 1, followed by one 2 mL injection of 125 mg of amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.
  - Amlitelimab 62.5 mg with 125 mg loading dose treatment group: one initial loading dose of 125 mg of amlitelimab (two 2 mL injections of 62.5 mg of amlitelimab) on Day 1, followed by one 2 mL injection of 62.5 mg of amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.
  - Placebo treatment group: one initial dummy loading dose of only placebo (two 2 mL injections of placebo matching amlitelimab) on Day 1, followed by one 2 mL injection of placebo matching amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.

Noninvestigational medicinal products

On a daily basis throughout the study, the participant will use an electronic diary (eDiary) to record daily use of ICS in combination or administered concurrently with other controllers as used just prior to screening.

The recognized asthma controllers for the study will include the following 5 classes: ICS, LABA, LAMA, anti-leukotrienes and methylxanthines. Please refer to Section 10.10.3 for a list of commonly used asthma controller medication.

- Screening period:

  Prior to screening, participants must be on a stable background therapy for at least 3 months, composed of medium to high dose ICS (≥500 µg fluticasone propionate daily or comparable ICS dosage up to a maximum of 2000 µg/day of fluticasone propionate or clinically comparable ([1], see Section 10.10.1) in combination with a second controller medication (eg, LABA, LTRA, LAMA, methylxanthines) with stable doses ≥1 month prior to Visit 1. Participants requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1. For Japan, please see Section 10.8 for details.

  Route of administration: Oral inhalation

  If on chronic oral corticosteroid (OCS) treatment for the maintenance treatment of asthma, up to a maximum of 15 mg prednisone or equivalent daily or 30 mg every other day, must be on stable dose for ≥1 month prior to Visit 1 (see Section 10.10.2 for comparison of systemic glucocorticoid preparations).

  Route of administration: Oral tablets.

- Randomized treatment period:

  During this period, participants will continue to take their controller medication(s) used during the screening period and will use an eDiary to record daily use. The dose and regimen should not be changed, except for the OCS, for which the dose could be changed per Investigator medical judgement.

- Follow-up period:

  Upon completing the randomized treatment period, participants will proceed to be treated with the controller medication regimen and dose used during the randomized treatment period, which could be adjusted based on the medical judgment of the Investigator of the participants' asthma control status.

Reliever Medication

Participants may administer SABA metered dose inhaler (MDI) and dry powder inhaler (DPI) as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method, if previously used by the patient. Alternatively, low-dose ICS/formoterol may be used as reliever medication, per Global Initiative for Asthma (GINA) 2021 recommendation (2) and Investigator discretion. The class of reliever medication should not change during the study. Reliever medication use will be recorded in the eDiary. Please refer to Section 6.8.2 for a list of commonly used asthma reliever medications.

Route of administration: Oral inhalation

Devices:

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

- Electronic Diaries
- Spirometry devices
- Electronic Spirometry devices for remote spirometry and PEF measurement
- Digital inhalers to measure the reliever use (in certain countries, optional)
- Impulse oscillometry devices
- FeNO measurement devices
- Laboratory kits including tubes, needles, dipsticks
- IMP transportation material as described in the Pharmacy Manual

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

Duration of study intervention

Eligible participants who complete the treatment period will be offered the opportunity to participate in the LTS study with amlitelimab. Participants subsequently enrolled in the LTS study will not participate in the follow-up period of this trial but will have a follow up period after the LTS study.

Total duration would be approximately 76 weeks for participants not going into LTS study, including up to 4 weeks for screening period, approximately 60 weeks for randomized treatment period, and approximately 12 weeks for follow up period.

Total duration would be approximately 64 weeks for participants going into LTS study, including up to 4 weeks for screening period and approximately 60 weeks for randomized treatment period, then enrollment into LTS study.

Statistical considerations:

[redacted]

[redacted]

[redacted]

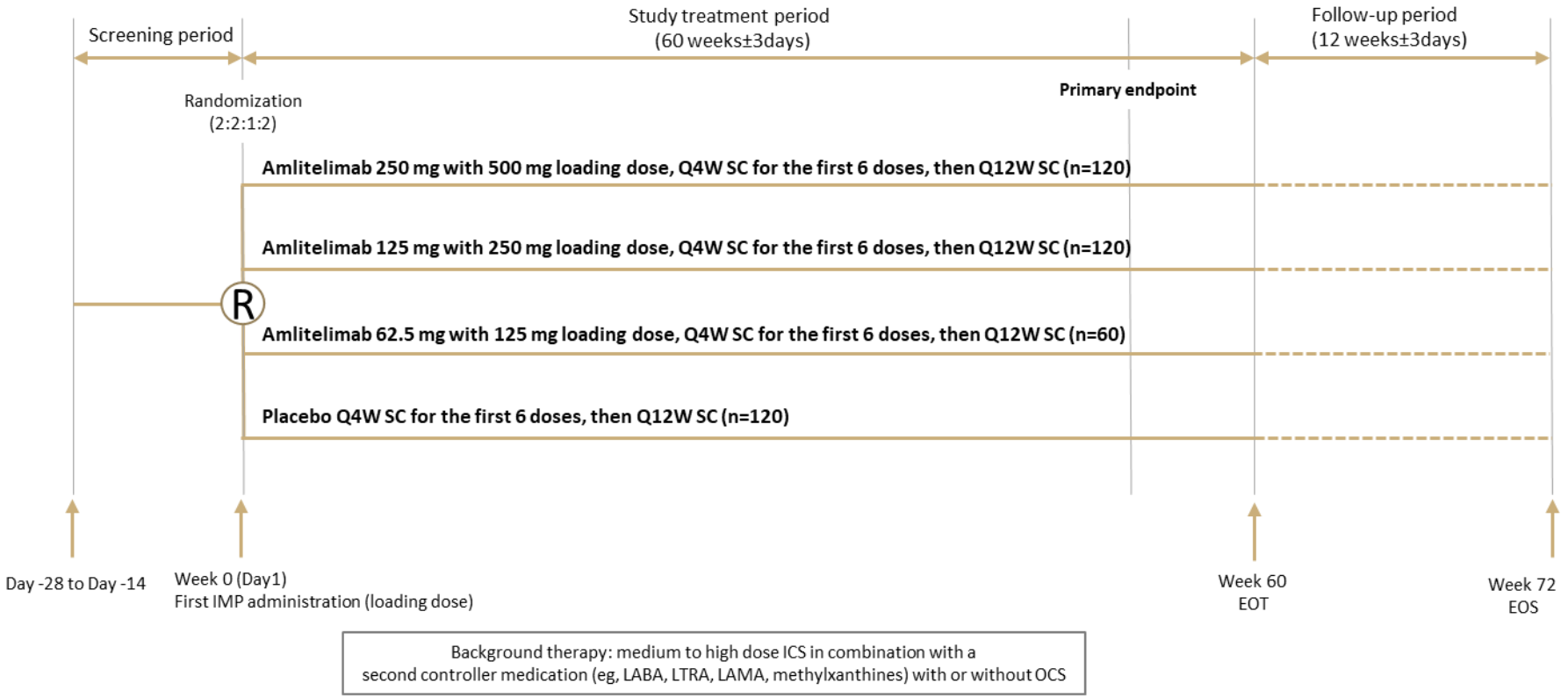
Data Monitoring/Other committee: Yes

A Data Monitoring Committee (DMC) has been appointed for this study. The DMC (board) is a group of independent physician and scientist experts who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

The DMC procedures and safety data to be reviewed by the DMC are described in the DMC charter. In the above 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.

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: mg: milligrams; Q4W: every 4 weeks; Q12W: every 12 weeks; SC: subcutaneous; EOT: end of treatment; EOS: end of study; LABA: long-acting beta agonist; LTRA: leukotriene receptor antagonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; OCS: oral corticosteroid; IMP: investigational medicinal product

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (Week -4 to -2)[aa]	Randomized treatment period (60 weeks)	Follow-up (12 weeks after EOT)	Early treatment discontinuation
Visit	[redacted]			
Visit Days				
Visit window (days)				
Visit Weeks				
Informed consent[a]				
Inclusion and exclusion criteria				
Demography				
Previous medical and surgical history				
Qualifying Spirometry and Reversibility[b]				
Prior & concomitant medications				
IVRS/IWRS				
Randomization				
Study intervention				
IMP administration[c]				
NIMP administration				
Safety				
Full physical examination[d]				

Procedure	Screening (Week -4 to -2)[aa]	Randomized treatment period (60 weeks)	Follow-up (12 weeks after EOT)	Early treatment discontinuation
Visit	[redacted]			
Visit Days				
Visit window (days)				
Visit Weeks				
Pregnancy test (WOCBP only, serum at Screening, urine thereafter)[e]				
HIV, Hepatitis B and C screening[f]				
Laboratory tests (include clinical chemistries)[g]				
12-lead ECG[h]				
Vital signs[i]				
TB assessment[j]				
COVID-19 testing[k]				
AE reporting, including SAEs				
Pharmacokinetics				
PK sampling[o]				
Anti-drug antibodies (serum)[o]				
Electronic Diary and digital devices[z]				
eDiary dispensation	[redacted]			
eDiary review				

Procedure	Screening (Week -4 to -2)[aa]	Randomized treatment period (60 weeks)	Follow-up (12 weeks after EOT)	Early treatment discontinuation
Visit	[redacted]			
Visit Days				
Visit window (days)				
Visit Weeks				
e-Spirometer dispensation[m]				
Digital inhaler dispensation and instruction (in certain countries)[l]				
[redacted]				
Exhaled nitric oxide (FeNO)[n]				
[redacted]				
Efficacy				
Spirometry (pre-BD) [t, n]				

Procedure	Screening (Week -4 to -2)[aa]	Randomized treatment period (60 weeks)	Follow-up (12 weeks after EOT)	Early treatment discontinuation
Visit	[redacted]			
Visit Days				
Visit window (days)				
Visit Weeks				
Spirometry (post-BD)[t, n]				
[redacted]				
Remote spirometry (pre-BD) training/instructions[u]				
Remote spirometry (pre-BD)[v]				
ACQ-7[w]				
ANSD (AM)[x]				
ADSD (PM)[x]				
PROs				
AQLQ(S)				
SGRQ				
[redacted]				

Abbreviations: EOT=End of Treatment; EOS=End of Study; IMP=investigational medicinal product; NIMP=Non investigational medicinal product; WOCBP=women of childbearing potential; IVRS/IWRS=interactive voice/web response system; HIV=human immunodeficiency virus; ECG=electrocardiogram; TB=tuberculosis; AE=adverse event; SAE=serious adverse event; PK=pharmacokinetics; PEF=peak expiratory flow;

eDiary=electronic Diary; e-Spirometer=electronic Spirometer; ADSD=Asthma Daytime Symptom Diary; ANSD=Asthma Nighttime Symptom Diary; FeNO=fraction of exhaled nitric oxide; IgE=Immunoglobulin E; DNA=deoxyribonucleic acid; BD=bronchodilator; ACQ-7=asthma control questionnaire-7; PRO=participant-reported outcome; SGRQ=St. George's Respiratory Questionnaire; AQLQ (S)=Asthma Quality Of Life Questionnaire with Standardized Activities; [redacted]

a Informed consent will cover study consent to all mandatory tests as per SoA. Optional consent will cover pharmacogenetics analysis and use of data and samples for future research.

b Participants with reversibility of at least 12% and 200 mL in FEV1 after administration of 2 to 4 puffs (200-400 μg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that meets these criteria within 12 months prior to Visit 1 is considered acceptable to meet this inclusion criteria (I 07). Alternatively, a Severe Asthma Research Program (SARP) method could be used: maximal change in FEV1 after the administration of 4, 6, and 8 puffs of albuterol (360, 540, 720 μg albuterol). If the participant does not meet the qualifying criteria for reversibility at Visit 1/Screening, up to 2 additional attempts during the screening period, each on a different day prior to Visit 2/Baseline, may be performed. When reversibility assessment is repeated during the screening period, the prebronchodilator FEV1 should again meet the inclusion criteria (I 05) of >40% and <80% of predicted normal.

c All eligible participants will be treated for 60 weeks, receiving a subcutaneous (SC) administration of IMP every 4 weeks (Q4W) for the first 6 doses and every 12 weeks (Q12W) thereafter with a loading dose (two SC injections) on Day 1.

d Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

e If urine pregnancy test is positive, a serum control must be done before IMP administration. Urine pregnancy testing should continue every 4 weeks after switching to Q12W regimen. Follow-up pregnancy test will be performed until [redacted] after the last administration of study intervention.

f Clinical laboratory testing at Screening (Visit 1) will include a hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), total hepatitis B core antibody (HBc Ab), IgM antibody to hepatitis B core antigen (IgM HBc Ab), hepatitis C virus antibodies (HCV Ab), HIV screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBs Ag (negative), and HBc Ab Total (positive), HBV DNA testing will be performed prior to randomization to rule out a false positivity to clarify the serological status. In case of results showing HCV Ab (positive), HCV RNA testing will be performed to rule out a false positivity. Please refer to Table 7 in Section 8.2.4.

g Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with five-part differential count, and total red blood cell count. Serum chemistry: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. The blood sample for serum chemistry must be taken with the participant in fasting state which means no intake of any food or drink except for water for at least 8 hours (if the visit can only be done at a different time of the day and the participant is not fasting, then he/she should be advised to eat light food and the site should document that serum chemistry was not obtained under fasting conditions). Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen, and bilirubin. If any urinalysis parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement. If urinalysis sample is abnormal for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory.

h The ECGs will be obtained prior to laboratory assessments and prior to spirometry.

i Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate will be measured at every visit. Height (cm) will be measured at screening (Visit 1) only. Body weight (kg) will be measured at Visit 1/Screening, Visit 2/Baseline, Visit 9, Visit 11, Visit 12/EOT, and Visit 13/EOS or early discontinuation. Vital sign should be done before IMP administration.

j TB assessment per local guidelines or, if not available, in central laboratory using a Quantiferon® test.

k COVID-19 test will be performed at screening, randomization and prior to each IMP administration (no administration if positive). Tests should be performed no more than 5 days prior to IMP administration. Method of testing as required per local guidelines.

l Further details will be available in a separate operational manual provided to the sites.

m Electronic spirometer (eSpirometer) will be dispensed at Visit 1. Further details on remote spirometry will be available in a separate operational manual provided to the sites.

n When FeNO, impulse oscillometry, and spirometry are scheduled at the same time, sequence of measurements will be in the following order: 1) FeNO; 2) impulse oscillometry; 3) spirometry.

o Samples will be collected prior to administration of IMP during the randomized treatment period. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

[redacted]

[redacted]

t Spirometry (pre-BD FEV1, post-BD FEV1, and PEF, FVC, FEF) should be performed in the morning if possible, but if it could only be done at a different time of the day, the spirometry should be done at approximately the same time of the day at each visit throughout the study. Spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 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), and prior to administration of investigational product. The post-BD spirometry may be repeated several times within 30 minutes after administration of bronchodilator.

u Remote spirometry training/instructions to be done during the screening period and at regular intervals throughout the study. Additional instructions will be provided and available to participants.

v Electronic spirometer (eSpirometer) will be used for FEV1 and PEF measurements to be performed daily in the AM and PM (see Section 8.1.3.9 for further instructions).

w To calculate ACQ-7, the ACQ-6 is completed in the participant's eDiary during clinic visits. ACQ-6 score will be used to follow up evaluations in all participants. ACQ-5 (the first 5 items of the ACQ-6) score is used for eligibility evaluation at Visit 1 and Visit 2 for all participants.

x ADSD and ANSD captured daily via eDiary; ANSD captures nocturnal asthma symptoms is to be completed upon awakening; ADSD captures daytime asthma symptoms is to be completed at end of day (before retiring for sleep).

[redacted]

z Electronic diary (eDiary) is a handheld device used for daily recording of reliever use, asthma controller drug use, ADSD and ANSD, and recording of participant's answers to the ACQ-5, ACQ-6, AQLQ(S), and other PROs questionnaires during the scheduled visits. This handheld device is dispensed at Visit 1 (including instructions for use) and recorded information is downloaded from this device on the other indicated days. For each site visit, the participants will bring their electronic devices and will complete the questionnaire on site. Electronic handheld devices will be returned to the vendor at EOS at the latest.

aa A maximum of 14 days is required to get IMP on site. Randomization of the participant must take this constraint into consideration. In case of severe asthma exacerbation during screening, screening period can be extended to up to 3 months. Please see Screen Failures section for instructions and for South Korea, please see Section 10.8.2 for details.

2 INTRODUCTION

Amlitelimab (also known as KY1005 or SAR445229) is a novel human anti-OX40L mAb (subclass IgG4PE kappa) that is being developed to modulate the persistent inflammation caused by autoreactive memory T cell (Tmem) populations and may provide a means of inducing immune tolerance to exogenous or autoantigens (eg, in immune mediated/autoimmune disease) or alloantigens (eg, following transplants).

2.1 STUDY RATIONALE

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema and mucus plugging. The inflammation component of asthma is thought to involve many cell types including epithelial cells, T lymphocytes, eosinophils, mast cells, neutrophils, innate lymphoid cells type 2 (ILC2) and their biological products. Patients with asthma most often present with symptoms of wheezing, shortness of breath, cough, and chest tightness (3).

Despite current treatment options, uncontrolled asthma continues to carry a significant burden, with more than 1 million moderate-to-severe asthmatic adolescents and adults in the U.S. having uncontrolled symptoms on ICS combined with bronchodilator drug(s) or systemic corticosteroid therapy (4). These patients are prone to severe exacerbations and contribute disproportionately to the overall morbidity in this condition, including more hospital days, emergency room visits, and lost work/school days than matched controls with good asthma control. Additionally, they are likely to experience co-morbidities such as anxiety, depression, and insomnia (5, 6). Furthermore, systemic corticosteroids, while modestly effective, are associated with significant side effects, such as fluid retention and swelling, weight gain, glaucoma, increased blood pressure, increased risk of infections, diabetes, osteoporosis, and impaired growth in children (7).

For severe uncontrolled asthma patients, there are several currently approved biologics (8). In the severe, corticosteroid-refractory allergy-induced asthma population, the anti-immunoglobulin E (IgE) agent omalizumab (Xolair®) has shown efficacy. In the severe population with an eosinophilic phenotype, the two currently approved anti interleukin (IL)-5 agents, mepolizumab (Nucala®) and reslizumab (Cinqair®), and the anti-IL5 receptor benralizumab (Fasenra®) have shown efficacy as well. These anti-IL5 agents now provide additional therapeutic options with important limitations. Even in the high eosinophilic group, 36% of patients on mepolizumab had no decrease in OCS dose or had a lack of asthma control (9), suggesting that targeting a single cytokine in a heterogenous disease such as asthma is not sufficient. To address these limitations, dupilumab, an anti-IL4-Rα antibody that blocks the biologic activities of both IL-4 and IL-13 was more recently developed and approved (10). Most recently, Tezepelumab (Tezspire®), a thymic stromal lymphopoietin (TSLP) blocker, was approved in December 2021 for the treatment of severe asthma (11). However, even when using currently available biologics, substantial proportions of patients continue to experience exacerbations and may benefit from agents that target different molecular pathways (12, 13, 14). Therefore, despite these additional therapeutic options, there is still a clear unmet medical need among patients with severe asthma, both within

the eosinophilic ("Type 2-high") subset of asthmatics specifically targeted by most of the currently available biologics, and in the non-eosinophilic ("Type 2-low") subset which currently benefits from few if any effective asthma therapies. Furthermore, treatment with currently approved biologics is associated with certain adverse events (AE), including infections, eye disorders, headache, injection site reactions. Xolair and Cinqair are associated with a black box warning of potential for anaphylaxis (15, 16). The main objectives for new therapies are to further improve asthma symptoms, lung function, quality of life and prevent exacerbations, while optimizing safety and tolerability of treatment.

Amlitelimab (also known as KY1005 or SAR445229) binds OX40L and blocks interaction with its receptor, OX40. The engagement between OX40 and OX40L occurs during the T-cell-antigen-presenting cell (APC) interaction, after antigen recognition, and provides essential signals for the generation and survival of Tmem, the enhancement of the T helper (Th) cell (such as Th1, Th2, Th17 and Th22) response and the prolongation of inflammatory responses (17). Asthma is a heterogeneous disease, with approximately half of asthma patients showing evidence of Type 2 inflammation, elevated Th2 cytokines (IL-5, IL-13, and IL-4) and eosinophilic infiltration, the target of current biologics. Few effective therapies are currently in place for asthma patients showing evidence of non-eosinophilic, Type 2-low inflammation (18). [redacted]

Amlitelimab data collected to this stage of development in two healthy volunteer studies and a single Phase 2a study in participants with moderate-to-severe atopic dermatitis (AD) suggest an unremarkable safety profile with no specific identified risk from nonclinical/clinical programs so far.

The objective of this DRI17509 study is to assess the efficacy and safety of amlitelimab, a human anti OX40L mAb, in participants with moderate-to-severe asthma which is not well controlled on ICS in combination with other controller medication(s) with or without OCS therapy.

2.2 BACKGROUND

Overview of amlitelimab

Amlitelimab binds OX40L to block the interaction with its receptor, OX40 (CD134). The Fc regions were modified to the IgG4PE variant to reduce Fc receptor binding and stabilize the antibody hinge region. The resulting molecule is therefore expected to have null effector function (known not to deplete target cells) and would not undergo fragment antigen binding arm exchange as has been reported for natural IgG4.

OX40L is inducibly expressed on professional antigen presenting cells, such as B cells, dendritic cells (DC) and macrophages upon activation (19). Other cells such as endothelial cells, smooth muscle cells, mast cells and natural killer cells can also be induced to express OX40L (20). OX40L interacts "monogamously" with OX40, which is expressed on activated T cells (21), CD4 and CD8 T cells, inducing differentiation towards Th2, Th1, Th17, and Th22. The OX40/OX40L axis has also been shown to enhance the proliferation and activation of Tmem and abrogate

forkhead box P3 positive regulatory T cells (Treg) function (22). OX40-OX40L interaction is also necessary for the differentiation of activated B cells into highly Ig-producing cells.

The interaction between OX40 and OX40L occurs during the T cell DC interaction, following inducible expression of OX40L on DCs between hours and days after antigen recognition. After disengaging from DCs, the OX40 expressing T cell may then interact with other OX40L expressing cells, which in turn provide essential signals for the generation of Tmem with a drive to Th2 polarization and the prolongation of the inflammatory responses. OX40 signals render T cells resistant to Treg cell mediated suppression and furthermore, OX40 signaling in Treg cells directly inhibits their suppressive function.

Expression of OX40 and OX40L is reportedly increased in the lungs (lamina propria) of mild asthma patients and serum OX40L is elevated in pediatric asthma patients (23, 24). In a Phase 2 trial, oxelumab, an OX40L antagonist depleting mAb given to mild atopic asthma participants, resulted in a 17% reduction in total IgE levels and 75% reduction in sputum eosinophils, however ultimately oxelumab did not attenuate early- or late-phase asthmatic responses upon an allergen challenge and did not have an effect on airway hyper-responsiveness or blood eosinophils compared to placebo (25). The reasons for an OX40L antagonist not improving clinical outcomes in allergic airway disease are unknown. [redacted]

Allergic asthma is one subset of the Type 2-high asthma endotype. Production of alarmins IL-25, TSLP and IL-33 by the respiratory epithelium downstream of viral infections, allergens and pollutants plays a major role in initiating Type 2 inflammation. OX40L expression on ILC2 cells is regulated by IL-33 and is considered a checkpoint of type 2 inflammation (26), while TSLP is thought to partly exert its effects via OX40L expression on DCs to modulate type 2 inflammation (27). [redacted]

[redacted]

Non-clinical Data

In Vitro Characterization

Amlitelimab has high affinity for human OX40L and blocks its interaction with OX40 in biochemical assays in vitro. [redacted]
Demonstration of poor or no binding to human Fcγ receptors indicates that amlitelimab is unlikely to cause Fcγ receptor mediated OX40L superclustering and consequent activation of target downstream pathway(s).

In Vivo Characterization

Treatment of cynomolgus monkeys with amlitelimab resulted in inhibition of the T-dependent antibody response (TDAR). [redacted]

Pharmacokinetics and Non-clinical Safety

Amlitelimab has been evaluated in multiple toxicity studies in cynomolgus monkeys, including Good Laboratory Practice (GLP)-compliant, 13-week and 26-week repeat dose studies.

[redacted]

No local or systemic toxicity was observed in the 13-week and 26-week IV repeated dose toxicity studies in monkeys and there was no effect on safety pharmacology parameters. There was no evidence of infection in either study. [redacted]

[redacted]

The potential for local toxicity of amlitelimab in the formulation intended for SC administration in humans was evaluated in a GLP-compliant local tolerance and PK study in cynomolgus monkeys. [redacted] Details of these and additional non-clinical studies can be found in the amlitelimab (KY1005) Investigator's Brochure (IB).

Clinical Data

Amlitelimab has been administered to healthy volunteers (studies KY1005-CT01 and KY1005-CT04) and to participants with moderate-to-severe AD (study KY1005-CT02, study KY1005-CT05). These studies are summarized below. Further information can be found in the amlitelimab (KY1005) IB.

Study KY1005-CT01

Study KY1005-CT01 was the first-in-human (FIH) study of amlitelimab that explored the safety and tolerability of single and repeat doses of amlitelimab in healthy volunteers.

This study was conducted at a single investigative site, in line with a typical FIH dose escalation design. Eight cohorts were studied, [redacted] All cohorts comprised 8 healthy volunteers allocated at random to either active (6 participants) or matching placebo (2 participants).

Overall, this study identified no meaningful safety or tolerability concerns and provided PK and pharmacodynamics (PD) data to support the dose selection for the Phase 2a KY1005-CT02 study.

Regarding immunization whilst not causing complete suppression it was noted that the response to the neo-antigen KLH was blunted by the administration of amlitelimab in HVs. For the recall antigen tetanus toxin (TT), no observable effect of amlitelimab was noted for anti-TT IgG, although anti-TT IgM suppression was numerically greater than placebo, but not dose dependent.

Further information can be found in the IB.

Study KY1005-CT02

The Phase 2a (KY1005-CT02; NCT03754309), randomized, double blind, placebo controlled, parallel group, multicenter study was designed to explore the efficacy and safety of monotherapy amlitelimab in adult participants with moderate-to-severe AD who have a documented history, within 6 months prior to baseline, of either inadequate response to topical treatments or inadvisability of topical treatments.

Participants (n=89) were randomized in a 1:1:1 ratio to receive either an IV lower dose (200 mg loading/100 mg maintenance) or higher dose (500 mg loading/250 mg maintenance) of amlitelimab, or matching placebo. Participants received amlitelimab or placebo Q4W from baseline to Day 85/Week 12 when the last dose was received.

Meaningful efficacy differences in the key endpoints (Eczema Area and Severity Index [EASI] and SCORing of atopic dermatitis [SCORAD]) between those receiving amlitelimab and placebo were observed from Day 15 and maintained to the primary endpoint (Day 113). Supporting efficacy, an improvement in pruritis was also observed. No meaningful difference between the amlitelimab treatment arms was noted. In those participants achieving a Investigator Global Assessment (IGA) of 0/1 at Day 113, additional efficacy assessments through the safety follow-up demonstrated a maintenance of response in the majority of participants of up to 5.5 months (end of study [EOS]) following the last dose of amlitelimab.

The most common AEs in the study were exacerbation of AD and nasopharyngitis, the incidence of which were numerically higher in the placebo group compared to those receiving KY1005. Overall, no meaningful differences were observed when considering TEAEs.

Further detailed information regarding the safety outcomes from the Phase 2a study can be found in the IB.

Study KY1005 CT04

KY1005-CT04 (NCT04449939) was a Phase 1, open label study to assess the PK, safety and tolerability of KY1005 after single dose administration by the SC and IV routes in male healthy volunteers. The purpose of this study was to assess the PK of KY1005 after SC administration and to compare the safety and tolerability of KY1005 when given via SC injection and IV infusion, to support SC administration. Intravenous KY1005 was included as a reference treatment. Twenty-four healthy volunteers were enrolled as 3 treatment groups of 8 healthy male participants (250 mg IV, 125 mg SC, 250 mg SC).

The primary endpoint was the characterization of the PK of SC and IV administered KY1005 after a single dose. Key secondary endpoints included safety and tolerability.

There were no clinically meaningful trends noted in the incidence or nature of the AEs or abnormal laboratory results and KY1005 was well tolerated when given SC with low incidence of injection site pain/reactions.

A full description of the KY1005-CT04 study together with the results can be found in the IB.

Study KY1005-CT05

The Phase 2b (KY1005-CT05; NCT05131477), randomized, double blind, placebo controlled, parallel group, multicenter dose ranging study designed to explore the efficacy (including dose/exposure response) and safety of KY1005/SAR445229 across a range of doses/exposures (500 mg loading dose followed 28 days later and thereafter with 250 mg Q4W, or 250 mg Q4W, or 125 mg Q4W, or 62.5 mg Q4W, or Placebo Q4W) for a maximum duration of 52 weeks in adult participants with moderate-to-severe AD who have had an inadequate response to topical therapies or where topical therapies are not advised. The study is ongoing.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected AEs of amlitelimab may be found in the amlitelimab IB and participant information leaflet.

2.3.1 Risk assessment

Amlitelimab specific risks, including any associated with SC administration, have not been identified to date from the non-clinical or clinical program. Potential risks include hypersensitivity and/or anaphylactic reactions, serious and opportunistic infections (including helminthic infections), decreased antibody response to neoantigens and/or new vaccinations, injection site reactions, malignancy (discussed further in the IB). These potential risks are in common with other immunomodulatory drugs and there is no evidence to date to suggest these will be exaggerated in the specific case of OX40/OX40L blockade. One participant in the prior healthy [redacted]

[redacted]

In the Phase 2a KY1005-CT02 study, no meaningful differences in TEAEs were observed between the amlitelimab groups or between the amlitelimab and placebo groups. The most common AEs in the study were exacerbation of AD and nasopharyngitis, the incidence of which were numerically higher in the placebo group compared to those receiving amlitelimab. Fourteen events of headache were reported, 12 of which were in 3 participants in the high dose amlitelimab group. Of note, 3 participants reported an event of conjunctivitis: 1 event of infectious conjunctivitis (low dose amlitelimab mild intensity, not deemed related), 1 allergic conjunctivitis (high dose amlitelimab, moderate intensity, not related), and 1 haemorrhagic conjunctivitis (high dose amlitelimab, mild intensity, not related). In all 3 cases, participants received management, and all completed the study.

[redacted]

There are no available data with the use of amlitelimab in pregnancy to evaluate a drug-associated risk of birth defects, miscarriage, or adverse maternal or fetal outcomes. Women of childbearing potential (WOCBP) who are not taking adequate birth control measures will not be included in the study. Pregnancy is an adverse event of special interest in this study. Testing and adequate contraceptive precautions are included for study participation.

No meaningful clinical events were reported in the KY1005-CT04 SC healthy volunteer study. Injection site reactions/pain are a known risk with SC administration. Three out of 16 participants receiving SC amlitelimab reported local injection site pain/tenderness. All were mild in severity and resolved without sequelae.

In the KY1005-CT05 AD study, one participant with moderate-to-severe AD was hospitalized for bullous and pustular dermatitis following 2.5 months of amlitelimab (125 mg Q4W) treatment. While some clinical features at initial presentation raised the possibility of a hypersensitivity reaction or Stevens-Johnson syndrome/toxic epidermal necrolysis, the final diagnostic workup and clinical course did not support either of these diagnoses, and the final etiology remains unclear. The skin biopsy showed features more suggestive of acute generalized exanthematous pustulosis, although pustular psoriasis was also in the differential diagnosis, as well as possible infectious etiology (infectious work-up was not performed). The patient recovered on hospitalization Day 12, after treatment with ceftriaxone and methylprednisolone, and amlitelimab was discontinued.

Further details can be found in the IB.

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Hypersensitivity and/ or anaphylactic reactions	Class effect with monoclonal antibodies. Large protein molecules, despite humanization, can be immunogenic. Amlitelimab is a biologic therapeutic protein and hypersensitivity risk is considered as a class effect with monoclonal antibodies. [redacted]	Exclude participants with or history of hypersensitivity or allergy to any of the excipients or IMP or other allergy that, in the opinion of the Investigator, contraindicates participation in the study. Evaluate for severe allergies and atopy prior to initiating treatment with the IMP. Stop IMP if reaction develops and manage according to standard of care. Study centers are required to have procedures and personnel trained and experienced in the management of emergencies such as systemic and localized allergic reactions and cytokine release syndrome. To further characterize this potential risk, allergic reaction is an adverse event of special interest (AESI) for amlitelimab.
Serious and opportunistic infections (including Helminthic infections)	Serious infections are common to immunomodulatory drugs and there is no evidence to suggest these will be exaggerated in the specific case of OX40/OX40L blockade. Since the physiological role of T cells is host defense against infections, treatment with an OX40L blocker may be associated with a risk of reduced control of infections [redacted] in the clinical program to date, including KY1005-CT01 (Phase 1, healthy volunteers) and KY1005-CT02 (Phase 2, participants with moderate-to-severe atopic dermatitis [AD]). More detailed information is available in the IB.	Evaluation for serious infection prior to initiating treatment with the IMP is recommended. Routine monitoring of serious infection via indicative clinical signs and symptoms. If signs or symptoms of clinically important acute infection occur, IMP will be withheld, and the infection managed according to standard of care. Helminthic Infections: Exclusion of participants with chronic or active helminth infections. All such infections should be treated before initiating therapy with the IMP. If participants become infected while receiving the IMP, the IMP should be discontinued until infection is resolved. The following are considered exclusion criteria from study participation: • Known history of or suspected significant current immunosuppression, including history of invasive opportunistic or helminthic infections despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged duration. • Any active or chronic infection requiring systemic treatment within 2 weeks prior to baseline (1 week in the event of superficial skin infections). • Active or latent TB infection • Active/chronic infections including helminthic infection.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		In the event of any infection, Investigators will determine whether temporary or permanent discontinuation of IMP is necessary. To further characterize this potential risk, any severe or opportunistic viral, bacterial, or fungal infection and/or any uncommon, unanticipated or persistent infection (viral, parasitic, bacterial, or fungal) are considered an AESI for amlitelimab.
Decreased antibody response to neoantigens and/or new vaccinations	Clinical observation In phase I study in healthy volunteers, SAR445229 appeared to have a pharmacodynamic effect from doses of 0.45 mg/kg and above based on the attenuation of the neoantigen (anti-KLH IgG and anti-KLH IgM) response. Potential impact on new vaccine response should be considered. [redacted]	Assure that all pending and necessary vaccination (especially live/attenuated as well as for COVID-19) occurs per local recommendations and well in advance of dosing. • Exclusion of vaccination with a live (attenuated) immunization within 12 weeks prior to Baseline; completion of required administrations of COVID-19 vaccine within 14 days prior to Baseline. • In cases where booster vaccinations are recommended per local regulations it is not recommended that participants receive their COVID-19 vaccinations/boosters within less than 14 days immediately prior to or following the IMP administration.
Injection site reactions	[redacted]	Routine monitoring for all events of injection site reactions. On IMP administration days, local skin reactions around the site of injection will be assessed by the Investigator or other appropriately trained site personnel 30 minutes after the injection. Light pressure will be applied at the injection site and any pain, itchiness, tenderness, erythema, and induration will be recorded in the eCRF. Pain and tenderness will be assessed according to the following scale: Definitions of pain and tenderness: • None: nothing. • Mild: easily tolerated. • Moderate: interferes with daily activities. • Severe: prevents normal everyday activities or sleep. Erythema and induration will be measured using a ruler, or a template supplied by the Sponsor. Severe injection site reactions that last longer than 24 hours are considered AESI.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Malignancy	The OX40/OX40L axis modulates the antineoplastic T cell response, which is involved in tumor surveillance and defense. Inhibition of OX40L may therefore lead to impaired immune surveillance and control of established tumors (growth, metastasis, and re-emergence). [redacted]	Evaluation for malignancy will be made prior to IMP initiation and participants with known existing/prior history of neoplasm will be excluded based on the following criteria: • Participants with a history of any type of malignancy to be excluded, with the exception of basal and squamous cell skin cancer or in situ cervical carcinoma that has been excised and cured in >3 years prior to baseline. Based on routine monitoring for clinical signs and symptoms, IMP will be held in case of suspected diagnosis of a malignancy during the study and permanently discontinued immediately upon confirmed diagnosis. To further characterize the risk, routine monitoring will be performed. Malignancy is considered an AESI, and all cases of malignancy will be reviewed periodically by an Independent Data Monitoring Committee (IDMC).

2.3.2 Benefit assessment

[redacted]

In the KY1005-CT02 study in participants with moderate-to-severe AD, amlitelimab provided meaningful improvements in the signs and symptoms of AD and no safety or tolerability issues were noted with 12 weeks of treatment.

[redacted]

2.3.3 Overall benefit/risk conclusion

Overall, blockade of OX40/OX40L in humans is precedented without acute severe adverse consequences. These findings suggest that OX40L mediated clearance is not relevant at pharmacological doses and that such binding, in disease states in which OX40L is upregulated, does not lead to common adverse reactions. Mitigation of the theoretical risks is possible through selection of appropriate study populations and monitoring in clinical trials.

The design of the present study (DRI17509) including selection criteria of the study population, risk mitigation strategy, and monitoring of safety variables, should maintain the positive balance

regarding the expected efficacy/safety ratio for amlitelimab in the treatment of participants with asthma.

[redacted]

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of different doses of amlitelimab compared to placebo in participants with moderate-to-severe, uncontrolled asthma.	• Annualized rate of severe exacerbation events over 48 weeks, defined as: - Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of oral corticosteroids (OCS) for the treatment of asthma, a doubling of the dose for 3 or more days; or - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids
Secondary	
• To evaluate the effects of amlitelimab compared to placebo on lung function as measured by forced expiratory volume in 1 second (FEV1)	• Change from baseline in pre-bronchodilator (BD) FEV1 at Week 48 (**key secondary endpoint)** • Change from baseline in post-BD FEV1 at Week 48 • The absolute change in the percent predicted FEV1 from baseline to Week 48 (pre-BD and post-BD)
• To evaluate the effects of amlitelimab on Asthma Control Questionnaire 5 (ACQ-5)	• Change from baseline in ACQ-5 score at Week 48 (**key secondary endpoint**) • Change from baseline in ACQ-5 score at Weeks 2, 4, 8, 12, 24, 36, and 60
• To evaluate the effects of amlitelimab on time to first severe exacerbation event	• Time to first severe exacerbation event
• To evaluate the effects of amlitelimab on other spirometry assessments	• Change from baseline in pre-BD and post-BD FEV1 and other lung function measurements (peak expiratory flow [PEF], forced vital capacity [FVC], and forced expiratory flow [FEF] 25-75%) at each spirometry endpoint
• To evaluate the effects of amlitelimab on fraction of exhaled nitric oxide (FeNO)	• Change from baseline in FeNO at Weeks 2, 4, 8, 12, 16, 24, 36, 48 and 60

Objectives	Endpoints
• To evaluate the effects of amlitelimab compared to placebo on reducing the incidence of "loss of asthma control" (LOAC) events	• Annualized rate of LOAC events, during 48 weeks of treatment, defined by one or several of the following criteria: - A 30% or greater reduction from baseline in morning PEF on 2 consecutive days. - ≥6 additional reliever puffs of short-acting beta 2-agonists (SABA) OR ≥4 additional puffs of low-dose ICS/formoterol in a 24-hour period (compared to baseline) on 2 consecutive days - Increase in ICS ≥4 times than the Visit 2 dose - Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of OCS for the treatment of asthma, a doubling of the dose for 3 or more days - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids severe exacerbation event
• To evaluate the effects of amlitelimab on time to first LOAC event	• Time to first LOAC event
• To evaluate the effects of amlitelimab on asthma symptoms	• Change from baseline in the Asthma Daytime Symptom Diary (ADSD) 6-item daily morning score and in the Asthma Nighttime Symptom Diary (ANSD) 6-item daily evening scores at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
• To evaluate the effects of amlitelimab on reducing the incidence of severe asthma exacerbations requiring hospitalization or emergency room or urgent care visit	• Annualized rate of severe asthma exacerbations requiring hospitalization or emergency room or urgent care visit during 48 weeks of treatment
• Assess the effect of amlitelimab on BD therapy	• Change from baseline in the numbers of inhalations/day of SABA or low-dose ICS/formoterol for symptom relief at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
• To evaluate the pharmacokinetics (PK) of amlitelimab and anti-drug antibodies to amlitelimab in participants with asthma	• Serum amlitelimab concentrations measured throughout the study • Incidence of anti-amlitelimab antibody positive response
• To evaluate the safety of amlitelimab in participants with asthma	• Percentage of participants with treatment-emergent adverse events (TEAEs), including local reactions, adverse events of special interest (AESIs), serious adverse events (SAEs) • Incidence of potentially clinically significant laboratory test, vital signs, and ECG abnormalities in the treatment period

Objectives	Endpoints
• To evaluate the effects of amlitelimab on participant reported outcomes (PROs)	• Change from baseline in Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered Score at Week 48 **(key secondary endpoint)** • AQLQ (S) Self-Administered Score at Weeks 2, 4, 8, 12, 24, 36, and 60 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Weeks 2, 4, 8, 12, 24, 36, 48, and 60 • Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 48
• To evaluate the effects of amlitelimab on ACQ-6 and ACQ-7	• Change from baseline in ACQ-6 score and ACQ-7 at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
Tertiary/Exploratory	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

Primary estimands defined for primary and key secondary efficacy endpoints are provided in Section 9.2.

3.1 APPROPRIATENESS OF MEASUREMENTS

The primary and key secondary efficacy and safety assessments used in this study are standard for the evaluation of therapy in participants with moderate-to-severe asthma, which have been used or are being used in similar designed Phase 2 and 3 studies using dupilumab (Liberty Asthma QUEST, Phase 3, NCT02414854,) and tezepelumab (PATHWAY, Phase 2, NCT02054130, and NAVIGATOR, Phase 3, NCT03347279).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of add-on therapy with amlitelimab in adult participants (aged 18-75 years, inclusive) with moderate-to-severe asthma who are not well controlled on ICS plus a second controller medication (eg, LABA, LTRA, methylxanthines, LAMA) with or without oral prednisone for the maintenance treatment of asthma. Participants requiring a third controller are allowed to participate in this study (please see Section 5.1). Study treatments are amlitelimab 250 mg with 500 mg loading dose on Day 1, amlitelimab 125 mg with 250 mg loading dose on Day 1, amlitelimab 62.5 mg with 125 mg loading dose on Day 1, or matching placebo, administered during the 60 weeks treatment period.

The primary endpoint is the annualized rate of severe asthma exacerbation events over 48 weeks (28). Maintenance of effect will be evaluated at Week 60. Severe exacerbations will be recorded by the Investigator and are defined as either worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of OCS for the treatment of asthma, a doubling of the dose for 3 or more days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. For exacerbation events to be counted as 2 separate events, they must be separated by at least 7 days between courses of systemic corticosteroids or doubling of the dose of stable background OCS.

For efficacy endpoint analysis, the primary population will be the intent-to-treat (ITT) population (Section 9). The efficacy analysis of subgroups will be detailed in the statistical analysis plan (SAP).

Randomization will be stratified by region, screening blood eosinophil count (<300 cells/µL and ≥300 cells/µL), and number of severe asthma exacerbations in the previous 12 months (=1 exacerbation or >1 exacerbations). During the randomization procedure, the eosinophil count at Screening (Visit 1) must be entered in the IVRS/IWRS system. To ensure enrollment according to intended distribution of exacerbation history and eosinophil count, the number of participants enrolled into each stratification group will be controlled and monitored as follows:

- Only 1 severe asthma exacerbation in the previous 12 months: not more than approximately 50% of participants (210 participants).
- Eosinophils <300 eosinophils/µL: not more than approximately 50% of participants (210 participants).

The clinical trial consists of three periods, as outlined below:

- Screening period (up to 4 weeks) to determine whether participants meet entry criteria and to establish level of asthma control before randomization.
    - The screening of a participant triggers the IMP shipment to site in IVRS/IWRS system. A maximum of 2 weeks is required to get IMP on site. Randomization of the

participant must take this constraint into consideration (up to 2 weeks will need to be allowed for IMP shipment between screening and randomization).

- Randomized treatment period (60 weeks)
- Follow-up period (12 weeks) to monitor participants after treatment
  - Eligible participants who complete the treatment period will be offered the opportunity to participate in the LTS study with amlitelimab. Participants subsequently enrolled in the LTS study will not participate in the follow-up period of this trial but will have a follow up period after the LTS study.

Participants must have been on existing treatment with medium-to-high doses of ICS therapy (≥500 µg of fluticasone propionate daily or comparable ICS dosage up to a maximum of 2000 µg/day of fluticasone propionate or clinically comparable) in combination with a second controller (eg, LABA, LTRA, LAMA, methylxanthines) for at least 3 months with a stable dose≥1 month prior to Screening (Visit 1) and must stay on their established controller medication for asthma throughout the duration of the study, with the exception of OCS used for maintenance treatment of asthma. The class of reliever medication should not change during the study. For Japan, please see Section 10.8 for details.

All eligible participants will be randomized (2:2:1:2) to one of the following IMP treatment groups to be administered for 60 weeks by SC administrations Q4W for the first 6 doses and Q12W thereafter until Week 48:

- Amlitelimab 250 mg with 500 mg loading dose on Day 1
- Amlitelimab 125 mg with 250 mg loading dose on Day 1
- Amlitelimab 62.5 mg with 125 mg loading dose on Day 1
- Matching placebo

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, placebo-controlled study design where the effect of the IMP is assessed on top of standard of care background therapy (medium-to-high doses of ICS in combination with a second controller) is considered to be the most appropriate design to examine the efficacy and safety of a novel biologic therapy in asthma. Annualized rate of severe asthma exacerbations was selected as the primary endpoint as it is generally considered to be the most clinically relevant outcome in asthma. Asthma exacerbations constitute the greatest risk to patients, increase the risk of asthma mortality, are a cause of anxiety to patients and their families, result in the greatest stress on health care providers, and generate the greatest cost to the health care system (28). The 60-week duration of this study allows for assessment of the broad range of short-term and mid-term effects amlitelimab may have on annualized asthma exacerbation rate, lung function, health-related quality of life (HRQoL), and symptom control, while reducing the impact of seasonal variations observed in exacerbations.

The study is dose-ranging to gather information for the selection of the ultimate dose for future clinical development. A total of 3 dosing groups plus placebo will be tested in this study.

Based on the inclusion criteria for this study, all study participants will meet criteria for GINA definition of moderate-to-severe asthma step 4 and 5 (3). The GINA Guidelines recommend the following maintenance regimens for management of step 4 and 5 participants: medium-to-high dose of ICS-LABA with consideration of additional controllers (LAMA, LTRA, etc) and referral for phenotypic assessment for biologics (anti-IgE, anti-IL5/5R, anti-IL4/4R). Therefore, the study will allow for the use of double or triple controller therapy.

[redacted]

4.2.1 Participant input into design

A report of participant insights was provided in November of 2021 for the DRI17509 protocol. Feedback was obtained from various past participant insights collected by Sanofi, including participant panels. Feedback related to at-home spirometry, PROs/questionnaires, visit schedule, recruitment and retention was taken in consideration while developing the current protocol.

4.3 JUSTIFICATION FOR DOSE

[redacted]

[redacted]

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the EOS Visit of the last participant in the study.

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

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

I 01. Participant must be 18 to 75 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. A physician-diagnosed moderate-to-severe asthma for ≥ 12 months based on GINA definition step 4 and 5 (3) (Section 10.10.1).

I 03. Participants with existing treatment with medium-to-high doses of ICS therapy (≥500 µg of fluticasone propionate daily or comparable ICS dosage up to a maximum of 2000 µg/day of fluticasone propionate or clinically comparable) in combination with a second controller (eg, LABA, LTRA, LAMA, methylxanthines) for at least 3 months with a stable dose ≥1 month prior to Visit 1.

Note: Participants requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1.

Note for Japan: participants must be on ≥400 µg of fluticasone propionate daily or equivalent.

I 04. ≥1 severe asthma exacerbation in the past year, with at least one exacerbation occurring while on treatment with medium to high doses of ICS therapy (≥500 µg of fluticasone propionate daily or comparable ICS dosage), and defined as:

- Treatment with systemic corticosteroids (oral or parenteral) for ≥3 days for worsening asthma; in case of a stable maintenance regimen of OCS, a doubling of the dose for 3 or more days, OR
- Hospitalization or emergency medical care visit for worsening asthma, requiring systemic corticosteroids.

Note for Japan: at least one severe exacerbation occurring while on treatment with ≥400 µg of fluticasone propionate daily or equivalent.

I 05. Participants with pre-BD FEV1>40% and <80% of predicted normal (29, 30) at Visit 1/Screening.

I 06. 5-item ACQ-5 score >1.5 at screening and randomization.

I 07. Participants with reversibility of at least 12% and 200 mL in FEV1 after administration of 2 to 4 puffs (200-400 µg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that meets these criteria within 12 months prior to Visit 1 is considered acceptable to meet this inclusion criterion.

- Alternatively, a Severe Asthma Research Program (SARP) method could be used: maximal change in FEV1 after the administration of 4, 6, and 8 puffs of albuterol (360, 540, 720 µg albuterol) (31)

I 08. If on chronic OCS treatment for the maintenance treatment of asthma, up to a maximum of 15 mg prednisone or equivalent daily or 30 mg every other day is allowed, must be on stable dose for ≥1 month prior to Visit 1.

Weight

I 09. Weight ≥40 kg and ≤150 kg at Baseline.

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

I 10. All

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

Male participants with partners of childbearing potential and who are eligible to participate if they agree to the following during the study intervention period and until 5 months after the last administration of study intervention or the early termination visit:

- Refrain from donating or cryopreserving sperm

  Plus either:

[redacted]

b) Female participants

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

[redacted]

Informed Consent

I 11. Capable of giving signed informed consent as described in Section 10.1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Chronic lung disease other than asthma.

E 02. Current smoker or former smoker with cessation within 6 months of screening or history of >10 pack-years. Active vaping of any products and/or marijuana smoking within 6 months of screening.

E 03. Participants who experience a deterioration of asthma that results in emergency treatment or hospitalization, or treatment with systemic steroids within 1 month prior to the Screening Visit.

Note: counting from the date of completion of treatment for asthma exacerbation.

E 04. Participants who have experienced an upper or lower respiratory tract infection within the 4 weeks prior to screening.

E 05. Suspicion of, or confirmed, coronavirus disease 2019 (COVID-19) infection or in contact with known exposure to COVID-19 at Screening or during the screening period; known history of COVID-19 infection within 4 weeks prior to Screening; history of requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) secondary to COVID-19 within 3 months prior to Screening; participants who have had a COVID-19 infection prior to Screening who have not yet sufficiently recovered to participate in the procedures of a clinical trial.

E 06. Known history of, or suspected, significant current immunosuppression, including history of invasive opportunistic or helminthic infections despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged duration.

E 07. Active/chronic infections including helminthic infection.

E 08. Any active or chronic infection requiring systemic treatment within 2 weeks prior to Baseline (1 week in the event of superficial skin infections).

E 09. For participants on chronic OCS use for the maintenance treatment of asthma: history of a serious infection requiring hospitalization.

E 10. Participants with active tuberculosis (TB), latent TB, a history of incompletely treated TB, suspected extrapulmonary TB infection, 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 prior to Screening.

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

a) have a history of prior documented completed chemoprophylaxis for latent TB infection (with a treatment regimen as per local guidelines), OR treated for active TB infection,

AND

b) have obtained consultation with a specialist to rule out or treat active TB infection,

AND

c) for whom review and approval from Sponsor have been granted are eligible.

E 11. A history of malignancy of any type (excluding basal and squamous cell skin cancer and in situ cervical carcinoma that has been excised and cured >3 years prior to baseline).

E 12. History of solid organ transplant.

E 13. Participants positive for human immunodeficiency virus; participants with any of the following result at Screening (Visit 1): Positive (or indeterminate) hepatitis B surface antigen (HBs Ag) or positive IgM antibody to hepatitis B core antigen (IgM HBc Ab) or positive total hepatitis B core antibody (HBc Ab) confirmed by positive hepatitis B virus (HBV) DNA or positive hepatitis C virus total antibody (HCV Ab) confirmed by positive hepatitis C virus (HCV) RNA. Guidance on hepatitis serology eligibility interpretation is provided in Table 7 in Section 8.2.4.

Note for Japan: For Japan, the presence of HBsAg with/without positive HBV-DNA test result or the presence of HBc Ab or the presence of HBs Ab with positive HBV-DNA test result at screening or within 3 months prior to the screening visit is an exclusion criterion.

E 14. Clinically significant laboratory abnormalities at Screening (Visit 1):

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times upper limit of normal range (ULN).
- Serum total bilirubin >1.5 × ULN (participants with Gilbert's syndrome can be included with total bilirubin >1.5 × ULN as long as direct bilirubin is <1.5 × ULN).
- Hemoglobin <10 g/100 mL for male and <9 g/100 mL for female.
- Neutrophils <1500/µL (<1000/µL for those of African descent).
- Platelets <100 000/µL.
- Creatinine ≥150 µmol/L.

E 15. Severe concomitant illness that would in the Investigator's opinion inhibit the participant's participation in the study, including for example, but not limited to, hypertension, renal disease, neurological conditions, heart failure and pulmonary disease.

E 16. History (within last 2 years prior to Baseline) of prescription drug or substance abuse, including alcohol, considered significant by the Investigator.

E 17. Elective surgery planned to be scheduled for any time in the period up to 3 months following the last dose of IMP.

Prior/concomitant therapy

E 18. Anti-IgE mAb therapy (eg, omalizumab [Xolair]) within 130 days prior to Visit 1 or any other biologic therapy (including anti-IL4/4R, IL-5/5R, or anti-TSLP mAb) or systemic immunosuppressant (eg, methotrexate) to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) and other diseases, within 2 months or 5 half-lives prior to Visit 1, whichever is longer, except stable dose OCS used for the maintenance treatment of asthma.

E 19. Participants who have received bronchial thermoplasty within 2 years prior to Visit 1 or plan to begin therapy during the screening period or the randomized treatment period.

E 20. Treatment with a live (attenuated) immunization within 12 weeks prior to Baseline; completion of required administration of COVID-19 vaccine within 14 days prior to Baseline.

E 21. History of hypersensitivity or allergy to any of the excipients or IMP or other allergy that, in the opinion of the Investigator, contraindicates participation in the study. Known or suspected hypersensitivity to amlitelimab or excipients used in the presentation of amlitelimab or in preparation for administration.

E 22. Any prior use of anti-OX40 or anti-OX40L mAb, including amlitelimab.

Prior/concurrent clinical study experience

E 23. Investigational therapy for the treatment of asthma or other conditions within 5 half-lives or the limit of PD effects or 3 months where the $t_{1/2}$ is unknown.

E 24. Concurrent participation in any other clinical study, including noninterventional studies.

Diagnostic assessments

Not applicable.

Other exclusions

E 25. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 26. Any country-related specific regulation that would prevent the participant from entering the study – see Appendix 8 (Section 10.8) of the protocol (country-specific requirements).

E 27. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 28. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 29. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

No meals and dietary restrictions are required, except for the FeNO test and blood sample for serum chemistry.

Participants should not eat or drink 1 hour prior to having the FeNO test, as this may affect the results.

The blood sample for serum chemistry must be taken with the participant in fasting state which means no intake of any food or drink except for water for at least 8 hours (if the visit can only be done at a different time of the day and the participant is not fasting, then he/she should be advised to eat light food and the site should document that serum chemistry was not obtained under fasting conditions).

5.3.2 Caffeine, alcohol, and tobacco

Smoking and/or vaping and/or smoking marijuana will not be allowed from 6 months prior to Screening (Visit 1) until after the final follow-up visit.

Use of alcohol and caffeine is allowed. However, 8 hours prior to spirometry, no alcohol should be consumed (for details, refer Section 8.1.3.1).

5.3.3 Activity

Participants should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the center.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Participants who are eligible for rescreening may be rescreened once for any reason, except for PRO criteria (ie, ACQ-5<1.5), which will lead to screen failure without an option for rescreening. Please note exceptions for South Korea, please refer to Section 10.8.2. 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. Participants who are rescreened are required to sign a new ICF.

In the case of technical malfunction of equipment during spirometry, the participant may be retested. A participant who is unable to complete a successful spirometry effort as defined by American Thoracic Society/European Respiratory Society (ATS/ERS) 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.

If the participant does not meet the qualifying criteria for reversibility at Visit 1/Screening (I 07), up to 2 additional attempts during the screening period, each on a different day prior to Visit 2/Baseline, may be performed. When reversibility assessment is repeated during the screening period, the prebronchodilator FEV1 should again meet the inclusion criteria (I 05) of >40% and <80% of predicted normal.

Participants with an upper or lower respiratory tract infection during the screening period may be rescreened after 4 weeks or 14 days after recovery, ie, completion of the therapy, whichever is longer.

Participants who experience an asthma exacerbation that results in emergency treatment or hospitalization, or treatment with systemic steroids during the screening period may remain in screening and proceed with randomization 1 month after they have completed their course of OCS or returned to their maintenance dose of OCS. Screening period in this case can be extended to up to 3 months. Note: extension of screening is not allowed in South Korea, please refer to Section 10.8.2.

If certain dynamic laboratory tests do not meet the inclusion criteria at Screening (Visit 1), these laboratory assessments may be repeated, at the discretion of the Investigator, if the parameter result is judged to be likely to return to acceptable range for study inclusion within the screening period prior to Baseline/Randomization (Visit 2). There is no need to screen fail such participants if the test finally meets the inclusion criteria.

It is intended to include approximately 50% of participants with blood eosinophils<300 cells/µL and 50% of participants with blood eosinophils ≥300 cells/µL. By including up to approximately 50% of participants with high blood eosinophils, it is expected to have adequate power to evaluate treatment effects in these important subgroups of asthma participants. If one of the stratification groups is filled, the IVRS/IWRS will close enrollment in this group. As other studies are recruiting participants with blood eosinophils ≥300 cells/µL, there will be increased competition for this subset of participants. Having this control measure in place, this should guarantee sufficient number of participants in both blood eosinophil count subgroups. New participants should be prescreened based on their historical eosinophil value that needs to be confirmed at Screening (Visit 1). Retesting of the eosinophil count is allowed up to 3 times during the screening period if needed. If a participant does not finally meet the required eosinophil count before randomization the participant should be screen failed.

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

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): Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

The IMP is to be administered every 28±3 days (Q4W) for the first 6 doses and every 84±3 days (Q12W) thereafter during the 60 weeks treatment period (Table 4).

[redacted]

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 Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

Table 3 - Study intervention(s) administered

Intervention label	Amlitelimab	Amlitelimab matching placebo
Intervention name	Amlitelimab	Placebo
Intervention description	One initial loading dose of amlitelimab (two 2 mL injections) on Day 1, followed by one 2 mL injection of amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48	One initial loading dose of amlitelimab matching placebo (two 2 mL injections) on Day 1, followed by one 2 mL injection of amlitelimab matching placebo Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.
Type	Drug	Drug
Dose formulation	Vial	Vial
Unit dose strength(s)	125 mg/mL	Dummy dose of placebo, to match amlitelimab
Dosage level(s)	Amlitelimab 250 mg with 500 mg loading dose, Amlitelimab 125 mg with 250 mg loading dose or Amlitelimab 62.5 mg with 125 mg loading dose	Dummy dose of placebo, to match amlitelimab
Route of administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP

Packaging and labeling	IMP will be provided in 2 mL Type 1 clear glass vial. Each vial will be labeled as required per country requirement.	IMP will be provided in 2 mL Type 1 clear glass vial. Each vial will be labeled as required per country requirement.
[Current/former name(s) or alias(es)]	KY1005	NA

Table 4 - Study arm(s)

Arm title	Amlitelimab 250 mg with 500 mg loading dose	Amlitelimab 125 mg with 250 mg loading dose	Amlitelimab 62.5 mg with 125 mg loading dose	Placebo
Arm type	Experimental	Experimental	Experimental	Placebo
Arm description	Participants will receive one initial loading dose of 500 mg of amlitelimab on Day 1, followed by one injection of 250 mg of amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.	Participants will receive one initial loading dose of 250 mg of amlitelimab on Day 1, followed by one injection of 125 mg of amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.	Participants will receive one initial loading dose of 125 mg of amlitelimab on Day 1, followed by one injection of 62.5 mg of amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.	Participants will receive one initial dummy loading dose of only placebo matching amlitelimab on Day 1, followed by one injection of placebo matching amlitelimab Q4W until Week 20 (inclusive) and Q12W starting from Week 24 and thereafter until Week 48.
Associated intervention labels	Amlitelimab	Amlitelimab	Amlitelimab	Placebo

Amlitelimab

[redacted]

A complete description of amlitelimab and its proper preparation and handling will be provided in the Pharmacy Manual available to the clinical site.

Non-investigational medicinal products(s)

Participants must continue their established controller and reliever therapy.

Participants must continue the controller therapy regimen and continue to use the same dose, except for the OCS (see Section 6.8).

- Formulation: DPI, MDI, nebulizer

- Route of administration: oral inhalation for LABA, ICS, LAMA, ICS+LABA, LAMA+LABA, or LAMA+LABA+ICS
- Dose regimen: as per prescribed

If on maintenance treatment with OCS, the dose could be changed per Investigator medical judgement.

- Formulation: tablets
- Route of administration: oral
- Dose regimen: as per prescribed

Participants may administer SABA or low-dose ICS/formoterol (per GINA 2021 recommendation [3]) as reliever medication. The class of reliever medication should not change during the study.

- Formulation: DPI, MDI, nebulizer
- Route of administration: oral inhalation
- Dose regimen: as per prescribed

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

6.1.1 Devices

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

- Electronic Diaries
- Spirometry devices
- Electronic Spirometry devices for remote spirometry (FEV1) and PEF measurement
- Digital inhalers to measure the reliever use (in certain countries, optional)
- Impulse oscillometry devices
- FeNO measurement devices
- Laboratory kits including tubes, needles, dipsticks
- IMP transportation material as described in the Pharmacy Manual

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

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, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

Packaging, Labelling and storage conditions

All packaging, labeling, and production of IMP will be in compliance with current Good Manufacturing Practices, or local applicable regulations, where necessary. The IMP labels and external packaging will include all appropriate information as per local labeling requirements. Storage conditions and use-by-end date (when required by country regulations) are part of the label text.

[redacted]

[redacted]

Additional details regarding packaging, labelling and storage conditions will be available in the Pharmacy Manual.

Allocation of IMP

This is a double-blind study, the IMPs to be administered to a participant will be assigned centrally using an IVRS/IWRS.

The study visits for IMP allocation are summarized in the SoA (Section 1.3). The IVRS/IWRS will allocate for each participant the kit numbers corresponding to the visit.

Before the study is initiated, the login information and the instructions for the IVRS/IWRS management will be provided to each site.

The site will contact the IVRS/IWRS prior to the start of study IMP administration for each participant at each visit where IMP is administered. The site will record the IMP assignment on the applicable case report form, if required.

Study Treatment Administration

Amlitelimab will be administered as a SC injection Q4W until Week 20 (inclusive) and Q12W [redacted]

IMP should not be administered at the site of a recent injection or in areas which in the Investigator's opinion are not suitable eg, tender, bruised, red or hard.

[redacted]
Details of administration will be documented in the study specific Pharmacy Manual.

[redacted]

[redacted]

Additional information regarding treatment allocation, preparation and administration are available in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomized intervention kit number list is generated centrally by Sanofi. The IMPs (amlitelimab or placebo) are packaged in accordance with this list.

All participants will be centrally assigned to randomized study intervention using an IVRS/IWRS. Before the study is initiated, the log in information and directions for the IVRS/IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in the SoA. Details of the IVRS/IWRS procedure will be provided in the IVRS/IWRS Site Manual.

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

Randomized participants are defined as all participants from screened population who have been allocated to a randomized intervention by IVRS/IWRS regardless of whether the intervention was received. Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately. Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

Randomization will be stratified by region, screening blood eosinophil count (<300 cells/µL and ≥300 cells/µL), and number of asthma exacerbations in the previous 12 months (=1 exacerbation or >1 exacerbations). During the randomization procedure, the eosinophil count at Screening (Visit 1) must be entered in the IVRS/IWRS system. To ensure enrollment according to intended distribution of exacerbation history and eosinophil count, the number of participants enrolled into each stratification group will be controlled and monitored as follows:

- Only 1 severe asthma exacerbation in the previous 12 months: not more than approximately 50% of participants (210 participants).
- Eosinophils <300 eosinophils/µL: not more than approximately 50% of participants (210 participants).

A participant cannot be randomized more than once in the study.

On Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the participant's assignment to one of the 4 arms of the study, according to the randomization schedule generated prior to the study by the Statistics Department at Sponsor. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number, throughout the study.

Blind break

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted (eg, in case of available antidote). In case of an AE/SAE, the code can be broken only in circumstances when knowledge of the study IMP is required essential for treating the study participant. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable. If the code is broken, the participant must withdraw from IMP administration.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

Methods of blinding

Amlitelimab and placebo will be provided in identically matched 1 mL vials. To protect the blind, each treatment kit of 1 mL (amlitelimab/placebo) glass vials will be identical and indistinguishable and labeled with a treatment kit number. A specific volume in each vial will be collected in order to prepare syringes such that the treatments (amlitelimab and its matching placebo) are identical and indistinguishable.

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

6.4 STUDY INTERVENTION COMPLIANCE

Participants will receive study intervention directly from the Investigator or designee at the site, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. 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.

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 Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.5 DOSE MODIFICATION

Not applicable.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Eligible participants who complete the treatment period will be offered the opportunity to participate in the LTS study with amlitelimab. Participants subsequently enrolled in the LTS study will not participate in the follow-up period of this trial but will have a follow up period after the LTS study.

6.7 TREATMENT OF OVERDOSE

For this study, any administration of [redacted] will be considered an overdose. No antidote is available for amlitelimab.

Amlitelimab has a [redacted] If severe adverse reactions occur after an overdose of amlitelimab, then plasmapheresis (or infusion of albumin) to reduce the drug exposure may be considered.

NIMP overdose: any dose in excess of the maximum dose recommended in the respective medication labeling.

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

- Contact the Sponsor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Obtain a serum sample for PK analysis within 7 days from the date of the last dose of IMP if requested by the Sponsor (determined on a case-by-case basis).
- Document appropriately in the eCRF and report the overdose as an AESI (if symptomatic) within 24 hours of learning of the event.

6.8 CONCOMITANT THERAPY

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

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

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

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

Paracetamol/acetaminophen, at doses of ≤2 g/day, is permitted for use any time during the study.

6.8.1 ICS in combination with one or two other controllers

On a daily basis throughout the study, the participant will use an eDiary to record daily use of ICS in combination with one or two other controllers as used just prior to screening.

The recognized asthma controllers for the study will include the following 5 classes: ICS, LABA, LAMA, anti-leukotrienes and methylxanthines. Please refer to Section 10.10.3 for a list of commonly used asthma controller medication.

6.8.1.1 Screening period

Prior to screening, participants must be on a stable background therapy for at least 3 months, composed of medium to high dose of ICS (≥500 µg of fluticasone propionate daily or comparable ICS dosage to a maximum of 2000 µg/day of fluticasone propionate or clinically comparable [1]) in combination with a second controller medication (eg, LABA, LTRA, LAMA, methylxanthines), with or without third asthma controller medication. The second and third controller both should be used for at least 3 months with a stable dose ≥1 month prior to Visit 1. Participants requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1. For Japan, please see Section 10.8 for details.

If on chronic OCS treatment for the maintenance treatment of asthma, up to a maximum of 15 mg prednisone or equivalent daily or 30 mg every other day, must be on stable dose for ≥1 month prior to Visit 1 (see Section 10.10.2 for comparison of systemic glucocorticoid preparations).

6.8.1.2 Randomized treatment period

During this period, participants will continue to take their controller medication(s) used during the screening period and will use an eDiary to record daily use. The dose and regimen should not be changed, except for the OCS, for which the dose could be changed per Investigator medical judgement.

6.8.1.3 Follow-up period

Upon completing the randomized treatment period, participants will proceed to be treated with the controller medication regimen and dose used during the randomized treatment period, which could be adjusted based on the medical judgment of the Investigator of the participants' asthma control status.

6.8.2 Reliever medication

Please refer to Table 15 for a list of commonly used asthma reliever medications in Section 10.10.3. Participants may administer SABA MDI and DPI as reliever medication as

needed during the study. Nebulizer solutions may be used as an alternative delivery method. Alternatively, low-dose ICS/formoterol may be used as reliever medication, per GINA 2021 recommendation (2) and Investigator's discretion. Reliever medication use will be reported by participants in the eDiary.

If a nebulizer is used, the dose administered via nebulizer must be converted to puffs using the nebulizer-to-puff conversion factor (Table 5, Table 6) (32) and entered in the eDiary.

Table 5 - Conversion of salbutamol/albuterol nebulizer solution dose to number of puffs

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

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

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

Table 6 - Conversion of levosalbutamol/levalbuterol nebulizer solution dose to number of puffs

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

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

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

6.8.3 Allowed concomitant medication

Medications that have not been listed as exclusion criteria are permitted for use during the trial. These include the following:

- Oral contraceptives

- Intranasal, ocular or topical corticosteroids
- Previously initiated immunotherapy will be allowed to continue during the study.
- Antihistamines
- Paracetamol/acetaminophen
- COVID-19 vaccination:
  - To allow for an optimal immune response as well as protection against COVID-19, it is strongly recommended that participants complete their COVID-19 vaccination schedule (per local requirements) a minimum of 14 days prior to Baseline. The safety profile and effectiveness of COVID-19 vaccines in people with compromised immune systems or therapies (such as amlitelimab) that modify or that suppress their immune response is not yet established.
  - While vaccination with an approved COVID-19 vaccine (including booster dose) is widely recommended (33), a participant's decision to have a COVID-19 booster during the study should only be made after discussing with his/her physician and the Investigator to assess the benefits/risks of receiving a COVID-19 vaccination during this study. In this instance, if the vaccine is authorized, available, and recommended by the local regulatory health authority, it should be administered according to the label or local health authority recommendations. The vaccine should not be administered within less than 14 days immediately prior to or following the IMP administration. Details of the COVID-19 vaccine should be recorded in the eCRF.

6.8.4 Prohibited concomitant medication

The following concomitant treatments are not permitted during the screening or treatment phases:

- Systemic steroids for more than 7 consecutive days (except systemic steroids to treat asthma exacerbations and for maintenance treatment of asthma within allowed doses initiated before participation in the study)
- Systemic immunosuppressant within 2 months or 5 half-lives prior to Visit 1, whichever is longer (eg, methotrexate, any anti-TNF mAbs, B and/or T cell targeted immunosuppressive therapies)
- Intravenous Ig (IVIG) therapy
- Anti-IgE therapy (eg, omalizumab [Xolair]) within 130 days prior to Visit 1 or any other biologic therapy within 2 months or 5 half-lives prior to Visit 1, whichever is longer
- Live Attenuated Vaccines within 12 weeks prior to baseline (see Section 10.10.4)
- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with stable dose at least 1 month prior to Visit 1)
- Asthma relievers other than SABA and low-dose ICS/formoterol: their use is not recommended during the study period. In case of use in exceptional circumstances (eg, prescribed by a physician not participating in the study), their use will be documented in the participant's file and reported in the eCRF.

- Initiation of immunotherapy
- Other investigational drugs

6.8.5 Prohibited rescue medication and procedures

Rescue medications and procedures could be used per Investigator's medical judgement. The following rescue medications and procedures constitute a treatment failure:

- Anti-IL4R mAb (eg, dupilumab [Dupixent®])
- Anti-IL5 or IL-5R mAb (eg, benralizumab [Fasenra], mepolizumab [Nucala], or reslizumab [Cinqair])
- Anti-IgE mAb (eg, omalizumab [Xolair])
- Anti-TSLP mAb (eg, Tezepelumab [Tezspire®])
- Bronchial thermoplasty
- Initiation of continuous oral corticosteroid treatment during the study beyond 14 days consecutively

The date and time of rescue medication administration as well as the name, route of administration, reason for starting and dosage regimen of the rescue medication must be recorded.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1.9).

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 visit with all assessments planned for the EOT Visit. See the SoA (Section 1.3) for data to be collected at the time of early discontinuation of study intervention.

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

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

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

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research)
- If, in the Investigator's opinion, continuation in the study would be detrimental to the participant's well-being
- At the specific request of the Sponsor
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor
- Pregnancy
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Appendix 10 [Section 10.10.5])
- Severe intercurrent illness
- Diagnosis of a malignancy during study, excluding squamous or basal cell carcinoma of the skin
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (Appendix 10 [Section 10.10.6])
- Severe laboratory abnormalities:
  - Absolute neutrophil count $\leq 0.5 \times 10^9$/L

- Platelet count ≤50×10^9/L
- Serum ALT >3 ULN and total bilirubin >2 ULN
- Serum ALT >5 ULN if baseline ALT ≤2 ULN or ALT >8 ULN if baseline ALT >2 ULN
- Note: Any clinically significant abnormal laboratory value will be immediately rechecked for confirmation after 24 hours before making a decision of permanent discontinuation of the IMP for the concerned participant. If the laboratory abnormality is considered causally related to the IMP, the IMP will be permanently discontinued. In cases where a causal relationship to the IMP can be reasonably excluded (ie, an alternative cause is evident), the IMP will be discontinued but it may be resumed when the laboratory abnormality is sufficiently normalized.

- Occurrence of AEs, that, in the opinion of Investigator/Sponsor, may jeopardize participant's safety or data integrity
- Treatment with any prohibited systemic concomitant medication or procedure (see Section 6.8.4)
- Treatment with any prohibited rescue medication or procedure (see Section 6.8.5)

See the SoA (Section 1.3) for data to be collected at the time of definitive intervention discontinuation and follow-up and for any further evaluations that need to be completed. Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (within 48 hours) before making a decision of definitive discontinuation of the IMP for the concerned participant.

Handling of participants after permanent intervention discontinuation

Participants will be encouraged to remain in the study visits and to participate in all assessments according to schedule, 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. Their study data collected during their continued involvement is important to the study efficacy analysis and study value.

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

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

7.1.2 Liver chemistry stopping criteria

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

7.1.3 Temporary discontinuation

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]: Contingency measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF. Following a temporary interruption or missed dose, the IMP treatment should be reinitiated at the next scheduled visit, maintaining the original dose.

For the purpose of this study, a temporary discontinuation is defined as no more than 1 missed IMP administration. Two or more missed IMP administrations during the study will be considered permanent and relevant eCRF sections should be populated.

7.1.4 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (refer to Section 5).

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

7.1.4.1 Study intervention restart or rechallenge after liver stopping criteria are met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are 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, 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.

  Note: Safety follow-up (EOS, end-of-study) visit should be performed [redacted] after the last IMP.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

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

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

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

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

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

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

7.3 LOST TO FOLLOW UP

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

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.9 Study and site start and closure).

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, 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 timeframe defined in the SoA.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- In case a study procedure in 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.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be within a safe limit for human clinical trials as recommended by the local Institutional Review Boards (IRB) and Independent Ethics Committees (IEC).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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

- PROs and other questionnaires
- ECG
- Procedures:
  - FeNO measurement
  - Impulse oscillometry
  - Spirometry
  - eDiary download
  - Safety and laboratory assessments
  - Administration of IMP

Remote spirometry (pre-BD) and PEF measurements to be performed by participants daily in the AM and PM.

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

8.1 EFFICACY ASSESSMENTS

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

8.1.1 Primary endpoint

The primary endpoint for this study is the annualized rate of severe exacerbation events over a period of 48 weeks.

8.1.1.1 Severe asthma exacerbation events

Severe asthma exacerbation event is defined as:

- Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of OCS for the treatment of asthma, a doubling of the dose for 3 or more days; or
- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids.

8.1.2 Secondary endpoints

8.1.2.1 Key secondary endpoints

Key secondary endpoints include:

- Change from baseline in pre-BD FEV1 at week 48
- Change from baseline in ACQ-5 score at Week 48
- Change from baseline in AQLQ (S) Self-Administered Score at Week 48

8.1.2.2 Efficacy endpoints

Other secondary efficacy endpoints include:

- Change from baseline in post-BD FEV1 at week 48
- The absolute change in the percent predicted FEV1 from baseline to week 48 (pre-BD and post-BD)
- Change from baseline in ACQ-5 score at Weeks 2, 4, 8, 12, 24, 36, and 60

- Time to first severe exacerbation event
- Change from baseline in pre-BD and post-BD FEV1 and other lung function measurements (PEF, FVC, and FEF 25-75%) at each spirometry endpoint
- Change from baseline in FeNO at Weeks 2, 4, 8, 12, 16, 24, 36, 48, and 60
- Annualized rate of LOAC events, during 48 weeks of treatment, defined by one or several of the following criteria:
  - A 30% or greater reduction from baseline in morning PEF on 2 consecutive days.
  - ≥6 additional reliever puffs of SABA OR ≥4 additional puffs of low-dose ICS/formoterol in a 24-hour period (compared to baseline) on 2 consecutive days
  - Increase in ICS ≥4 times than the Visit 2 dose
  - Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of OCS for the treatment of asthma, a doubling of the dose for 3 or more days
  - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids severe exacerbation event
- Time to first LOAC event
- Change from baseline in the ADSD 6-item daily morning score and in the ANSD 6-item daily evening scores at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
- Annualized rate of severe asthma exacerbations requiring hospitalization or emergency room or urgent care visit during 48 weeks of treatment
- Change from baseline in the numbers of inhalations/day of SABA or low-dose ICS/formoterol for symptom relief at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
- Change from baseline in AQLQ (S) Self-Administered Score at Weeks 2, 4, 8, 12, 24, 36, and 60
- Change from baseline in SGRQ at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
- Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 48
- Change from baseline in ACQ-6 and ACQ-7 score at Weeks 2, 4, 8, 12, 24, 36, 48, and 60

8.1.3 Disease-specific efficacy measures

8.1.3.1 Spirometry

Spirometry will be performed in accordance with the ATS/ERS guidelines (34) and prior to administration of IMP at the planned time point (Section 1.3, SoA). For pre-BD measured parameters, including FEV1, PEF, FVC and FEF 25%-75%, spirometry will be performed after a wash out period of bronchodilators according to their action duration, following the guidance of the ATS/ERS 2019 guidance (34). For example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 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. In addition, participants are asked to avoid consuming alcohol 8 hours prior to spirometry, and to avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments.

At all site visits, spirometry will be performed preferably in the morning, afternoon is allowable in the exceptional circumstance when morning spirometry cannot be performed. Spirometry will 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. Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every site visit, if possible.

Reversibility is defined as an increase of the absolute FEV1 after administration of bronchodilator and is measured by spirometry as post-BD increase in FEV1 in percent of the pre-BD FEV1. After spirometry for measuring pre-BD FEV1, participants will receive 2-4 puffs of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed MDI. Reversibility may be performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol, if it is consistent with usual office practice (to be documented). The post-BD spirometry may be repeated several times within 30 minutes after administration of bronchodilator.

Further details on spirometry will be available in a separate operational manual provided to the sites.

8.1.3.2 *Asthma Control Questionnaire,* versions 5, 6, and 7

The ACQ is a questionnaire that measures the adequacy of asthma control and any changes in asthma control that may occur spontaneously or as a result of treatment. The ACQ-5 has five questions on the asthma symptoms and patients are asked to recall how their asthma has been during the previous week. The ACQ-6 includes an additional item that scores the average number of daily puffs needed from a SABA bronchodilator during the past week and the ACQ-7 includes this SABA item, plus a final clinic-assessed item scoring FEV1% predicted. Each item of the ACQ is measured on a 7-point response scale (0=no impairment, 6=maximum impairment). The ACQ score is the mean of the item responses and ranges from 0 (totally controlled) and 6 (severely uncontrolled). A high score indicates low asthma control. Participants with a score below 1.0 reflect adequately controlled asthma and participants with scores above 1.0 reflect inadequately controlled asthma (35). On the 7-point scale of the ACQ questionnaires, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer (36).

Measurement properties such as reliability and ability to detect change have been documented in the literature (36). Participants will complete the questionnaires in an eDiary during on-site visits as described in the SoA (Section 1.3).

8.1.3.3 Fractional Exhaled Nitric Oxide

Fractional Exhaled Nitric Oxide (FeNO) is a measure of nitric oxide in exhaled breath produced by epithelial cells in the lung and considered as a biomarker of Type-2 inflammation in asthma. FeNO levels (ppb) will be collected on site with a dedicated medical device (such as a commercially available hand worn device NIOX VERO®]). The FeNO test needs to be completed prior to impulse oscillometry and spirometry in order to avoid any impact on the nitric oxide measurement. In addition, participants should not eat or drink 1 hour prior to having the FeNO test, as this may affect the results. Further details on the procedure for measuring exhaled nitric oxide with NIOX VERO will be provided in a separate instruction manual.

8.1.3.4 Electronic diary

Electronic diary (eDiary) is a handheld device used for daily recording of reliever use, asthma controller drug use, ADSD and ANSD, and recording of participant's answers to the ACQ-6, AQLQ(S), and other PROs questionnaires during the scheduled visits. This handheld device is dispensed at Visit 1 with including instructions for use and recorded information is downloaded from this device on the other indicated days. For each site visit, the participants will bring their electronic devices and will complete the questionnaire on site. Electronic handheld devices will be returned to the vendor at EOS at the latest.

On a daily basis throughout the study, the participant uses an eDiary to:

- Respond to the morning and evening asthma symptom score ADSD/ANSD questions.
- Indicate the number of inhalations/day of reliever medications for symptom relief.
- Record the use of controller medications per day.

8.1.3.5 Loss of asthma control events

Annualized rate of LOAC events, during 48 weeks of treatment, defined by one or several of the following criteria:

- A 30% or greater reduction from baseline in morning PEF on 2 consecutive days.
- ≥6 additional reliever puffs of SABA OR ≥4 additional puffs of low-dose ICS/formoterol in a 24-hour period (compared to baseline) on 2 consecutive days
- Increase in ICS ≥4 times than the Visit 2 dose
- Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of OCS for the treatment of asthma, a doubling of the dose for 3 or more days
- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids severe exacerbation event

Participants will measure their PEF using electronic spirometer (e-Spirometer) (Section 8.1.3.9). Reliever medication use will be recorded in the eDiary (Section 8.1.3.4).

8.1.3.6 Asthma Daytime Symptom Diary and Asthma Nighttime Symptom Diary

The ADSD and ANSD are PRO measures developed by the PRO Consortium' Asthma Working Group. Both instruments have been designed to measure asthma symptoms in adult and adolescent (12 years of age and older) patients diagnosed with mild-to-severe asthma. ADSD and ANSD assess asthma severity based on patient self-report of asthma core symptoms, ie, difficulty of breathing; wheezing; shortness of breath; chest tightness; chest pain; and cough. Patients are asked to complete the ADSD every night before they go to bed, thinking about their asthma symptoms today, from when they got up this morning until now; the ANSD when getting up, thinking about their asthma symptoms last night from when they went to bed until now. They have demonstrated adequate evidence of content validity and cross-sectional measurement properties (ie, internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of asthma. Average scores are calculated for both the morning and evening diaries, referred to as the "6-Item ADSD Daily Morning Score" and "6-Item ANSD Daily Evening Score", respectively, using 6 out of 6 of the ADSD items (note: no weighting so each item contributes equally).

Both the ADSD and ANSD are composed of 6 items rated using an 11-point NRS that ranges from 0=None to 10=As bad as you can imagine (37). The participants will record their daytime and nighttime asthma symptoms in an eDiary, once in the evening and once in the morning, respectively. The participants will complete the ADSD and the ANSD as per SoA (Section 1.3).

8.1.3.7 Asthma Quality of Life Questionnaire with Standardized Activities Self-administered Score

The AQLQ(S) was designed as a self-administered participant reported outcome to measure the functional impairments that are most troublesome to adolescents and adults ≥12 years of age as a result of their asthma over the past two weeks. The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (11 items)
- Activity limitation (12 items, 5 of which are individualized)
- Emotional function (5 items)
- Environmental Exposure (4 items)

A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life. The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The MCID for AQLQ(S) is 0.5 (38). Participants will complete the questionnaire in an eDiary during on-site visits as described in the SoA.

8.1.3.8 St. George's Respiratory Questionnaire

The SGRQ is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation (39, 40). A global score ranges from 0 to 100. Scores by

dimension are calculated for three domains: Symptoms (8 items), Activity (16 items) and Impacts (26 items) as well as a total score. Lower score indicates better quality of life (QoL). The first part ("Symptoms") evaluates symptomatology, including frequency and severity of cough, sputum production, wheeze, breathlessness and the duration and frequency of attacks of breathlessness or wheeze. The second part has two components: “Activity” and “Impacts”. The “Activity” section addresses disturbances to patients’ daily physical activities. The "Impacts" section covers a range of effects that chest troubles may have on patients’ daily life and psycho-social functions (eg, daily life activities and functioning, employment, physical functioning, emotional impact, stigmatization, and patients’ perceptions when treated). The MCID is 4 points for SGRQ (41). The recall period of the questionnaire is over the past 4 weeks.

The following efficacy parameters will be analyzed by assessing exploratory endpoints:

8.1.3.9 Remote spirometry

On a daily basis throughout the study, the participant uses an e-spirometer to measure morning and evening FEV1, and PEF. E-spirometer will be dispensed at screening (Visit 1). Initial training and written instructions will be provided for participants during screening with additional reminder training/instructions at regular intervals throughout the study.

The following instructions will be provided to the participant and are described in the study manual:

- Participants will be instructed to perform expiratory flow maneuvers
- AM e-spirometry is to be performed within 15 minutes after arising (between 5:30 AM and 12:00 PM) prior to taking any reliever medication (SABA or low-dose ICS/formoterol).
- PM e-spirometry is to be performed in the evening (between 5:30 PM and 12 AM) prior to taking any reliever medication (SABA or low-dose ICS/formoterol).
- Participants should try to withhold reliever medication (SABA or low-dose ICS/formoterol) for at least 6 hours prior to e-spirometry.
- Three e-spirometry efforts will be performed by the participant; all 3 values will be recorded by the e-spirometer, and the highest value will be used for evaluation.

Baseline AM e-spirometry data (FEV1 and PEF) will be the mean AM measurement recorded for the 7 days prior to the first dose of investigational product, and baseline PM data will be the mean PM measurement recorded for the 7 days prior to the first dose of investigational product. Period stability limit is defined as the respective mean AM or PM data obtained over the last 7 days prior to Day 1. There should be at least 4 days’ measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available.

8.1.3.10 [redacted]

[redacted]

[redacted]

[redacted]

8.1.3.11 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.3.12 Digital inhaler to measure the use of bronchodilator therapy

Digital inhalers will be optional and will be available in certain countries to measure the reliever medication use (bronchodilator therapy, inhalations/day). Further details will be available in a separate operational manual.

8.1.3.13 [redacted]

[redacted]

8.1.3.14 [redacted]

[redacted]

[redacted]

8.1.3.15 [redacted]

[redacted]

[redacted]

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AEs which are presented in Section 8.3.

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

8.2.1 Physical examinations

- A complete physical examination will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Height and weight will also be measured and recorded at Screening (the participant is allowed to wear indoor, daytime clothing with no shoes). Weight will also be measured and recorded at the Baseline/Randomization (Visit 2), Week 24 (Visit 9), Week 48 (Visit 11), EOT (Visit 12) and EOS (Visit 13) or early discontinuation.
- 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.

Local Skin Reactions

On IMP administration days, local skin reactions around the site of injection will be assessed by the Investigator or other appropriately trained site personnel 30 minutes after the injection. Light pressure will be applied at the injection site and any pain, itchiness, tenderness, erythema, and induration will be recorded in the eCRF. Pain and tenderness will be assessed according to the following scale:

- Definitions of pain and tenderness:
  - None nothing
  - Mild easily tolerated
  - Moderate interferes with daily activities
  - Severe prevents normal everyday activities or sleep

Erythema and induration will be measured using a ruler, or a template supplied by the Sponsor.

8.2.2 Vital signs

- Oral/Tympanic/Rectal/Axillary/Skin/Temporal artery temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3 Electrocardiograms

- Single 12-lead electrocardiogram (ECG(s)) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. The ECGs will be obtained prior to laboratory assessments and prior to spirometry. A qualified Investigator or appropriate designee (qualified physician) should review the ECGs in a timely manner to determine if there are any safety concerns and for clinical management of the participant. In case of abnormal findings identified by the qualified Investigator or appropriate designee (qualified physician), the ECG should be provided to the cardiologist for further confirmation and description of findings. The Investigator must always date and sign the ECG and comment on the assessment before filing this in the medical records. In the event of any clinically significant abnormal finding that meet the definition of an AE (Section 10.3), the Investigator will continue to monitor the participant with additional ECGs until the ECG findings return to baseline ECG findings or the Investigator determines that follow-up is no longer necessary.
- Any clinically significant ECG related to a preexisting condition at Screening (Visit 1) that does not affect the conduct of the study per the Investigator's judgment will need to be well documented in the source documentation.

8.2.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory 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 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

- All protocol-required laboratory 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, Central Laboratory will contact the site.
- Special procedures for collection, storage, and shipping of serum are described in the Central Laboratory Manual.
- At Screening, hepatitis serology testing is performed in order to rule out active or chronic infection. Guidance on hepatitis serology eligibility interpretation is provided in Table 7.

Table 7 - Hepatitis serology testing

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

DNA = deoxyribonucleic acid; HBc Ab = total hepatitis B core antibody; HBc Ab IgM = IgM antibody to hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBs Ab = hepatitis B surface antibody; HCV = hepatitis C virus; Ig = immunoglobulin.

8.2.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female participant with an early undetected pregnancy.
- See SoA (Section 1.3) for the timing and type of pregnancy testing to be conducted during the study.
- 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 AEs can be found in Appendix 3 (Section 10.3).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative [LAR]) that meet the definition of an AE or SAE and remain responsible for following up all AEs (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 ICF until EOS visit at the timepoints specified in the SoA (Section 1.3).

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

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and 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 nonleading 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 pre-specified 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, IRB/IEC, and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information in the 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, if indicated, female partners of male participants will be collected after the start of study intervention and [redacted] after the last administration of study intervention.
- 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 participant/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Cardiovascular and death events

Not applicable.

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

Not applicable.

8.3.8 Adverse events of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment. For AESI, the Sponsor is to be informed immediately (ie, within 24 hours), as per SAE notification guidelines, even if a seriousness criterion is not met, using the corresponding pages of the CRF (to be sent) or screens in the eCRF.

- 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 Section 8.3.5)
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator and defined as any administration of [redacted]
  - NIMP: any dose in excess of the maximum dose recommended in the respective medication labeling.
- Increase in ALT>3×ULN - see the "Increase in ALT" flow chart in Appendix 6 (Section 10.6).
- Other project specific AESI(s)
  - Systemic or localized allergic reactions that require immediate treatment (in the event that a participant has a systemic allergic reaction that requires immediate treatment, blood samples should be withdrawn as soon as feasible [not to interfere with treatment

of the reaction] for the analysis of ADA, serum tryptase, C1q, C1 inhibitor, C3 and C4, and repeated at 4 hours and 24 hours)

- Severe injection site reactions that last longer than 24 hours
- Any severe or opportunistic viral, bacterial or fungal infection whose nature or course may suggest an immunocompromised status and/or any uncommon, unanticipated or persistent infection (viral, parasitic, bacterial, or fungal; for example, but not limited to tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis)
- Diagnosis of a malignancy during the study.

8.3.9 Guidelines for reporting product complaints

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

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

8.4 PHARMACOKINETICS

- Blood samples will be collected for measurement of serum concentrations of amlitelimab as specified in the SoA (Section 1.3).
- Additional samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate document. The actual date and time of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.
- Samples collected for analyses of amlitelimab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

Population PK approaches will be used for amlitelimab and will be reported as stand alone.

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

8.5 [redacted]

[redacted]

8.6 [redacted]

[redacted]

[redacted]

8.7 IMMUNOGENICITY ASSESSMENTS

Instructions for the collection and handling of these samples will be provided by the Sponsor in a separate document. Antibodies to amlitelimab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. The actual date and time of each sample will be recorded. These samples will be tested by the Sponsor or Sponsor's designee using a validated assay method.

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

All samples collected for detection of antibodies to study intervention may also be evaluated for study intervention serum concentration to enable interpretation of the antibody data.

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, mechanism of action, or possible 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 (leftover) and/or extra (additional) clinical samples, data and samples may be used 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.

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol. Results from future research will not be entered into the study database and will be reported separate from the CSR.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used in alignment with the information provided to participants in the ICF Part 2 (future research). For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These 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).

Relating data and biological samples for future research 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.

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

9 STATISTICAL CONSIDERATIONS

[redacted]

9.1 POPULATIONS FOR ANALYSES

[redacted]

Table 8 - [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.2 STATISTICAL ANALYSES

[redacted]

9.2.1 General considerations

[redacted]

[redacted]

[redacted]

9.2.2 Primary endpoint(s) analyses

[redacted]

[redacted]

[redacted]

9.2.3 Secondary endpoint(s) analyses

9.2.3.1 Key secondary endpoints

[redacted]

[redacted]

[redacted]

9.2.3.2 Other secondary endpoints

Table 9 - [redacted]

[redacted]

[redacted]

[redacted]

9.2.4 Tertiary/exploratory endpoint(s) analyses

[redacted]

[redacted]

Table 10 - Tertiary/exploratory endpoints

[redacted]

9.2.5 Multiplicity adjustment

[redacted]

Table 11 - [redacted]

[redacted]

9.2.6 Safety analyses

9.2.6.1 Adverse events

[redacted]

[redacted]

9.2.6.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

[redacted]

[redacted]

Table 12 - [redacted]

[redacted]

[redacted]

9.2.7 Other analyses

[redacted]

9.3 INTERIM ANALYSES

An administrative interim analysis (IA) will be performed when the last randomized participant has completed 24 weeks. The purpose of the IA is to support the planning of subsequent clinical studies of amlitelimab in asthma. The results of the administrative IA will not be made available to the study team, Investigators or study participants, who will all remain blinded. A small group of Sponsor individuals independent from the study team will be unblinded. No alpha will be spent on the interim analysis as the analysis results will not make an early claim on the treatment effect of efficacy endpoints and the study will continue unchanged irrespective of the interim analysis results. The statistical analysis plan will describe the planned interim analyses in greater detail.

9.4 SAMPLE SIZE DETERMINATION

[redacted]

[redacted]

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
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation-GDPR)
- The protocol, protocol amendments, ICF, IB, [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, European regulation 536/2014 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 Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participants or their LAR and answer all questions regarding 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 GDPR and of the French law, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- In addition to “main” protocol ICF required for study participation, the participant can consent to the following optional assessments:
  - Pharmacogenetic RNA/DNA assessments
  - Future Use of Samples
  - Home nursing visits
- Prior to any additional optional assessment, such as collection of blood for pharmacogenetics, the optional section of ICF (written) should be completed by the participant, and by the person who conducted the informed consent discussion.
- The screening period starts on the day of ICF signature. The registration of Visit 1 in the IVRS/IWRS should also be performed on the day of ICF signature.
- 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: Contingency measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. 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 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 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.
- 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).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations.

The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.

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

10.1.5 Committees structure

10.1.5.1 Data Monitoring Committee

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 composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

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 to the Sponsor regarding the stopping of a study for efficacy, for harms, or for futility. 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 termination of a dose or trial.

10.1.5.2 Adjudication Committee

Adjudication will be performed by experts independent of the Sponsor for asthma exacerbations. Adjudicators will adjudicate and confirm these events in a consistent and unbiased manner throughout the study.

10.1.6 Dissemination of clinical study data

Study participants

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

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

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available 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 "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 the CRF completion instructions.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in study manuals and monitoring guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

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

The first act of recruitment is the first site open 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 but are not limited to:

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s)

used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the 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 laboratory.
- Local laboratory results are only required in the event that:
  - the central laboratory results are not available in time for either study intervention administration and/or response evaluation, or
  - in case the participant cannot come to the clinic due to travel restrictions related to a pandemic and the blood sample cannot be obtained at the participant's home using the central laboratory kit supplied by the vendor (after Sponsor approval).
  - Local regulation does not allow the transportation of (specific) samples outside of the country of origin (after Sponsor approval).
  - If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- TB testing must be done using local laboratory according to local guidelines. In case no local guidelines are available, or local TB testing is not possible, a blood sample can be sent to the central laboratory for a Quantiferon test.
  - For TB testing, see Section 5.2 exclusion criteria 11.

- In case a TB test result is positive or indeterminate, a repeat test is allowed. In case the repeated test is negative, or in case the first AND the second tests are indeterminate, an Investigator assessment should take place. If the Investigator confirms the participant has no signs of infection, AND the participant is not at high risk of contracting TB AND the participant is not from a TB endemic area, AND specialist consultation has ruled out active disease, the participant can be randomly assigned if eligible.

- Pregnancy testing will be performed at screening with a blood test using a central laboratory, and at subsequent visits using Sponsor-provided urine tests.

Table 13 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose (fasting or random)
	Potassium
	Sodium
	Calcium
	Creatine phosphokinase (CPK)
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total bilirubin (case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin)
	Total protein
	Uric acid
	Total cholesterol
	Albumin
	Lactate dehydrogenase
	Chloride
	Bicarbonate
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b]

Laboratory tests	Parameters
Other screening tests	• Serology (HIV antibody, hepatitis B surface antigen [HBs Ag], and hepatitis C virus antibody or specify other tests) • Tuberculosis testing according to local guidelines (local laboratory) or if not available, in central laboratory (Quantiferon test) at Screening (Visit 1) • Tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes coronavirus disease 2019 [COVID-19]) at Screening (Visit 1), randomization and prior to each IMP administration (no administration if positive). Tests should be performed no more than 5 days prior to IMP administration. Method of testing as required per local guidelines • All study-required laboratory tests will be performed by a central laboratory, with the exception of tuberculosis testing and COVID-19 testing

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

Investigators must document their review of each laboratory safety report.

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

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 or LAR who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants/LARs 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/LAR concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/LAR will be collected during an interview with the participants/LAR 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 condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- 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.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

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

a) Results in death

b) Is life-threatening

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

c) Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d) Results in persistent or significant disability/incapacity

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

e) Is a congenital anomaly/birth defect

f) Other situations:

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

10.3.3 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 one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Assessment of causality

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

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- 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 offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the site initiation training slides.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the site initiation training slides.

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 should 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.

Women in the following categories are considered WONCBP:

1. Any female with permanent infertility due to one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.
2. Postmenopausal female
   - 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 FSH level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.
   - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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

10.4.2 Contraception guidance

- Participants should be given advice about donation and cryopreservation of germ cells prior to the start of the study intervention, in line with the fact that study intervention may affect [redacted] after the last administration of study intervention or early termination visit. (See Section 5.1 inclusion criteria).

- 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.

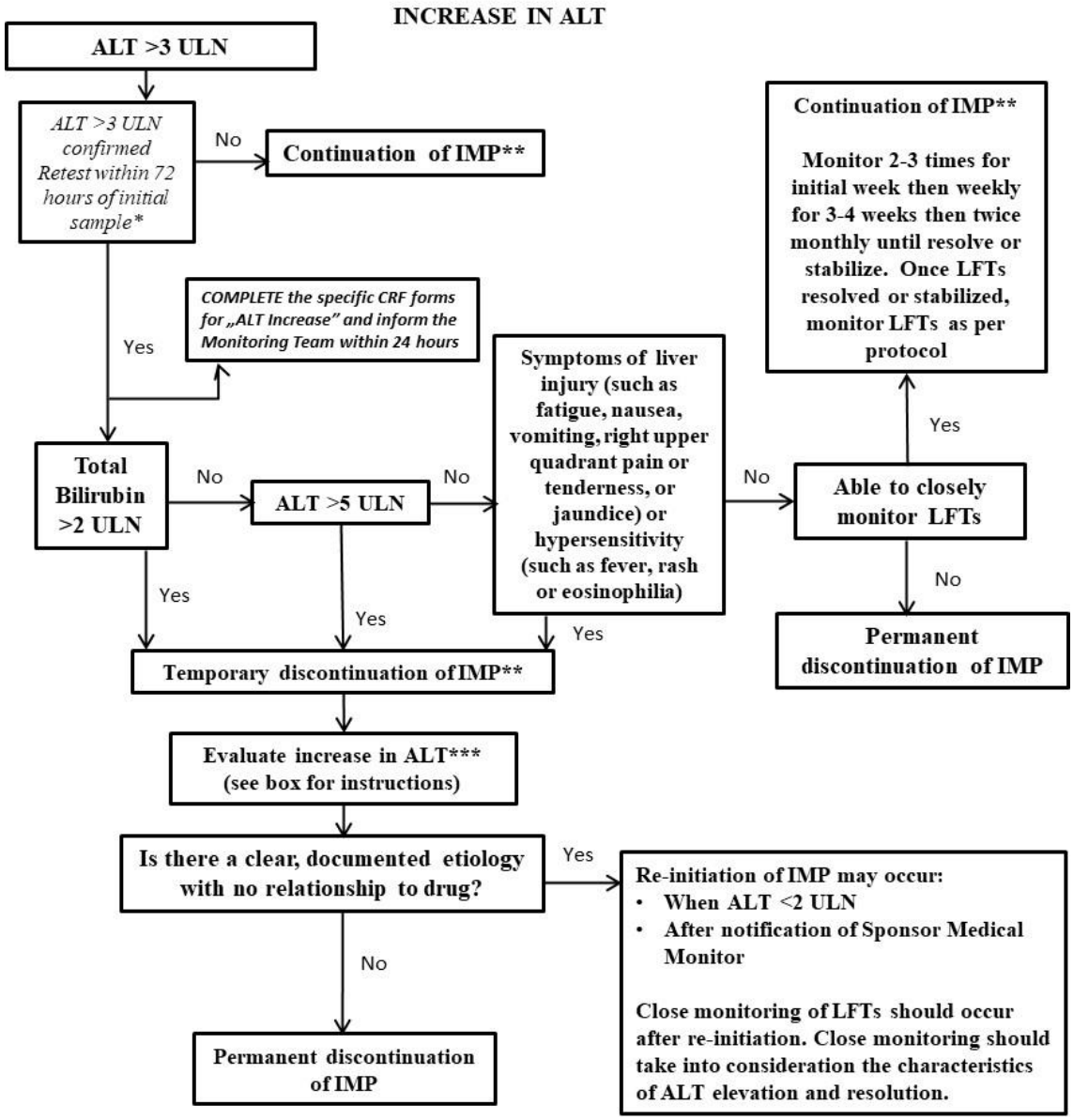
c Male condoms should be used in addition to hormonal contraception

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).

10.5 APPENDIX 5: [redacted]

[redacted]

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



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

** Unless a protocol-defined criterion for permanent discontinuation is met

*** See box below

Note:

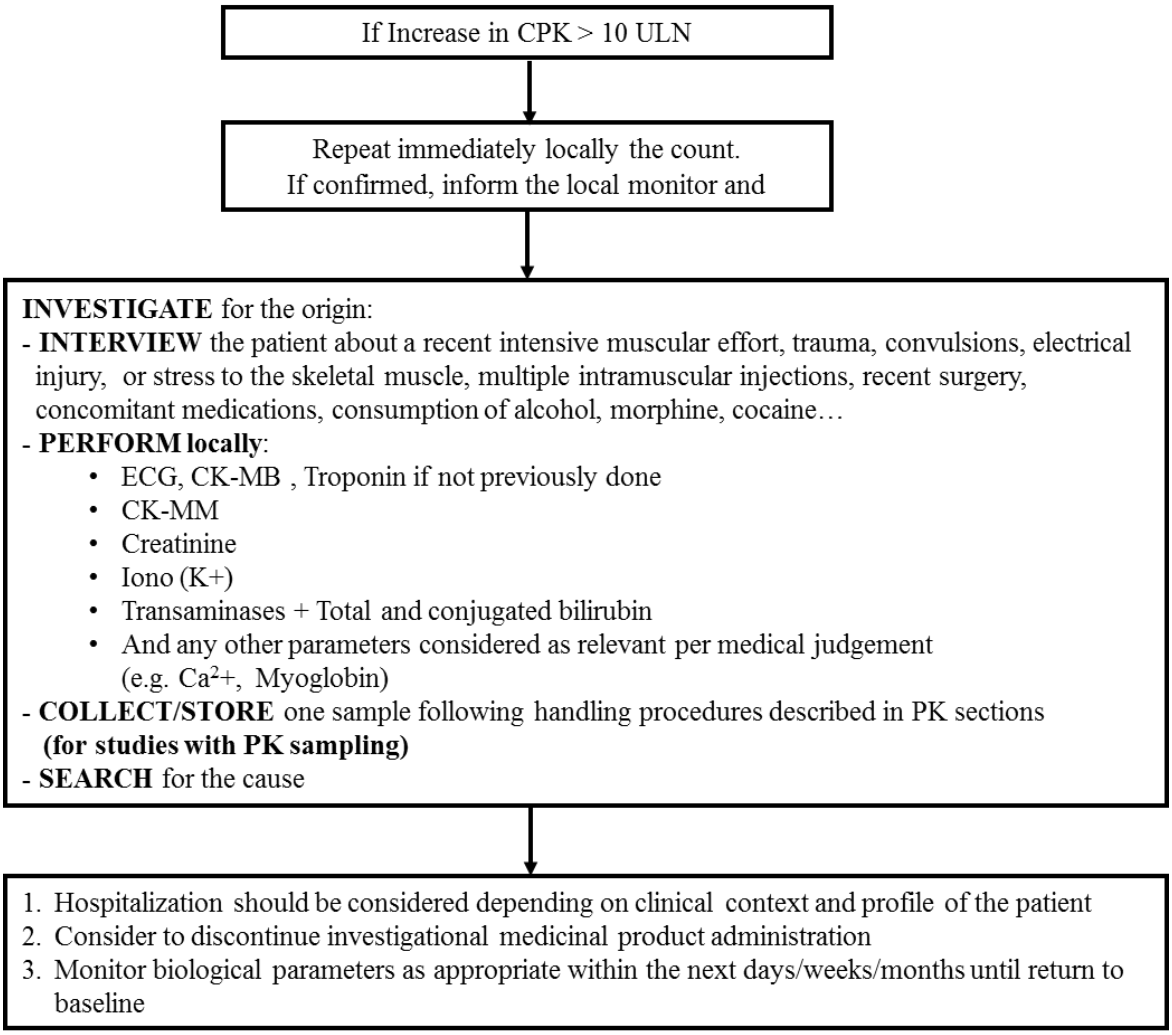
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 10.3.4 for guidance on safety reporting.

Evaluate Increase in ALT***

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

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



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.3.3 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

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

10.8.1 Japan-specific requirements

Section 5.1 Inclusion criteria (see Section 5.1)

For I 03, participants must be on ≥400 µg of fluticasone propionate daily or equivalent.

For I 04, at least one severe exacerbation occurring while on treatment with ≥400 µg of fluticasone propionate daily or equivalent.

Section 5.2 Exclusion criteria (see Section 5.2)

For E 13, for Japan, the presence of HBs Ag with/without positive HBV-DNA test result or the presence of HBc Ab or the presence of HBs Ab with positive HBV-DNA test result at screening or within 3 months prior to the screening visit is an exclusion criterion.

10.8.2 South Korea specific requirements

Section 5.4 Screen failures (see Section 5.4)

For South Korea, in case of an asthma exacerbation during the screening period that results in emergency treatment or hospitalization, or treatment with systemic steroids, eligible participants will be screen failed and can be rescreened 1 month after they have completed their course of OCS or returned to their maintenance dose of OCS. In those cases, participants are allowed to be rescreened one additional time (ie, one rescreening is allowed for any reason other than PRO criteria [ACQ-5<1.5], per Section 5.4, and one additional rescreening is allowed in case of an asthma exacerbation during screening as described above).

When rescreening, participants will sign a new ICF and will repeat all screening procedures in accordance with the SoA (Section 1.3); a different participant identification number will be issued.

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 5.5, Section 6, Section 7.1, Section 8, Section 9.2.7, and Section 10.1.3 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/randomization, and administration of study intervention may be temporarily delayed/halted.
- For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the 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):

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor) may be planned for the IMP administration and collection of possible safety and/or efficacy data.

  Vital signs, hematology and clinical chemistry, routine urine analysis plus dipstick test (pregnancy) and AE reporting should have priority from a safety perspective. The asthma exacerbation reporting, spirometry (if remote spirometry is available/possible) and PROs (ACQ, AQLQ, ADSD/ANSD, SGRQ, etc) should have priority from an efficacy perspective.
- If onsite visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely (eg, spirometry visit window ±2 weeks for the randomized IMP treatment period).
- 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 Sanofi contact on a real-time basis.

10.10 APPENDIX 10: ADDITIONAL APPENDICES

10.10.1 Low, medium, and high ICS doses: adults/adolescents

Daily doses in this table are shown as metered doses. See product information for delivered doses.

Low, medium and high ICS doses: adults/adolescents

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	**Total daily ICS dose (mcg) – see notes above**		
	Low	**Medium**	**High**
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI, or pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

This is NOT a table of equivalence. These are suggested total daily doses for the 'low', 'medium' and 'high' dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler; * see product information

Source: GINA (1, 3).

10.10.2 Comparison of systemic glucocorticoid preparations

	Equivalent doses (mg)
Glucocorticoids	
Short acting	
Hydrocortisone (cortisol)	20
Cortisone acetate	25
Intermediate acting	
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Triamcinolone	4
Long acting	
Dexamethasone	0.75
Betamethasone	0.6

For example, to convert a cortisone total daily dose to a prednisone equivalent total daily dose, a multiplication factor of 0.2 = 5/25 should be used.

Source: (53)

10.10.3 Examples of commonly used asthma controller therapies and reliver medications

Table 14 - Examples of commonly used asthma controller therapies

Controller groups	Medications
ICS	Beclomethasone dipropionate CFC
ICS	Beclomethasone dipropionate HFA
ICS	Budesonide
ICS	Ciclesonide
ICS	Fluticasone propionate
ICS	Mometasone furoate
ICS	Triamcinolone acetonide
ICS	Fluticasone furoate
ICS/LABA	Fluticasone Propionate / Salmeterol
ICS/LABA	Fluticasone Propionate / Formoterol
ICS/LABA	Fluticasone Furoate / Vilanterol
ICS/LABA	Budesonide /Formoterol
ICS/LABA	Mometasone Furoate / Formoterol
ICS/LABA	Mometasone furoate/indacaterol
ICS/LABA	Beclometasone Dipropionate/ Formoterol
LABA	Salmeterol
LABA	Formoterol
LABA	Bambuterol
LABA	Clenbuterol
LABA	Tulobuterol
LABA	Vilanterol
LABA	Olodaterol
LABA	Indacaterol
LAMA	Tiotropium
LAMA	Glycopyrronium bromide
LAMA	Aclidinium bromide
LAMA	Umeclidinium
Anti-Leukotrienes	Montelukast
Anti-Leukotrienes	Pranlukast
Anti-Leukotrienes	Zafirlukast
Anti-Leukotrienes	Zileuton

Controller groups	Medications
Methylxanthines	Aminophylline
Methylxanthines	Theophylline
Methylxanthines	Dyphylline
Methylxanthines	Oxtriphylline
Methylxanthines	Diprophylline
Methylxanthines	Acebrophylline
Methylxanthines	Bamifylline
Methylxanthines	Doxofylline

Table 15 - List of commonly used asthma reliever medications

Group	Medication
SABA	Albuterol/salbutamol
SABA	Levalbuterol/Levosalbutamol
SABA	Terbutaline
Low dose ICS-LABA*	Budesonide-formoterol

*LABA formoterol has an onset of action similar to albuterol (5 to 20 minutes), so combination inhalers that contain inhaled corticosteroid and formoterol (eg, budesonide-formoterol) can be used for relief of acute asthma symptoms in addition to long-term maintenance (3).

10.10.4 Non-exhaustive list of live-attenuated vaccines

Table 16 - List of live (attenuated) vaccines

Live (attenuated) vaccines
Chickenpox (Varicella), Intranasal influenza, Measles (Rubeola), Measles-mumps-rubella (MMR) combination, Mumps, Oral polio (Sabin), Oral typhoid, Rubella, Smallpox (Vaccinia), Shingles (Herpes zoster), Bacille Calmette-Guerin, Yellow fever.

10.10.5 Definition of anaphylaxis

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (54).

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

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

10.10.6 List of opportunistic infections

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along the Mississippi and Ohio Rivers)
- Candidiasis - only systemic, extensive mucosal or cutaneous candidiasis.
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes simplex (severe/disseminated)
- Herpes zoster
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)
- Tuberculosis (TB)

This list is indicative and not exhaustive.

10.11 APPENDIX 11: ABBREVIATIONS AND DEFINITIONS

ACQ:	Asthma Control Questionnaire
AD:	atopic dermatitis
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
ANSD:	asthma nighttime symptom diary
AQLQ(S):	Asthma Quality of Life Questionnaire with Standardized Activities
AST:	aspartate aminotransferase
ATS/ERS:	American Thoracic Society/European Respiratory Society
AUC:	area under the serum concentration curve
BDR:	bronchodilator response
C_{max}:	maximum observed serum/plasma drug or metabolite concentration
CSR:	clinical study report
DC:	dendritic cell
DMC:	Data Monitoring Committee
DPI:	dry powder inhaler
EASI:	Eczema Area and Severity Index
ECG:	electrocardiogram
eCRF:	electronic case report form
eDiary:	electronic diary
EOS:	end of study
EOT:	end of treatment
[redacted]	
e-Spirometer:	electronic spirometer
FeNO:	Fractional Exhaled Nitric Oxide
FEV1:	forced expiratory volume in 1 second
FEV6:	forced expiratory volume in 6 seconds
FIH:	first-in-human
FSH:	follicle-stimulating hormone
FVC:	forced vital capacity
GCP:	good clinical practice
GDPR:	General Data Protection Regulation
GINA:	global initiative for asthma
GLP:	good laboratory practice
HBc Ab:	hepatitis B core antibody
HBs Ag:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCV Ab:	hepatitis C virus antibody
HLGT:	high-level group term

HLT:	high level term
HRQoL:	health-related quality of life
HRT:	hormonal replacement therapy
IA:	interim analysis
IB:	Investigator’s Brochure
IC90:	90% inhibitory concentration
ICF:	informed consent form
ICS:	inhaled corticosteroid
IDFU:	investigational directions for use
IE:	intercurrent event
IEC:	Independent Ethics Committees
IFNγ:	Interferon-gamma
Ig:	immunoglobulin
IGA:	Investigator Global Assessment
IgE:	immunoglobulin E
IL:	interleukin
ILC2:	innate lymphoid cells type 2
IRB:	Institutional Review Boards
ITT:	Intent-to-treat
IV:	intravenous(ly)
IVRS/IWRS:	interactive voice/web response system
KLH:	keyhole limpet haemocyanin
LABA:	long-acting beta agonist
LAMA:	long-acting muscarinic antagonist
LAR:	legally authorized representative
LOAC:	loss of asthma control
LS:	least squares
LTRA:	leukotriene receptor antagonist
LTS:	long term safety
mAb:	monoclonal antibody
MCID:	Minimal Clinically Important Difference
MDI:	metered dose inhaler
NOAEL:	no observed adverse effect level
OCS:	oral corticosteroid
OX40L:	OX40 ligand
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
PEF:	peak expiratory flow
[redacted]	
PK:	pharmacokinetics
PRO:	Participant-reported outcome
PT:	preferred term
Q12W:	every 12 weeks
Q4W:	every 4 weeks
QoL:	quality of life

QTL:	Quality tolerance limit
Rrs:	Respiratory resistance
SABA:	short-acting beta 2-agonists
SAE:	serious adverse event
SAP:	statistical analysis plan, statistical analysis plan
SARP:	Severe Asthma Research Program
SC:	subcutaneous
[redacted]	
SoA:	schedule of activities
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
TARC:	Thymus and Activation-Regulated Chemokine
TB:	tuberculosis
TEAE:	treatment-emergent adverse event
Th:	T helper
Tmem:	memory T cells
TNF:	Tumour necrosis factor
Treg:	Regulatory T cell
TSLP:	thymic stromal lymphopoietin
ULN:	upper limit of normal range
VAS:	Visual Analog Scale
WOCBP:	woman of childbearing potential
WONCBP:	woman of nonchildbearing potential
Xrs:	Respiratory reactance

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

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

The primary reasons for first protocol amendment are summarized below.

Amended protocol 01 (17 June 2022)

This amended protocol (amendment 01) is considered to be nonsubstantial 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 because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment to Protocol DRI17509 is to fulfil requirement from the Medicines and Healthcare products Regulatory Agency (MHRA), UK.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	"Tests should be performed no more than 5 days prior to IMP administration" is added and "COVID-19 molecular test will be performed at screening (Day -1)" is revised to "COVID-19 test will be performed at screening" in footnote k.	Clarification on COVID testing for the investigators.
Section 10.2 Appendix 2: clinical laboratory tests	The text for COVID-19 testing in table 13 is revised as: "Tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes coronavirus disease 2019 [COVID-19]) at Screening (Visit 1), randomization and prior to each IMP administration (no administration if positive). Tests should be performed no more than 5 days prior to IMP administration. Method of testing as required per local guidelines".	
Section 5.2 Exclusion Criteria E14	"Serum total bilirubin >1.5 x ULN (participants with Gilbert's syndrome can be included with total bilirubin >1.5 x ULN as long as direct bilirubin is <1.5 x ULN)" is added in E14.	To fulfil requirement from MHRA, UK.
Section 6.8 Concomitant Therapy	"Other concomitant medications may be considered on a case-by-case basis by the Investigator in consultation with the medical monitor if required" is removed.	To fulfil requirement from MHRA, UK.
Section 7.1.1 Permanent Discontinuation	"A decision to resume the IMP will be made jointly by the Investigator and Medical Monitor (Medical Monitor's written approval is required)" is removed.	To fulfil requirement from MHRA, UK.
Section 10.2 Appendix 2: clinical laboratory tests	"Creatine phosphokinase (CPK)" is added in Table 13.	Clarification to align with the footnote g under the SoA. The inconsistency was pointed out by FDA.
Section 10.12 Appendix 12: Protocol Amendment History	Updated	Changes made based on Sanofi standard.
Section 11 References	Reference 25 is corrected.	Correction of the reference.
Cover page	"NCT05421598" is added.	Update on ClinicalTrials.gov identifier number.
Throughout the document	Other minor editorial changes (eg, grammatical, stylistic, and minor typographical corrections).	To increase the clarity or consistency of the protocol.

Amended protocol 02 (23 November 2022)

This amended protocol (amendment 02) is considered to be nonsubstantial 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 because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment to DRI17509 amended protocol 01 is to remove all references to China, since China is removed from participation in the study. Some editorial and operational modifications are made.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 6.1.1 Devices	The text "(in certain countries)" is deleted after impulse oscillometry devices	Clarification on the supply of impulse oscillometry devices by Sanofi or designees
Section 1.1 Synopsis and Section 6.2 Preparation, handling, storage and accountability	The text for the route of administration is changed to: "SC injection, to abdomen or outer thigh. IMP should not be administered at the exact site of a recent injection or in areas which in the Investigator's opinion are not suitable (eg, tender, bruised, red or hard)."	Clarification to align with amlitelimab program
Section 1.3 Schedule of Activities (SoA)	[redacted]	[redacted]
	Remote spirometry (pre-BD) is performed daily throughout the study during the Screening as it is during the rest of the study	Clarification of remote spirometry (pre-BD) measurements during the Screening
	ANSD (AM) and ADSD (PM) will be performed at screening as preformed throughout the study	Clarification of ANSD and ADSD measurements schedule
	In footnote b, the timelines "15 to 30 minutes" is deleted for the reversibility of at least 12% and 200 mL in FEV1 after administration of 2 to 4 puffs (200-400 µg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that meets these criteria within 12 months prior to Visit 1.	The timeframe for reversibility testing is unnecessarily restrictive and not mandated by the 2019 ATS-ERS guideline
	Footnote w is changed to "To calculate ACQ-7, the ACQ-6 is completed in the participant's eDiary during clinic visits. ACQ-6 score will be used to follow up evaluations in all participants. ACQ-5 (the first 5 items of the ACQ-6) score is used for eligibility evaluation at Visit 1 and Visit 2 for all participants."	To align with ACQ-7 assessment listed as efficacy outcome in the schedule of activities (SOA) table
	In the footnote aa, the sentence "In case of severe asthma exacerbation during screening, screening	

Section # and Name	Description of Change	Brief Rationale
	period can be extended to up to 3 months. Please see Screen Failures section for instructions" is added.	
Section 5.1 Inclusion criteria	Inclusion criterion I 06 is changed to "5-item ACQ-5 score >1.5 at screening and randomization.	5-item ACQ-5 score >1.5 is required at screening for eligibility which is stated in the SoA and in the Screen Failures section; I 06 language updated accordingly
	In inclusion criterion I 07, the timelines "15 to 30 minutes" is deleted for the reversibility of at least 12% and 200 mL in FEV1 after administration of 2 to 4 puffs (200-400 µg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that meets these criteria within 12 months prior to Visit 1.	The timeframe for reversibility testing is unnecessarily restrictive and not mandated by the 2019 ATS-ERS guideline
Section 5.2 Exclusion criteria	Exclusion criterion E03 is updated. Participants are excluded if they experience a deterioration of asthma within 1 month prior to the Screening Visit." A clarifying note is added: "counting from the date of completion of treatment for asthma exacerbation"	Clarification of exclusion of participants for deterioration of asthma
Section 5.4 Screen failures	The text "without an option for rescreening" is added to the sentence "Participants who are eligible for rescreening may be rescreened once for any reason, except for PRO criteria (ie, ACQ-5<1.5), which will lead to screen failure."	Editorial change
	The text for technical malfunction of equipment during spirometry is revised as: "In the case of technical malfunction of equipment during spirometry, the participant may be retested".	Operational clarification
	The text for the participants who experience an upper or lower respiratory tract infection during the screening period is revised as:" Participants with an upper or lower respiratory tract infection within the 4 weeks prior to screening or during the screening period may be rescreened (Exclusion criterion E 04) after 4 weeks or 14 days after recovery, ie, completion of the therapy, whichever is longer."	Clarification of rescreening timelines for the participants who experience an upper or lower respiratory tract infection during the screening period
	The text for "Participants who experience an asthma exacerbation that results in emergency treatment or hospitalization, or treatment with systemic steroids during the screening period" is updated to "remain in screening and proceed with randomization 1 month after they have completed their course of oral corticosteroid (OCS) or returned to their maintenance dose of OCS. Screening period in this case can be extended to up to 3 months."	Clarification of extension of screening period for participants who experience an asthma exacerbation that results in emergency treatment or hospitalization, or treatment with systemic steroids during the screening period
Section 8 Study assessments and procedures	In the list of assessments/procedures performed at site, the text "spirometry pre-BD and spirometry post-BD" are simplified to "spirometry".	Clarification of assessments/procedures performed at site
Section 8.1.3.4 Electronic diary	ACQ-5 is changed to ACQ-6	Typo

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
Section 10.2 Appendix 2: Clinical laboratory tests: Table 13	Random is added to fasting for glucose measurement.	Clarification of glucose measurement
	Direct bilirubin measurement is deleted. Conjugated and non-conjugated bilirubin measurements are added when total bilirubin is above normal range.	Clarification of bilirubin measurement
Section 10.8.1 China-specific requirements	Section removed and subsequent section is re-numbered.	China is removed from participation in the study
Section 10.9 Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency	Cotinine is deleted in the sentence: "Vital signs, hematology and clinical chemistry, routine urine analysis plus dipstick test (pregnancy) and AE reporting should have priority from a safety perspective."	Cotinine measurement is deleted as priority from a safety perspective; typo
Section 10.10.1. Low, medium, and high ICS doses: adults/adolescents	The text: "Daily doses in this table are shown as metered doses. See product information for delivered doses", is added	Clarification of inhaled corticosteroid treatments
Section 10.12 Appendix 12: Protocol amendment history	The text of summary of changes for protocol amendment 01 is added	Appendix 12 is updated to reflect the document history of previous amendment, ie, amendment 01
Throughout the document	All references to China are removed	China is removed from participation in the study
Throughout the document	The text moderate-to-high doses of ICS therapy is changed to medium-to-high doses of ICS therapy	Wording accuracy

Amended protocol 03 (03 April 2023)

This amended protocol (amendment 03) is considered to be nonsubstantial 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 because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The overall rationale for the amendment is to respond to the Health Authorities (Ministry of Food and Drug Safety [MFDS]) requests: to implement conditions and set a limited number of two rescreening options during the screening period (one rescreening due to asthma exacerbation and one additional rescreening for any reason other than PRO criteria [ACQ-5<1.5]) in South Korea since 3-month extended screening period is not allowed in that country.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SOA)	Under footnote aa, a reference to Section 10.8.2 was newly added for South Korea.	Regulatory Authority (MFDS) request
5.4 Screen failures	The following wording was added: “Please note exceptions for South Korea” and “Note: extension of screening is not allowed in South Korea”. References to Section 10.8.2 were added.	
10.8.2 South Korea specific requirements	A new subsection was added to adapt the process of rescreening in case of screen failures for study participants from South Korea.	
10.1.6 Dissemination of clinical study data and results	The following website “clinicalstudydatarequest.com” was updated to “vivli.org”.	To update due to recent change of website.

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