AMENDED CLINICAL TRIAL PROTOCOL 03

Protocol title:	**Randomized, double blind, placebo controlled study to evaluate the effect of dupilumab on airway inflammation through assessments of lung function, mucus plugging and other lung imaging parameters in patients with asthma**
Protocol number:	**LPS15834**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR231893 dupilumab**
Study phase:	**Phase 4**
Short title:	**VESTIGE**
Sponsor name:	**Sanofi SAG**
Legal registered address:	**54-56, Rue la Boétie, 75008 Paris France**
Monitoring team's representative name and contact information	

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Other:	Not applicable

Date: 13-Apr-2023 Total number of pages: 114

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	13 April 2023, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	All	15 March 2021, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01	All	12 March 2020, version 1 (electronic 1.0)
Original Protocol		09 January 2020, version 2 (electronic 2.0)

Amended protocol 03 (13 April 2023)

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for amended protocol 03 is evolving interest to evaluate FeNO as an airway inflammatory biomarker related to structural lung changes. Therefore, the primary endpoint FEV_1 is proposed to be replaced with the secondary endpoint of FeNO, leading to an overall reduction in sample size.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2 Introduction	Information from various literature sources for FeNO assessment added. The following text is deleted "and effect on lung function, airway inflammation and the relationship between imaging dynamics and FeNO, and the link with asthma control as perceived by the patient"	To support the rationale for promoting FeNO to a primary endpoint. The text has been deleted as it is a redundant information.
Section 1.1 Synopsis Section 3 Objectives and Endpoints	The primary endpoint pre-BD FEV_1 has been replaced by FeNO.	To update primary objective to assess the role of dupilumab on airway inflammation related to structural changes in the lung in addition to imaging.
Section 1.1 Synopsis Section 3 Objectives and Endpoints	Minor clarifications on the terminology of the primary and secondary functional respiratory imaging (FRI) endpoints.	To more accurately describe the FRI endpoints.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3 Objectives and Endpoints	Following endpoint has been moved from primary to secondary • Change from baseline to Week 24 in pre-bronchodilator FEV_1	To reflect the shift of this endpoint from primary to secondary.
Section 1.1 Synopsis Section 3 Objectives and Endpoints	Following endpoint has been moved from tertiary/exploratory to secondary and updated as follows: • Change from baseline to Week 24 in global lung mucus scoring (UCSF mucus scoring)	This change is proposed due to the increased interest in the assessment of presence of mucus plugs in the airways.
[redacted]		
Section 1.1 Synopsis Section 9.2 Sample Size Determination and Preservation of Type I Error For The Primary Endpoints	The text is updated for sample size calculation. New text added for power calculation and hypotheses for the new primary endpoint.	Updates to the sample size calculation and hypotheses reflecting the change to the primary endpoint.
Section 1.1 Synopsis Section 9.4.2 Safety analyses	The statement of multiplicity control procedure and the selected list of secondary endpoints was simplified and the details will be reported in the Statistical Analysis Plan.	According to the new template, details of testing for secondary endpoints are reported in the Statistical Analysis Plan.
Section 2.3 Benefit/Risk Assessment	The section is updated with the most recent data on exposure to dupilumab and regulatory information.	To incorporate the most recent exposure data for dupilumab and regulatory information.
Section 8.1 Efficacy Assessments	Asthma Control Questionnaire 7-question version Details of clinic staff score for FEV_1% predicted added. Text updated for Asthma Quality of Life Questionnaire with Standardized Activities (Self-Administered) details on overall score calculation.	Clarification on clinical staff score for FEV_1% predicted. Clarifications on overall score calculation.
Section 9.1 Statistical Hypotheses Section 9.2 Sample Size Determination and Preservation of Type I Error for the Primary Endpoints	New text added for hypotheses for the updated primary endpoints, and simplified testing procedure.	Use sequential testing for the primary endpoints; according to new template, details of testing for secondary endpoints are reported in the Statistical Analysis Plan.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.1 Efficacy analyses Table 7 Efficacy analyses	Following sentence is added to the text Data may be logarithmically transformed prior to analysis if extreme skewness was observed based on blinded data review. The table for efficacy analyses is updated.	The efficacy analyses are updated based on changes to the endpoints.
Section 10.1.7 Data Quality assurance	Text for quality tolerance limits is removed.	This paragraph is not applicable.
Throughout the text	Following sections are updated Section 6.3-Measures to minimize bias: Randomization and Blinding Section 8.3-Adverse events and serious adverse events Appendix 1 Section 10.1.4-Data protection Appendix 1 Section 10.1.6-Dissemination of clinical study data and results Appendix 1 Section 10.1.9-Study and site start and closure Appendix 9-Contingency Measures for a regional or national emergency that is declared by a governmental agency	Template related changes
Throughout the text	Minor grammatical, editorial, and/or administrative changes.	To improve the readability and/or clarity of the protocol.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

Randomized, double blind, placebo controlled study to evaluate the effect of dupilumab on airway inflammation through assessments of lung function, mucus plugging and other lung imaging parameters in patients with asthma

Short title:

VESTIGE

Rationale:

Chronic airway inflammation is a characteristic feature of asthma (**1**). Chronic inflammation is associated with mucus production, airway smooth muscle contraction and hypertrophy, airway hyperresponsiveness, and structural airway remodeling (2).

Although the pathophysiology of airway remodeling in asthma remains to be fully elucidated, key type 2 cytokines are believed to be involved in this process: IL-13 upregulate levels of fractional exhaled nitric oxide (FeNO) (3), which also affects airway smooth muscle function and mucus production, and may influence subepithelial fibrosis by secretion of periostin and other pro-fibrotic mediators. These effects may contribute to airway remodeling and obstruction (4).

IL-13 is implicated in tissue effects on goblet cells and airways smooth muscle cells, which impact on mucus secretion, smooth muscle contractility, and basement membrane thickening (5).

Airway remodeling in established asthma is poorly responsive to current therapies, such as inhalation of corticosteroids and administration of β2-agonists, anti-leukotrienes, theophylline, and biologics (6, 7). It is plausible that some potentially meaningful airway responses/changes involved in airway remodeling could fail to be detected or demonstrated due to the poor sensitivity of the conventional parameters utilized in these previous clinical studies.

Patients with normal forced expiratory volume in 1 second (FEV_1) can have regional airway structure changes. Functional imaging (FI) is a useful tool for sensitive assessment of structural and functional changes in the lungs after asthma treatment (8). According to previous studies (8, 9, 10, 11) functional respiratory imaging (FRI) technology has demonstrated a higher sensitivity to detect the effect of treatment on lung function than conventional assessments like FEV_1.

Type 2 biomarkers such as peripheral blood eosinophils and FeNO have been shown to identify different aspects of type-2 airway inflammation. Fractional exhaled nitric oxide is a simple, non-invasive biomarker that identifies IL-4/13 mediated airway inflammation at the level of the respiratory epithelium, leading to increased production of NO, which can be measured as FeNO, and is associated with pro-inflammatory effects, including excess mucus production, airway

remodeling, and increased bronchoconstriction (12, 13, 14). This inflammatory cascade could be identified via imaging including reduced airflow and increased airway wall thickness, as well as IL-13-mediated goblet cell production. Therefore, airway structural changes and FeNO levels could represent different biomarker components of IL-4 and IL-13 driven inflammation. FeNO has been shown to be a possible predictor of exacerbation risk and accelerated lung function decline and may indicate ongoing damage, although further investigations into this process are warranted (15, 16, 17, 18, 19, 20).

It is hypothesized that the changes in FEV_1 observed with dupilumab treatment are potentially related to reduction in airway inflammation and changes in airway volumes detectable by functional respiratory imaging.

The goal of this study is to gain further insight into the effect of dupilumab on lung inflammation, and also explore the effect on airway changes, biomarkers, and gain preliminary understanding of the potential interrelationships between these parameters.

A combination of classical lung function, patient-reported outcome parameters, and FI methods has the potential to enhance the description of the mode of action of new compounds (8). In addition, results from the recently published ATLANTIS study suggest that a combination of biomarkers (FeNO), physiological testing (FEV_1), and imaging approaches provides a comprehensive assessment of small airway dysfunction (SAD) in asthma (21).

The QUEST study (22) has shown significant and clinically meaningful effects of dupilumab on FEV_1 improvement, particularly in the high blood eosinophil count (≥300 cells/mm^3) population at baseline, as early as Week 2 and was sustained throughout 52 weeks.

Dupilumab also has the potential to exert an unplugging effect on the airways by reducing mucus production, due to the anti-inflammatory effect via direct inhibition of IL-13 signaling (3, 4, 5).

Therefore, by utilizing imaging results, coupled with clinical outcomes (FEV_1), biomarkers (FeNO), and patient-reported outcomes (Asthma Control Questionnaire [ACQ] and Asthma Quality of Life Questionnaire with Standardized Activities [AQLQ(S)]), the study is expected to further characterize dupilumab's unique mechanism of action (MoA).

Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the effect of dupilumab on lung inflammation and related changes in airway volumes detectable by functional respiratory imaging.	• Proportion of participants achieving FeNO <25 parts per billion (ppb) at Week 24 • Percent change from baseline to Week 24 in untrimmed distal airway volumes corrected for lung volume ([s]iVaw) at total lung capacity (TLC)
Secondary	
• To evaluate the effect of dupilumab at Week 24 on bronchodynamics, hyperinflation, airway resistance, airway wall thickness, ventilation defects and mucus plugging derived from high-resolution computed tomography (HRCT) scans, patient-reported outcomes, FeNO and spirometry.	Efficacy endpoints: • Percent change from baseline to Week 24 in untrimmed distal airway volumes corrected for lung volume ([s]iVaw) at functional residual capacity (FRC) • Percent change from baseline to Week 24 in trimmed distal airway resistance corrected for lung volume ([s]iRaw) at TLC • Percent change from baseline to Week 24 in trimmed distal airway resistance corrected for lung volume ([s]iRaw) at FRC • Change from baseline to Week 24 in global lung lobar volumes (iVlobes) at TLC • Change from baseline to Week 24 in HRCT-based internal airflow distribution (IAD) for each lung zone • Change from baseline to Week 24 in image-based ventilation/perfusion (iV/Q) at TLC for each lung zone • Change from baseline to Week 24 in global lung mucus scoring (UCSF mucus scoring) • Change from baseline to Week 24 in FeNO • Change from baseline to Week 24 in pre-bronchodilator FEV_1 • Change from baseline to Week 24 in post-bronchodilator FEV_1 • Change from baseline to Week 24 in ACQ-7
• To evaluate safety of dupilumab	Safety: • Incidence of treatment emergent adverse events (TEAE) and serious adverse events (SAE) including clinically significant changes in vital signs and laboratory abnormalities • Incidence of adverse events of special interest (AESI)
[redacted]	

Objectives	Endpoints
[redacted]	

Overall design:

A Phase 4 randomized, multinational study with 24-week double-blind placebo-controlled period to assess the effect of dupilumab on airway inflammation through assessments of biomarkers, mucus plugging, and other lung imaging parameters in participants with asthma.

Disclosure Statement: This is a Parallel Treatment study with 2 arms that is blinded for participants and/or caregivers and investigators.

Number of participants:

Approximately 97 participants will be randomly assigned to study intervention, respectively in a 2:1 ratio for dupilumab: placebo, such that 87 evaluable participants (58 to dupilumab group and 29 to placebo group) complete the study. Randomization will be stratified by dose level (medium/high - no less than 40% in 'high ICS' stratum) of inhaled corticosteroids (ICS) and region (Eastern Europe/ROW). In total, no more than 40% participants should be in "Eastern Europe" strata.

Intervention groups and duration:

Study participation for each participant will be a total of minimum 29 weeks and up to 41 weeks.

The study includes 3 study periods:

- Screening period: 4 weeks (±1 week), from signed informed consent to randomization.
- Randomized, placebo-controlled treatment period: 24 weeks from baseline (Day 1).
- Post treatment follow-up period: up to 12 weeks or until the participants switch to commercialized dupilumab (or other biologic products), whatever comes first.

Participants who fulfill the inclusion criteria and do not meet any of the exclusion criteria will be randomized (2:1) to one of the following investigational medicinal products (IMP).

- Dupilumab: participants will receive a loading dose of 600 mg of dupilumab (2 x 300 mg dupilumab SC on Day 1, followed by 300 mg every 2 weeks (Q2W) for 24 weeks.
- Placebo: participants will receive 2 x 2 mL placebo injections SC on Day 1, then 1 placebo injection Q2W for 24 weeks.

Study intervention(s)

Investigational medicinal product(s)

Dupilumab and matching placebo will be supplied in prefilled syringes that are visually indistinguishable.

Dupilumab 300 mg:

- Formulation: A 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in a 2 mL injection.
- Route of administration: SC injection.
- Dose regimen: Q2W after an initial loading dose of 600 mg (2 injections of 300 mg) on Day 1.

Matching Placebo:

- Formulation: Matching placebo will be supplied as an identical formulation to the active formulation without dupilumab, in a prefilled syringe to deliver placebo in a 2 mL injection.
- Route of administration: SC injection.
- Dose regimen: Q2W after an initial loading dose (2 injections) on Day 1.

Posttrial access to study medication: Posttrial access to study medication will be assessed in accordance to the country requirements and the legislation in place.

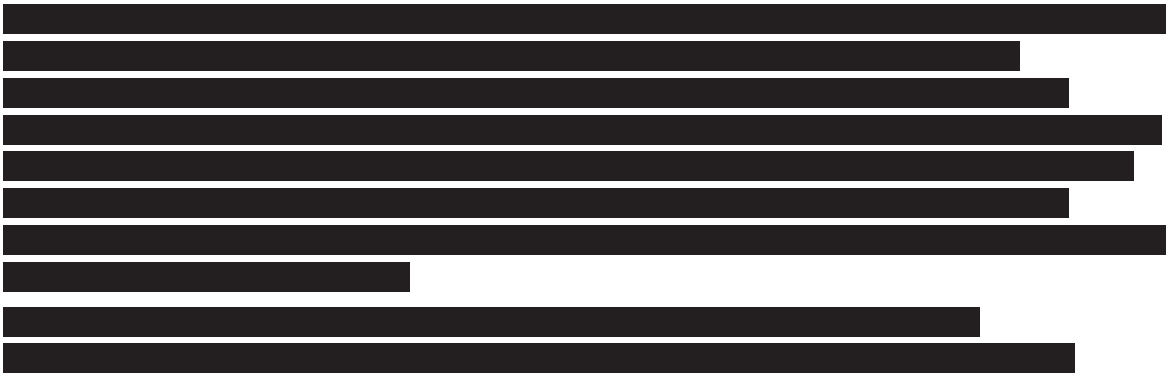
Statistical considerations:

- **Sample size calculations and preservation of Type I error for the two primary endpoints**

  To control the type-I error rate for the 2 primary endpoints, a hierarchical testing procedure will be applied at a 2-sided 5% significance level, ie, each hypothesis will be formally tested only if the preceding one is significant at 5% level. The hierarchy of the tests for primary endpoints will be:

  a) Proportion of participants achieving response of FeNO <25 ppb at Week 24

  b) Percentage change from baseline to Week 24 in untrimmed distal [s]iVaw at TLC



- **Primary analysis:**

  For the primary endpoint proportion of participants achieving FeNO <25 pbb at Week 24, the analysis will be conducted by Cochran-Mantel-Haenszel (CMH) test adjusted by stratification factors. Comparison of the proportions of responders between dupilumab and placebo will be derived, and corresponding odds ratios and 95% CI along with the p-value will be reported. For participants who discontinued the study treatment, off-treatment data will be used to determine the responder/non-responder status. Missing data at Week 24 will be considered as non-responders.

  Percent change from baseline to Week 24 in distal [s]iVaw at TLC will be analyzed using a mixed model repeated measures model (MMRM). The model will include percent change from baseline values up to Week 24 as the response variable, and treatment group, region (Eastern Europe/ROW), ICS dose level (medium/high), visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the within participants errors. No imputations for missing values will be carried out. The least square (LS) mean of each treatment group, the LS mean difference between the dupilumab group and placebo, and the corresponding 95% CI of the differences and p-values will be provided. For participants who discontinued the study treatment, off-treatment imaging data, as available, will be included in the analysis.

- **Analysis of secondary endpoints:**

  Secondary endpoints relating to change or percent change from baseline will be analyzed with MMRM model in a manner similar to that for the primary imaging endpoint.

- **Multiplicity considerations for the secondary endpoints:**

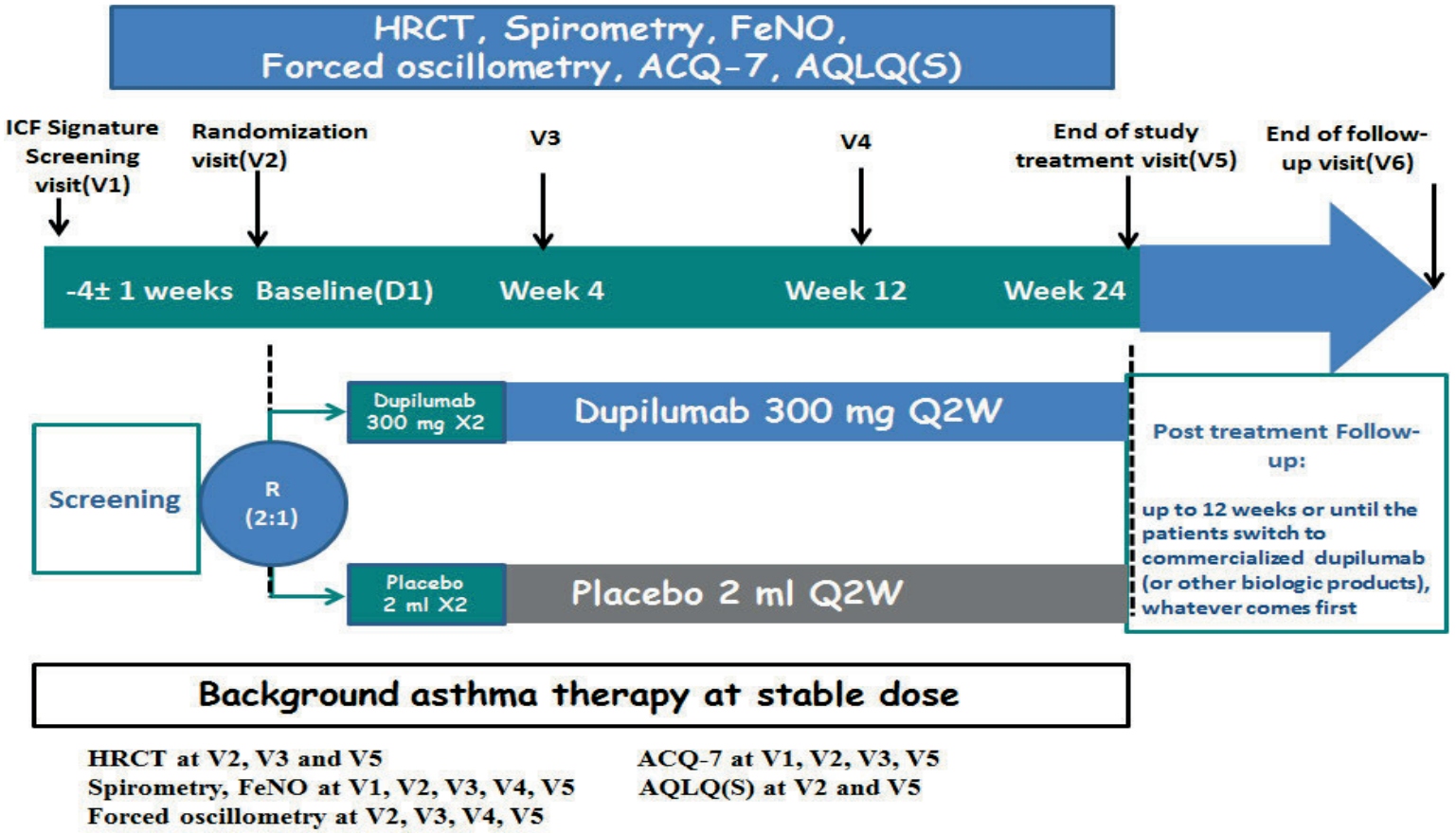
  A multiplicity control procedure and the selected list of secondary endpoints to be tested in the hierarchical order will be specified in the Statistical Analysis Plan. Regardless of eligibility to be declared significant, results for all comparisons will be presented. Descriptive statistics including number of participants, mean, standard deviation, and LS means will also be provided.

Safety analyses: All safety variables will be summarized using descriptive statistics.

Data Monitoring Committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



ACQ-7= 7-item Asthma Control Questionnaire; AQLQ(S) =Asthma Quality of Life Questionnaire with Standardized Activities; D=Day; FeNO= Fractional exhaled nitric oxide; FU= Follow-up; HRCT= High-resolution computed tomography; ICF=Informed Consent Form; mg=milligram; ml=milliliter; Q2W= every 2 weeks; R=Randomization; V=Visit

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening period 4 weeks ± 1 week (21 - 35 days) before Day 1	Randomized Treatment Period (D: day; W: week) Visit windows after D1 are ±3 days				Post-treatment Follow-up
		D1	W4	W12	W24	up to W36[c]
Visit (V)	Screening visit V1	Baseline (randomization) visit V2	V3	V4	End of treatment visit[a,b] V5	End of follow up visit V6[d]
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demography	X					
Smoking status	X					
Medical/Surgical history	X					
Vital signs[e]	X	X	X	X	X	
Physical examination[f]	X	X			X	
Reversibility test[g]	X					
12-lead ECG	X					
ACQ-7[h]	X	X	X		X	
AQLQ(S)[i]		X			X	
FeNO[j]	X	X	X	X	X	
HRCT scan[k]		X	X		X	
Forced Oscillometry[l]		X	X	X	X	
Pre - bronchodilator FEV_1[m]	X	X	X	X	X	

Procedure	Screening period 4 weeks ± 1 week (21 - 35 days) before Day 1	Randomized Treatment Period (D: day; W: week) Visit windows after D1 are ±3 days				Post-treatment Follow-up
		D1	W4	W12	W24	up to W36[c]
Visit (V)	Screening visit V1	Baseline (randomization) visit V2	V3	V4	End of treatment visit[a,b] V5	End of follow up visit V6[d]
Post - bronchodilator FEV_1[m]		X	X	X	X	
Pregnancy test (WOCBP only)[n]	X	X	X	X	X	X
Blood eosinophil count[o]	X	X	X	X	X	
Hepatitis B, C and HIV Serology tests[p] Tuberculosis testing[q]	X					
Home dosing diary Asthma background therapy diary [r]		X	X	X	X	
Randomization		X				
IVRS/IWRS call	X	X	X	X	X	X
Investigational product administration[s]		X	X	X	X	
Drug dispensation		X	X	X		
Prior and concomitant medication review	X	X	X	X	X	X
AE/SAE/AESI review	X	X	X	X	X	X

ACQ-7=7 item-Asthma Control Questionnaire; AE=Adverse Event; AESI=Adverse Event of Special Interest; AQLQ(S)=Asthma Quality of Life Questionnaire with Standardized Activities; ATS= American Thoracic Society; ECG=Electrocardiogram; ESD= Early Study Discontinuation; ETD=Early Treatment Discontinuation; FeNO=Fractional exhaled nitric oxide; FEV_1=Forced expiratory volume in 1 second; FOT= Forced oscillation technique; HRCT= High-resolution computed tomography; IVRS=Interactive voice recognition system; IWRS= Interactive web response system; SAE=Serious Adverse Event;

a Participants who prematurely discontinue the study intervention (prior to completing the 24-week treatment period) should attend an Early Treatment Discontinuation (ETD) visit at earliest convenience with all the assessments planned for the End of Treatment visit (V5), except HRCT scans and IMP. In particular cases when the ETD visit is closed to a regular study visit, ETD could be merged and will replace the regular visit. In addition, the participants will be asked and encouraged to complete all the remaining study visits according to the visit schedule until and including the EOT visit (V5). Under exceptional circumstances when a participant cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs and concomitant medication should be collected.

b Participants who prematurely discontinue the study should attend an Early Study Discontinuation (ESD) visit at earliest convenience with all the procedures planned for the End of Treatment Visit (Visit 5) except IMP. If the Investigator considers that the time from the last HRCT scan exposure is not acceptable, the investigation will not be done.

c Post-treatment Follow-up: up to 12 Weeks or until the participants switch to commercialized dupilumab (or other biologic products), whatever comes first.

d Visit 6 will be a telephone visit. For the participants who switch to commercialized dupilumab (or other biologic products), the call visit should be done prior to the first injection with commercialized dupilumab (or other biologic products).

e Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius).

f A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems and will be performed at V1, V2 and V5. Body weight (kg) will be measured at V1, V2 and V5. Height (cm) will be measured only at V1.

g Reversibility test: Three attempts may be performed during the screening period to meet the qualifying criteria for reversibility before randomization. This is only required if a reversibility test meeting eligibility criterion was not performed within 6 months prior to Visit 1.

h Asthma Control Questionnaire-7 (ACQ-7): items 1 to 6 should be completed by the participant, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The questionnaire should be completed by the participants before the consultation and/or clinical tests, in a quiet place. ACQ-5 scores (mean of the responses to the first 5 questions) and ACQ-6 (mean of the responses to the first 6 questions) will be derived from ACQ-7. The local values of FEV_1 will be considered for the ACQ-7 scores. For the statistical analysis we will use centrally read values.

i Asthma Quality of Life Questionnaire with Standardized Activities [AQLQ(S)] should be completed by the participant, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The questionnaire should be completed by the participants before the consultation and/or clinical tests, in a quiet place.

j FeNO should be conducted prior to spirometry and the participant should refrain from eating and drinking for ≥1 hour before the procedure. The test will be performed after a wash out period of bronchodilators according to their action duration as detailed in Table 4 (Section 8.1). Retesting of FeNO can be done one additional time during screening if the eligibility criterion for FeNO was not met at V1. FeNO will be re-checked at randomization visit (V2) for eligibility. Further details on the procedure for measuring FeNO will be provided in a separate instruction manual

k Centrally read. Scans are respiratory gated to avoid variations in lung and airway volume, as per scans protocol. Further details on the HRCT scan will be provided in a separate instruction manual. The wash out time of the asthma controllers and rescue medication before HRCT and lung function assessments is detailed in Table 4 (Section 8.1). If HRCT scan cannot be performed at D1 due to logistic reasons, it can be scheduled the next day. In this particular situation the investigator should ensure that the IMP loading dose is administered after the HRCT scan, at D1+1 day. At visits, the HRCT scan can be done before spirometry or before post-BD FEV1 or after (in the latter case the wash-out period of SABA should be ensured), as per Investigator's decision.

l FOT should be conducted prior to spirometry. Further details on FOT will be provided in a separate instruction manual.

m Centrally read. Spirometry test should be performed before IMP administration, in the morning if possible, but if testing can only be done at another time during the day, then the testing should be done at approximately the same time of day at each visit throughout the study. Spirometry will be performed after a wash out period of bronchodilators according to their action duration as detailed in Table 4 (Section 8.1). This will be verified before performing the measurements. A participant who is unable to complete a successful spirometry effort as defined by ATS criteria or evaluated by the investigator or did not meet the eligibility criterion for pre-BD FEV1 at V1 can be retested one additional time during the screening period. For spirometry the investigator will assess the eligibility based on the FEV_1 local values from V1 and V2 before randomization (the results from central reading will not be available on the same day). The recommendation is to perform the FeNO and FOT before spirometry

n Serum pregnancy test at screening visit (Visit 1) and urine pregnancy tests at the other visits using dipstick. A negative result must be obtained at Visits 1 and 2 for eligibility. In case of positive urinary test during the study, a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. A urine pregnancy test will be performed at home at the end of follow-up visit.

o Retesting of eosinophil count is allowed up to three times during the screening period to meet inclusion criteria for showing eosinophil count ≥300 cells/microliter (cells/mL) (I 06) before randomization. This is only required if the participant does not have the blood eosinophil count measured within 6 months prior to V1 in the absence of OCS treatment.

p Hepatitis screening covering hepatitis B surface antigen (HBs Ag), total hepatitis B core antibody (total HBcAb) including IgM HBcAb; hepatitis C virus antibodies (HCVAb). In case of results showing HBsAg (negative) and HBcAb (positive), HBV DNA testing will be performed to rule out a false positivity or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCVAb (positive), HCV RNA testing may be performed to rule out a false positivity. Human Immunodeficiency Virus (HIV) screening (Anti-HIV-1 and HIV-2 antibodies).

q Tuberculosis (TB) testing would only be performed on a country by country basis according to the routine clinical practice and the local guidelines if required by Regulatory Authorities or Ethics Committees.

r Should be completed by participants regularly to record investigational (home dosing diary) and non-investigational product (asthma background therapy diary) information. Recorded data will be collected by the investigator at each onsite visit.

s Investigational product administrations (Q2W) should be separated by at least 11 days. The administration is performed on site during planned visits alternating with Q2W home administration (participant, caregiver, or health care professional) or in a health care facility. At D1, loading dose dupilumab arm 600 mg (300 mg x 2 syringes/injections); 2 placebo syringes for the placebo arm. In case that the HRCT scan is performed one day after D1 due to logistic reasons, the IMP loading dose should be administered after the completion of HRCT scan (D1 +1 Day).

NOTE:

- The contingency measures for a regional or national emergency declared by a governmental agency are detailed in Appendix 9 (Section 10.9).
- In case of severe asthma exacerbations treated with systemic corticosteroids, the visits can be postponed up to 1 week to ensure the wash-out period (Table 4) is completed before performing HRCT scan, FeNO, FOT, and spirometry. In case this is not possible (eg, a participant experiences an exacerbation shortly before the scheduled visit), the procedures can be performed as planned, but it should be recorded that the participant had recently taken systemic corticosteroids.

2 INTRODUCTION

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation (**1**).

Type 2 inflammation is an important disease mechanism in a large subgroup of individuals with asthma. Airway type 2 immune responses are mediated by cytokines such as IL-4, IL-5, and IL-13, which occur in approximately 50% of patients with asthma (10).

Dupilumab is a fully human anti-IL-4 receptor α monoclonal antibody that blocks both IL-4 and IL-13 signaling. The results of dupilumab pivotal studies have demonstrated its efficacy in moderate-to-severe asthma patients by decreasing the rates of severe asthma exacerbation, improving the lung function and asthma control (22) as well as reducing oral glucocorticoid use (23).

Dupilumab is approved for the treatment of patients with moderate-to-severe asthma in the United States, and for the treatment of patients with severe asthma in Europe and Japan.

2.1 STUDY RATIONALE

Chronic airway inflammation is a characteristic feature of asthma (**1**). Chronic inflammation is associated with mucus production, airway smooth muscle contraction and hypertrophy, airway hyperresponsiveness, and structural airway remodeling (2).

Although the pathophysiology of airway remodeling in asthma remains to be fully elucidated, key type 2 cytokines are believed to be involved in this process: IL-13 upregulate levels of fractional exhaled nitric oxide (FeNO) (3), which also affects airway smooth muscle function and mucus production, and may influence subepithelial fibrosis by secretion of periostin and other pro-fibrotic mediators. These effects may contribute to airway remodeling and obstruction (4).

IL-13 is implicated in tissue effects on goblet cells and airways smooth muscle cells, which impact on mucus secretion, smooth muscle contractility, and basement membrane thickening (5).

Airway remodeling in established asthma is poorly responsive to current therapies, such as inhalation of corticosteroids and administration of β2-agonists, anti-leukotrienes, theophylline, and biologics (6, 7). It is plausible that some potentially meaningful airway responses/changes involved in airway remodeling could fail to be detected or demonstrated due to the poor sensitivity of the conventional parameters utilized in these previously clinical studies.

Patients with normal forced expiratory volume in 1 second (FEV_1) can have regional airway structure changes. Functional imaging is a useful tool for sensitive assessment of structural and functional changes in the lungs after asthma treatment (8). According to previous studies (8, 9, 10, 11) functional respiratory imaging (FRI) technology has demonstrated a higher sensitivity to detect the effect of treatment on lung function than conventional assessments like FEV_1.

Type 2 biomarkers such as peripheral blood eosinophils and FeNO have been shown to identify different aspects of type-2 airway inflammation. Fractional exhaled nitric oxide is a simple,

non-invasive biomarker that identifies IL-4/13 mediated airway inflammation at the level of the respiratory epithelium, leading to increased production of NO, which can be measured as FeNO, and is associated with pro-inflammatory effects, including excess mucus production, airway remodeling, and increased bronchoconstriction (12, 13, 14). This inflammatory cascade could be identified via imaging including reduced airflow and increased airway wall thickness, as well as IL-13-mediated goblet cell production. Therefore, airway structural changes and FeNO levels could represent different biomarker components of IL-4 and IL-13 driven inflammation. FeNO has been shown to be a possible predictor of exacerbation risk and accelerated lung function decline and may indicate ongoing damage, although further investigations into this process are warranted (15, 16, 17, 18, 19, 20).

It is hypothesized that the changes in FEV_1 observed with dupilumab treatment are potentially related to reduction in airway inflammation and changes in airway volumes detectable by functional respiratory imaging.

The goal of this study is to gain further insight into the effect of dupilumab on lung inflammation, and also explore the effect on airway changes, biomarkers, and gain preliminary understanding of the potential interrelationships between these parameters.

A combination of classical lung function, patient-reported outcome parameters, and FI methods has the potential to enhance the description of the mode of action of new compounds (8). In addition, results from the recently published ATLANTIS study suggest that a combination of biomarkers (FeNO), physiological testing (FEV_1), and imaging approaches provides a comprehensive assessment of small airway dysfunction (SAD) in asthma (21).

The QUEST study (22) has shown significant and clinically meaningful effect of dupilumab on FEV_1 improvement, particularly in the high blood eosinophil count ($\geq$300 cells/mm^3) population at baseline, as early as Week 2 and was sustained throughout 52 weeks.

Dupilumab also has the potential to exert an unplugging effect on the airways by reducing mucus production, due to the anti-inflammatory effect via direct inhibition of IL-4 and IL-13 signaling (**3**, **4**, **5**).

Therefore by utilizing imaging results, coupled with clinical outcomes (FEV_1), biomarkers (FeNO), and patient-reported outcomes [ACQ, and AQLQ(S)], the study is expected to further characterize dupilumab's unique mechanism of action (MoA).

2.2 BACKGROUND

Dupilumab is a fully human monoclonal antibody produced by recombinant deoxyribonucleic acid (DNA) technology in Chinese Hamster Ovary cell suspension culture. It inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit of the IL-4 and IL-13 receptor complexes.

The results of the conducted studies of dupilumab have demonstrated clinically meaningful and statistically significant improvements, with treatment compared to placebo, in lung function parameters such as FEV_1.

Forced expiratory volume in 1 second has been used as the primary endpoint of lung function in the majority of asthma clinical trials over the last 3 decades (24). However, FRI emerges as a novel technique that can simulate different outcomes such as ventilation, lung deposition, and perfusion of airway blood vessels (10).

Functional respiratory imaging can assess the airway wall volume not only at the respiratory bronchi 1 level such as in the Haldar study but also at all central and distal airways down to the 7^{th} to 10^{th} generation. In addition to changes in the airway wall volume, FRI can describe changes in airway lumen volume and airway resistance (8, 25, 26).

Although not yet demonstrated, dupilumab has the potential to act as mucolytic with a positive effect on mucus plugging. Functional respiratory imaging has been used to assess effects of mucolytic agents such as n-acetyl cysteine (27).

In addition to a reduction in inflammation in the larger airways, dupilumab most likely also reduces the inflammation in the small airways. Previous studies have suggested that regional hyperinflation appears to be a sensitive marker for small airways inflammation (9, 11, 28). Functional respiratory imaging can yield regional (lobar) levels of hyperinflation by visualizing and quantifying trapped air and by expressing the lobe volume as percent predicted (where values >115% are judged to be hyper inflated compared to a reference level).

Another parameter that can be derived from FRI is the image-based ventilation/perfusion ratio (iV/Q) (29). As the main function of the lung is to transfer oxygen, anti-inflammatory properties of dupilumab could potentially result in a reduction of inflammation in the larger airways of asthmatics as well as the small airways from the atmosphere into the blood; therefore, the iV/Q parameter is highly relevant from a pathophysiological and clinical perspective.

Previous studies did demonstrate that both FEV_1 and FRI based biomarkers of airway volume (iVaw) and resistance (iRaw) can evaluate the effects of treatment in asthma and chronic obstructive pulmonary disease (COPD). This study is designed to assess the effect of dupilumab on lung function, airway inflammation and the relationship between imaging dynamics and FeNO.

2.3 BENEFIT/RISK ASSESSMENT

Dupilumab solution for injection is approved for asthma in adults and adolescents (≥12 years) in over 60 countries worldwide and review for this indication is ongoing in several other countries worldwide. In the US, dupilumab is authorized for use as an add-on maintenance treatment of adults and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroids (OCS) dependent asthma; in the EU as an add-on maintenance treatment for adult and adolescent (12 years and older) patients as well as in children 6 to 11 years old with severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO who are inadequately controlled with appropriate combination therapy (high-dose ICS over 12 years or age, medium-to-high dose ICS in those younger) plus another medicinal product for maintenance treatment. In Japan, dupilumab is authorized for use in adults and adolescents (aged ≥12 years) with severe or refractory bronchial asthma.

Dupilumab is also approved in more than 60 countries worldwide, including US, EU, and Japan, for the treatment of adults with AD, in over 60 countries for use in adolescent patients (≥12 years) with atopic dermatitis (AD) and in over 50 countries for use in pediatric patients (age 6-11 years) with AD. In the US and Europe dupilumab is also approved for AD pediatric patients of 6 months to 5 years of age.

In addition, dupilumab is approved in over 50 countries worldwide, as an add-on maintenance treatment for the treatment of adults in chronic rhinosinusitis with nasal polyposis (CRSwNP).

Dupilumab is also approved in the US and Europe for the treatment of adult and pediatric patients, aged 12 years and older, with eosinophilic esophagitis (EoE), and for the treatment of adult patients with prurigo nodularis (PN).

This study in patients with asthma aims to gain insight into the effect of dupilumab on airway changes and on lung function improvement. The combination of clinical outcomes (FEV_1), Asthma Control Questionnaire (ACQ), forced oscillometry (FOT), biomarkers (FeNO) and functional imaging will provide further characterization of dupilumab's unique mechanism of action (MoA). The study is medically and scientifically justified. The imaging study is designed to fulfill an unmet need by providing further insights into how dupilumab may improve lung function and reduce airway inflammation, and if the aims are achieved, it will help HCPs understanding dupilumab's MoA, therefore supporting optimal therapeutic management.

The functional imaging will be performed using HRCTs which will provide scientifically useful information on bronchodynamics and hyperinflation, airway resistance, airway wall thickness, ventilation defects, mucus plugging that cannot be obtained with another method.

The protocol entails that each participant will receive 3 HRCT scans (at D1, W4 and W24), each comprised by 2 acquisitions, respectively on full inspiration (total lung capacity) and end expiration (functional residual capacity) utilizing respiratory gating. Therefore, each participant will be exposed to a total of 6 HRCT acquisitions.

The effective radiation dose estimated from each research HRCT, assuming an average acquisition protocol in a modern CT scanner (at least 64 slices with radiation reduction options) is approximately 1.8 mSv. Assuming 6 HRCT acquisitions per participant, the average cumulative dose per participant will be approximately 10.8 mSv (30, 31, 32, 33).

The natural background radiation exposure form natural sources is approximately 3.0 mSv. Hence, total radiation from the CT scans in this study is approximately equal to less than 3.5 years of exposure to natural background radiation.

The Health Physics Society recommends against quantitative estimation of health risks below an individual dose 50 mSv in one year, given that the risks of health effects are either too small to be observed or are nonexistent.

Radiation-related risks due to HRCT are exclusively stochastic effects, primarily cancer induction, given that current diagnostic doses of less than 10 mSv are well below the threshold for deterministic effects, which generally start at 2000 mSv (2 Gy) (2, 3).

The estimated additional relative risk of all cancers from the International Commission of Radiologic Protection published in 2007 (2) is 0.005% per each mSv of radiation dose. This is a

very small number in comparison with the baseline incidence of all cancers, which is orders of magnitude higher (it is estimated that the lifetime risk of developing any cancer can be as high as 30%). Therefore, the radiation risk of a single chest CT performed with dose-reduction techniques is considered negligible.

Based on the UK Health Protection Agency classification of health risks related to radiation exposure, the proposed study falls into the "low risk" category, which implies 1 in 10 000–1 in 1000 risk.

In summary, the risks associated with the total cumulative radiation doses of HRCTs performed as part of this study are either too small to be observed or nonexistent. Therefore, the low risks of radiation-induced carcinogenesis associated with 6 HRCT acquisition in this research protocol do not outweigh the benefits of dupilumab treatment.

For further information on radiation exposure, please refer to Appendix 9 (Section 10.9).

Dupilumab is being administrated as per already studied dose regimen (loading dose of 600 mg of dupilumab (2x 300 mg dupilumab SC) on Day 1, followed by 300 mg every 2 weeks (Q2W) which demonstrated positive benefit/risk (22, 34, 35).

No tissue targets or specific hazards to humans were identified in nonclinical general and reproductive toxicology studies.

As of 28 September 2022, overall approximately, 14 056 participants were enrolled in the development program for dupilumab and are included in the safety population: 564 as healthy volunteers, 5009 from AD studies (including hand and foot dermatitis), 468 from eosinophilic esophagitis studies, 275 from allergy (grass and peanut) studies, 59 from the bullous pemphigoid study, 51 from the allergic bronchopulmonary aspergillosis study and 7630 from asthma, CRSwNP, chronic rhinosinusitis without nasal polyposis, allergic fungal rhinosinusitis, COPD, PN, chronic spontaneous urticaria, chronic inducible cold urticaria and chronic pruritis of unknown origin studies.

Based on the available sales figures and World Health Organization defined daily dose of 21.4 mg for parenteral formulations, the cumulative patient exposure in marketed experience is estimated to be 926 369 patient years from 01 March 2017 through 30 September 2022, including 220 161 patient years during the interval period from 01 April 2022 through 30 September 2022. The adverse drug reactions identified to date for dupilumab include injection site reactions, conjunctivitis (including allergic and bacterial), oral herpes, herpes simplex, blepharitis, dry eye, eye pruritus, keratitis, ulcerative keratitis, eosinophilia, enterobiasis and anaphylactic reaction, angioedema, serum sickness and arthralgia. These adverse drug reactions occur with relatively low frequency with dupilumab treatment, and were generally mild or moderate, transient, and manageable. More significant serious allergic reactions were very rare. Importantly, no increased overall infection risk was observed in patients treated with dupilumab.

Systemic hypersensitivity has been established as an important identified risk with dupilumab. As protein therapeutics, all monoclonal antibodies are potentially immunogenic. Rare serious and systemic hypersensitivity reactions have been observed in the dupilumab program including serum sickness/serum sickness-like reaction in the adult AD program and anaphylaxis related to dupilumab in the adult asthma clinical trials.

An important potential risk for dupilumab is “eosinophilia associated with clinical symptoms in asthma patients”. The observed increase in eosinophil count is transient, which is consistent with the current understanding of the mechanism of action of dupilumab. In dupilumab asthma studies, a small number of patients with asthma experienced serious systemic eosinophilia presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events have been seen in other drug development programs for severe asthma and usually, but not always, have been associated with the reduction of OCS therapy suggesting possible unmasking of these conditions with tapering of corticosteroids during dupilumab therapy. The association of dupilumab treatment and these events has not been established. Health care providers should be alert to eosinophilia associated with vasculitic rash, worsening of pulmonary symptoms, pulmonary infiltrate, cardiac complications, and/or neuropathy presenting in their patients, especially upon reduction of systemic corticosteroids.

Patients with known helminth infections were excluded from participation in clinical studies, therefore it is not known if dupilumab will influence the immune response against helminth infections. Consequently, patients with pre-existing helminth infections should be treated for their helminth infection before initiating therapy with dupilumab.

The safety data available to date, in conjunction with the risk monitoring and mitigation strategies in the study protocol, and the clinical benefit of dupilumab demonstrated in multiple Type 2 approved indications (AD, asthma, CRSwNP) support a favorable benefit-risk profile for dupilumab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of dupilumab may be found in the in the Investigator’s Brochure (IB) and its updates.

Benefit/risk assessment related to COVID-19

The Sponsor recognizes that the coronavirus disease 2019 (COVID-19) pandemic is having an impact on the conduct of clinical trials. The Sponsor is monitoring the situation closely and may suspend study screening activities until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. The continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Thus, a mitigation plan has been put in place at study level, all the contingency measures are described in Appendix 9 (Section 10.9). The participants will be properly informed on all these options by the investigators before the implementation of the contingency measures, as mentioned in the Informed Consent Form. Implementation of such mechanisms may differ country by country, depending on country regulations and local business continuity plans.

Based on the aforementioned potential benefits to patients participating in LPS15834, and the appropriate precautions and mitigations instituted to manage any potential impact of COVID-19 on the conduct of the trial and the safety of the patients, the Sponsor assesses that the overall benefit-risk balance is positive for the conduct of and patient participation in this trial.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the effect of dupilumab on lung inflammation and related changes in airway volumes detectable by functional respiratory imaging.	• Proportion of participants achieving FeNO <25 parts per billion (ppb) at Week 24 • Percent change from baseline to Week 24 in untrimmed distal airway volumes corrected for lung volume ([s]iVaw) at total lung capacity (TLC)
Secondary	
• To evaluate the effect of dupilumab at Week 24 on bronchodynamics, hyperinflation, airway resistance, airway wall thickness, ventilation defects and mucus plugging derived from high-resolution computed tomography (HRCT) scans, patient-reported outcomes, FeNO and spirometry.	Efficacy endpoints: • Percent change from baseline to Week 24 in untrimmed distal airway volumes corrected for lung volume ([s]iVaw) at functional residual capacity (FRC) • Percent change from baseline to Week 24 in trimmed distal airway resistance corrected for lung volume ([s]iRaw) at TLC • Percent change from baseline to Week 24 in trimmed distal airway resistance corrected for lung volume ([s]iRaw) at FRC • Change from baseline to Week 24 in global lung lobar volumes (iVlobes) at TLC • Change from baseline to Week 24 in HRCT-based internal airflow distribution (IAD) for each lung zone • Change from baseline to Week 24 in image-based ventilation/perfusion (iV/Q) at TLC for each lung zone • Change from baseline to Week 24 in global lung mucus scoring (UCSF mucus scoring) • Change from baseline to Week 24 in FeNO • Change from baseline to Week 24 in pre-bronchodilator FEV_1 • Change from baseline to Week 24 in post-bronchodilator FEV_1 • Change from baseline to Week 24 in ACQ-7
• To evaluate safety of dupilumab	Safety: • Incidence of treatment emergent adverse events (TEAE) and serious adverse events (SAE) including clinically significant changes in vital signs and laboratory abnormalities • Incidence of adverse events of special interest (AESI)

Objectives	Endpoints
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy and exploratory assessments will be done using imaging results (HRCT), coupled with clinical outcomes (FEV_1), patient-reported outcomes [ACQ and AQLQ(S)], biomarkers (FeNO) and forced oscillation technique (FOT). The HRCT scans, spirometry, and FOT assessments will be performed using central reading.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 4 randomized, multinational study with a 24-week double-blind placebo-controlled period to explore the effect of dupilumab on airway inflammation through assessments of biomarkers, mucus plugging, and other lung imaging parameters in participants with asthma.

Study participation for each participant will be a total of minimum 29 weeks and up to 41 weeks.

The study includes 3 study periods:

- Screening period: 4 weeks (±1 week), from signed informed consent to randomization.
- Randomized, placebo-controlled treatment period: 24 weeks from baseline (Day 1).
- Post treatment follow-up period: up to 12 weeks or until the participants switch to commercialized dupilumab (or other biologic products), whatever comes first.

Participants who fulfill the inclusion criteria and do not meet any of the exclusion criteria will be randomized (2:1) to one of the following investigational medicinal products (IMP).

- Dupilumab: participants will receive a loading dose of 600 mg of dupilumab (2 x 300 mg dupilumab SC on Day 1, followed by 300 mg every 2 weeks (Q2W) for 24 weeks.
- Placebo: participants will receive 2 x 2 mL placebo injections SC on Day 1, then 1 placebo injection Q2W for 24 weeks.

Randomization will be stratified by ICS dose level (medium/high- no less than 40% in ‘high ICS’ stratum) and region (Eastern Europe/ROW). In total, no more than 40% participants should be in "Eastern Europe" strata.

Study intervention discontinuation follow-up

Participants who prematurely discontinue the study intervention (prior to completing the 24-week treatment period) should attend an Early Treatment Discontinuation (ETD) visit at the earliest convenience with all the assessments planned for the End of Treatment (EOT) visit (V5), except HRCT and IMP. In particular cases when the ETD visit is close to a regular study visit, ETD could be merged and will replace the regular visit (See Section 7.1.1).

In addition, the participants will be asked and encouraged to complete all the remaining study visits according to the visit schedule until and including the EOT visit (V5).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, placebo-controlled study design where the effects of the IMP is assessed over the stable dose of maintenance therapy is considered to be the most appropriate design to investigate the objectives of this study. A randomization ratio of 2:1 for the active treatment versus placebo was incorporated into the study design in order to limit the number of participants exposed to placebo.

4.3 JUSTIFICATION FOR DOSE

The dose regimen of SC dupilumab selected for this study is 300 mg Q2W. Participants will receive an initial loading dose of 600 mg (2 x 300 mg) dupilumab on Day 1, and Q2W dosing will commence 2 weeks after the loading dose. The administration of the loading dose of dupilumab will allow systemic concentrations to reach target saturation, potentially reducing the time to onset of clinical effect.

Proof of concept has been established in the ACT11457 study (34) with 300 mg weekly dosing. One hundred and 4 participants with persistent, moderate-to-severe asthma and a blood eosinophil count of at least 300 cells/μL or a sputum eosinophil level of at least 3%, partially controlled or uncontrolled by medium-to-high doses of ICS plus long-acting β2 agonists (LABA (fluticasone/salmeterol, budesonide/formoterol, or mometasone/formoterol) were randomized to the study. The study showed significant efficacy in a population of mostly severe asthmatics with poor asthma control and decreased lung function with mostly high doses of ICS in combination with a LABA.

The results from the Phase 2b dose ranging study (DRI12544) (35) showed that 300 mg Q2W and 200 mg Q2W treatment with dupilumab provided a significant improvement on FEV_1 at Week 12 and a statistically significant reduction in the annualized rate of severe exacerbations when compared to placebo. Both dose regimens provided comparable efficacy on most of the efficacy endpoints. Both doses were safe and well tolerated with a profile comparable to that seen with placebo except for an increased number of injection site reactions. To further characterize the optimal regimen for patients, both regimens were assessed in the Phase 3 study (QUEST) (22), which confirmed the findings from previous studies, showing comparable efficacy and safety profile in both 200 mg Q2W and 300 mg Q2W dose regimens, with an overall positive benefit-risk profile for dupilumab in comparison to placebo.

The focus of this study is to characterize the anti-inflammatory effect of dupilumab, which will be mainly evaluated using FRI analyses. In order to ensure maximum anti-inflammatory effect of dupilumab, the highest approved dose (300 mg) has been selected.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the post treatment follow-up visit (V6).

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

For the participants who permanently discontinue the planned treatment, the recommended follow-up is described in Section 4.1.

5 STUDY POPULATION

Selection criteria are in line with the approved indication and refer to labeling information. Contraindications, precautions of use and warnings were considered.

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. 18 to 70 years of age inclusive with the diagnosis of asthma based on Global Strategy for Asthma Management and Prevention (GINA) 2019 (**1**) at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. History of ≥1 exacerbation(s) in the previous year before V1.

Exacerbation is defined as deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids.

I 03. Uncontrolled moderate-to-severe asthma (ACQ-5 ≥1.5) at V1 and V2, prior to randomization.

I 04. Pre-bronchodilator FEV_1 ≤80% of predicted normal at V1 and V2, prior to randomization.

I 05. Exhibit bronchodilator reversibility (≥12% and 200 mL improvement in FEV_1 post SABA administration) during screening, prior to randomization.

I 06. Blood eosinophil ≥300 cells /µL and FeNO ≥25 ppb during screening and prior to randomization.

NOTES:

- Historical values of blood eosinophil count meeting the eligibility criterion measured within 6 months prior to SV1 in the absence of OCS treatment are allowed.
- FeNO value to be checked for eligibility at V2 as well.

I 07. Existing treatment with medium to high dose ICS in combination with a second controller (eg, LABA, LTRA) ± a third controller. The dose regimen should be stable ≥1 month prior V1 and during screening.

I 08. Willing and able to comply with all clinic visits and study related procedures.

Weight

Not applicable.

Sex

I 09. Male and Female

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

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly during the intervention period and up to 12 weeks after last dose of study intervention or until the participants switch to commercialized dupilumab (or other biologic products), whatever comes first, as described in Section 10.4 (Appendix 4).

Male participants are eligible to participate if they agree to contraception conditions described in Section 10.4 (Appendix 4) during the intervention period and up to 12 weeks after last dose of study intervention or until the participants switch to commercialized dupilumab (or other biologic products), whatever comes first.

Informed Consent

I 10. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Current smoker (cigarette or e-cigarette) or cessation of smoking within 1 year prior to randomization.

E 02. Previous smoker with a smoking history >10 pack-years.

E 03. Known hypersensitivity to dupilumab or any of its excipients.

E 04. A subject who experiences an asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids) during screening.

E 05. Current acute bronchospasm or status asthmaticus.

E 06. Diagnosed pulmonary (other than asthma) or systemic disease associated with elevated peripheral eosinophil counts.

E 07. Active tuberculosis, latent untreated tuberculosis or a history of incompletely treated tuberculosis or non-tuberculous mycobacterial infection unless it is well documented by a specialist that the participant has been adequately treated and the treatment with a biologic agent can be initiated, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing would only be performed on a country by country basis according to the routine clinical practice and the local guidelines if required by Regulatory Authorities or Ethics Committees.

E 08. History or clinical evidence of COPD including Asthma-COPD Overlap Syndrome (ACOS) or any other significant lung disease (eg, lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, bronchiectasis, Churg-Strauss Syndrome).

E 09. History or current evidence of clinically significant disease in any non-respiratory system (eg, cardiovascular, hepatic, nervous system, gastrointestinal, endocrinological, rheumatological, dermatological), which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study.

E 10. Current evidence of clinically significant oncological disease, which in the opinion of the investigator may interfere with the objectives of the study or put the subject at undue risk.

E 11. Participants with any of the following results at V1:
- Positive (or indeterminate) hepatitis B surface antigen (HBsAg) or,
- Positive IgM hepatitis B core antibody (HBcAb) or,
- Positive total HBcAb confirmed by positive HBV DNA or,
- Positive hepatitis C virus antibody (HCVAb) confirmed by positive HCV RNA.

E 12. History of human immunodeficiency virus (HIV) infection or positive HIV serology at V1.

Prior/concomitant therapy

E 13. Any biologic therapy (including experimental treatments and dupilumab) or any other biologic therapy/immunosuppressant within 3 months prior to V1.

E 14. Treatment with live (attenuated) vaccine within 4 weeks before V1.

For participants who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the end of the study, or preponed to before the start of the study without compromising the health of the participant:
- Participants for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.
- Participants who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

E 15. Treatment with oral corticosteroids (OCS) within 2 weeks prior to V1.

E 16. Enrolled in other ongoing studies regardless of the investigational product.

E 17. Treatment with an investigational drug within 1 month or within 5 half-lives (if known), whichever is longer, prior to V1.

Diagnostic assessments

E 18. Suspected or high risk of parasitic infection (helminthic infection), unless clinical and (if necessary) laboratory assessments have ruled out active infection prior to randomization.

Other exclusions

E 19. Females who are lactating, breastfeeding, or who are pregnant.

E 20. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.

E 21. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation [ICH] Good Clinical Practice [GCP] Ordinance E6).

E 22. 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.

E 23. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 24. Any country-related specific regulation that would prevent the subject from entering the study.

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently eligible to be 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 details, eligibility criteria, and any SAE.

Reasons for screen failure may be unfulfilled eligibility criteria and withdrawal of consent during screening period, between screening and randomization.

Participants who do not meet the eligibility criteria for participation in this study and for whom resolution of the screen failure reason may not be expected within a reasonable time frame, will be deemed as screen failure.

Rescreening: The participants may be rescreened once during the open screening period and all the screening procedures will be repeated; a different participant identification number will be issued.

There is no requirement for a waiting period between the screen failure date and the rescreening date. The Interactive voice recognition system (IVRS)/ Interactive web response system (IWRS) report will flag rescreened participants. Participants that are rescreened must sign a new consent form and all Visit 1 procedures must be repeated.

Retesting: If certain dynamic laboratory tests do not meet the eligibility criteria, these laboratory assessments may be repeated, at the discretion of the Investigator, if it is judged that they are likely to return to acceptable range for study inclusion within the screening visit window (21 to 35 days) prior to Day 1. These participants do not need to sign a new ICF and a new participant number will not be allocated.

Retesting of eosinophil values is allowed up to 3 times during the screening period to meet inclusion criteria for showing eosinophil count ≥300 cells/µL (I 06) before randomization. This is only required if the participant does not have the blood eosinophils measured within 6 months prior to V1 in the absence of OCS treatment.

A participant who is unable to complete a successful spirometry effort as defined by American Thoracic Society (ATS) criteria or assessed by the Investigator or did not meet the eligibility criterion for pre-BD FEV1 at V1 can be retested 1 additional time during the screening period.

Up to three attempts may be performed for the reversibility test during the screening period to meet the eligibility criterion. This is only required if a reversibility test meeting the eligibility criterion was not performed within 6 months prior to V1.

FeNO can be assessed one additional time during screening period if FeNO value measured at V1 does not meet the eligibility criterion.

5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING, RANDOMIZATION, OR STUDY INTERVENTION ADMINISTRATION

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

6 STUDY INTERVENTION

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

Table 2 - Overview of study interventions administered

Intervention name	Dupilumab	Placebo
Type	Biological/Vaccine	Other
Dose formulation	solution	solution
Unit dose strength(s)	150 mg/mL	Not applicable
Dosage level(s)	Loading dose of 600 mg at Day 1[a] following 300 mg Q2W injections	2 x 2 mL placebo injections at Day 1 following Q2W injections
Route of administration[b]	SC injection	SC injection
IMP and NIMP	IMP	IMP
Packaging and labeling	One glass prefilled syringe packed in a participant kit box. Both glass prefilled syringe and box will be labeled as required per country requirement.	One glass prefilled syringe packed in a participant kit box. Both glass prefilled syringe and box will be labeled as required per country requirement.

*a*If HRCT scan cannot be performed at D1 due to logistic reasons, it can be scheduled the next day. In this particular situation the investigator should ensure that the IMP loading dose is administered after the HRCT scan, at D1+1 day.
*b*A subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive administrations. Injection in the upper arms can only be done by a trained person (caregiver) trained by Investigator or delegate or health care professional but not the participants themselves.

Investigational medicinal product(s)

Dupilumab and matching placebo will be supplied in prefilled syringes that are visually indistinguishable.

The IMP is administered every 14±3 days (Q2W) during the 24-week treatment period.

Dupilumab 300 mg

- Formulation: a 150 mg/mL dupilumab solution in a prefilled glass syringe to deliver 300 mg in a 2 mL injection.
- Route of administration: SC injection.
- Dose regimen: Q2W after an initial loading dose of 600 mg (2 injections of 300 mg) on Day 1.

Matching Placebo

- Formulation: matching placebo will be supplied as an identical formulation to the active formulation without dupilumab, in a prefilled syringe to deliver placebo in a 2 mL injection.

- Route of administration: SC injection.
- Dose regimen: Q2W after an initial loading dose (2 injections) on Day 1.

In specific situations, between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to the on-site IMP dispensing, IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant.

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

Investigational medicinal product will be administered by the Investigator/health care professional or designee following clinical procedures and blood collection. Participants should be monitored for at least 30 minutes after administration of all IMP injections at site. The monitoring period may be extended as per country-specific or local site-specific requirements.

Subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive administrations. Injection in the upper arms can only be done by a trained person (caregiver) or health care professional but not by the participants themselves.

The Investigator or delegate will train the participant (or caregiver) how to prepare and inject IMP at Visit 2 and retrain if needed during the treatment period. The site staff will inject the first dose of the 2 injections at D1. The participant (or caregiver) will perform the second injection under the supervision of the Investigator or delegate. This training must be documented in the participant's study file. Participant or caregiver should be trained by the site staff to recognize potential signs and symptoms of hypersensitivity reaction and to self-monitor/monitor at home for at least 30 minutes (or longer per country specific or local site-specific requirements) following injection. In case of hypersensitivity symptoms, the participant should contact healthcare provider/emergency.

Participants should be instructed to avoid missing any dose of medication during the study. Any participant who misses one dose should be reminded to be diligent, in order to avoid further missing doses thereafter. In case of missed dose(s), no loading dose of 2 injections will be administered when restarting the treatment, whatever the number of missed doses. The participants should continue their scheduled IMP treatment and visits, even if more than 2 consecutive doses were missed.

Between the protocol-scheduled on-site visits, the investigational product (dupilumab or placebo) will be administrated at home by the participant himself/herself or by a caregiver or by a nurse or at the study site. A home dosing diary for collecting information related to at home injections will be provided. The home dosing diary will be kept as source data in the participant's study file.

Non-investigational medicinal product(s)

Participants should be on a stable dose of medium to high dose ICS in combination with a second controller medication (eg, LABA, LTRA, theophylline) ≥1 month prior to V1 and during the Screening Period (Table 3).

Participants requiring a third controller for their asthma will be considered eligible for this study, also at a stable dose ≥1 month prior to V1 and during the Screening Period.

- Formulation and route(s) of administration: refer to label.
- Dose regimen: As prescribed.

The asthma background therapy should be maintained on a stable dose during the study treatment period.

Short-acting β2 agonists (SABA) may be used as rescue medication during the study if needed. Systemic corticosteroids are allowed for the treatment of severe asthma exacerbations.

Table 3 - Low, medium and high daily doses of inhaled corticosteroids (mcg)

Inhaled corticosteroid	Low	Medium	High
Beclometasone dipropionate (CFC)	200-500	>500-1000	>1000
Beclometasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	>1000-2000	>2000

CFC= Chlorofluorocarbon propellant; DPI=Dry powder inhaler; HFA= Hydrofluoroalkane propellant

The GINA table above refers to metered doses. This is not a table of equivalence, but an estimated clinical comparability, based on available studies and product information. Categories of "low", "medium" and "high' doses are based on published information and available studies, including direct comparisons where available. Doses may be country-specific depending on labeling requirements. For new preparations, manufacturer's information should be reviewed carefully, products containing the same molecule may not be clinical equivalent (**1**). The list presents examples of ICS and might support future changes.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound must be managed according to the rules provided by the Sponsor in the Pharmacy manual.

The expiry date is mentioned on the IMP labels (when required by country regulation), and storage conditions are written on the IMP labels.

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).
4. Further guidance and information for the final disposition of used and unused study interventions are provided in a Pharmacy manual.

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 8.3.6).

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.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization

A randomized treatment kit number list will be generated centrally by Sanofi. The IMP (dupilumab or placebo) will be packaged in accordance with this list.

The Sanofi Clinical Supplies team will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system. This centralized treatment allocation system will generate the participant randomization list according to which it will allocate the treatments to the participants.

The Investigator obtains treatment kit numbers at randomization (V2) and subsequent scheduled visits via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) that will be available 24 hours a day.

Participants who meet the entry criteria will be randomized to receive either dupilumab or placebo. Participants will be randomized using a 2:1 randomization ratio for dupilumab 300 mg

Q2W and placebo Q2W. Randomization will be stratified by ICS dose level (medium and high-no less than 40% in 'high ICS' stratum) and region (Eastern Europe/ROW). In total, no more than 40% participants should be in "Eastern Europe" strata.

A randomized participant is defined as a participant who is registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file. A participant cannot be randomized more than once in the study.

Returned IMP from the participant's home should not be re-dispensed to the participants.

Blinding

Dupilumab and placebo will be provided in identically matched 2 mL prefilled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab/placebo) glass prefilled syringes will be prepared such that the treatments (dupilumab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Both the participant and Investigator will be blinded to assigned active drug or placebo. Study participants, investigators, and study site personnel will not have access to the randomization (treatment codes).

Randomization code breaking during the study

In case of an AE, the code must only be broken in circumstances when knowledge of the IMP is required for treating the participant.

Code breaking can be performed at any time by using the proper module of the IVRS/IWRS and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator must document the date, time of day, and reason for code breaking.

Participant withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the participant will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (ie, at the study level, as the Global Safety Officer is not site based), then the participant will not be withdrawn from treatment. Sponsor safety staff may unblind the intervention assignment for any participant with an SAE for the purpose of expedited regulatory reporting (see Section 8.3.2). Sponsor staff involved in the conduct of the study will remain blinded to the participant intervention assignment.

Participants who are withdrawn from treatment should be encouraged to remain in the study and the Investigator should discuss with them the key visits to attend (see Section 7.1.1).

6.4 STUDY INTERVENTION COMPLIANCE

Measures taken to ensure and document treatment compliance and IMP accountability include:

- Proper recording of treatment kit number as required on appropriate electronic case report form (e-CRF page for accounting purposes.
- All medication treatment kits (whether empty or unused) are returned by the participant at each visit when a treatment dispensing is planned:
  - The completed home dosing diary (returned to the site at each visit), returned treatment kit boxes and any unused prefilled syringes will be used for drug accountability purposes.
- The Investigator or designee tracks treatment accountability/compliance, either by home dosing diary, or by counting the number of used treatment kits and fills in the appropriate page of the participant treatment log.

The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the participant treatment log form.

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP received, dispensed, used, unused, and returned/destroyed. The product accountability and inventory form/system are to be updated each time IMP is dispensed.

All used, partially used, or unused treatments will be destroyed at each respective site, after accountability and reconciliation have been performed. The site must not destroy the unused IMP unless the Sponsor provides written authorization. Confirmation of destruction will be provided to the Sponsor.

6.5 CONCOMITANT THERAPY

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

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

Prohibited concomitant therapy:

- Any biologic therapy (including experimental treatments and dupilumab) or any other biologic therapy/immunosuppressant.
- Treatment with live (attenuated) vaccine.
- Treatment with systemic corticosteroids (systemic corticosteroids can only be used to treat an asthma exacerbation, and are not allowed to be used for other conditions)

During the FU period the asthma treatment will be administered based on Investigator's medical judgment and normal clinical practice.

6.6 RESCUE MEDICINE

The SABA rescue medications may be used. The rescue medication will be administered as prescribed by the physician. Systemic corticosteroids are allowed for the treatment of asthma exacerbations. Although the use of rescue medications is allowed at any time during the study, every attempt should be made to perform all necessary measurements prior to the use of rescue medications. If SABA rescue medications are given prior to any measurements, including HRCT, the measurements should be performed after a wash-out time mentioned in Table 4 (Section 8.1). In case of severe asthma exacerbations treated with systemic corticosteroids, the visits can be postponed up to 1 week to ensure the wash-out period (Table 4) is completed before performing HRCT scan, FeNO, FOT, and spirometry. In case this is not possible (eg, a participant experiences an exacerbation shortly before the scheduled visit), the procedures can be performed as planned, but it should be recorded that the participant had recently taken systemic corticosteroids. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.7 DOSE MODIFICATION

Not applicable.

6.8 INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Withdrawal of consent for treatment (ie, treatment discontinuation at participant request) should be distinguished from (additional) withdrawal of consent for follow-up visits. The site should document any case of withdrawal of consent.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive 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 remain in the study to be evaluated for safety and efficacy. See the schedule of activities (SoA) for data to be collected at the time of discontinuation of study intervention (Section 1.3).

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in the algorithm Increased in alanine aminotransferase (ALT) (Section 10.5) or if the Investigator believes that it is in best interest of the participant.

List of criteria for permanent discontinuation of study intervention

Every effort should be made to document the reason(s) for discontinuation of study intervention and this should be documented in the e-CRF.

Participants may be withdrawn from the study intervention 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.
- If the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level).
- Pregnancy.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Any opportunistic infection, such as tuberculosis or other infections whose nature or course may suggest an immunocompromised status.
- Serum ALT >3 upper limit of normal (ULN) and Total Bilirubin >2 ULN (see Section 10.5, Appendix 5).
- Serum ALT >5 ULN if baseline ALT ≤2 ULN or ALT >8 ULN if baseline ALT >2 ULN (see Section 10.5, Appendix 5). “Baseline” refers to ALT sampled at baseline visit or, if baseline value is unavailable, to the latest ALT value before the baseline visit.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of definitive discontinuation of the IMP for the concerned participant.

Handling of participants after permanent study intervention discontinuation:

Participants who prematurely discontinue the study intervention (prior to completing the 24-weeks treatment period) should attend an ETD visit at earliest convenience with all procedures required at the EOT visit, except HRCT and IMP. In particular cases when the ETD visit is closed to a regular study visit, ETD could be merged and will replace the regular visit. In addition, the participants will be asked and encouraged to complete all the remaining study visits according to the visit schedule until and including the EOT visit (V5). Participants will be followed-up according to the study procedures specified in this protocol in SoA (Section 1.3). Under exceptional circumstances when a participant cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs and concomitant medication should be collected.

All cases of permanent discontinuation of study intervention should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 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. For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

In addition, the following conditions will be causes for temporary discontinuation of study intervention:

- Infections or infestations that do not respond to medical treatment.
- Treatment with a live (attenuated) vaccine.
- Treatment with immunomodulating biologics (including experimental treatments).
- Treatment with systemic corticosteroids (except systemic corticosteroids used to treat an asthma exacerbation) or systemic immunosuppressive drugs.
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix 5 (Section 10.5).

7.1.2.1 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 event was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

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

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, compliance, or administrative reasons. This is expected to be uncommon.
- Participants who prematurely discontinue the study, should attend an Early Study Discontinuation (ESD) visit at the earliest convenience with all the procedures planned for the End of Treatment Visit (Visit 5) except IMP, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. If the Investigator considers that the time from the last HRCT scan exposure is not acceptable, the investigation will not be done.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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 adverse event (AE) information elicited must be documented.

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

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

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

7.3 LOST TO FOLLOW UP

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, 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 eosinophil count, reversibility test) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The lab tests will be done by the local laboratories, the maximum amount of blood collected from each participant over the duration of the study will be according to the routine clinical practice in each country and site. As the blood analysis will be performed by the local laboratories, any leftover blood sample will not be used for any other research purposes related to the study (re-analyses) or for future exploratory use (secondary use). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 EFFICACY ASSESSMENTS

Disease-specific efficacy measures

Spirometry

A spirometer that meets the American Thoracic Society(ATS)/European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with these recommendations (36).

For pre-bronchodilator measured parameters, including FEV_1 and FVC spirometry will be performed after withholding the standard of care asthma treatment as follows:

Table 4 - Wash out period of asthma controllers and rescue medication before HRCT scan and lung function assessments

Oral Xanthine derivatives	72 hours
Long-acting beta agonists (LABA) (eg, salmeterol)	24 hours
Long-acting muscarinic antagonist(LAMA) (eg, Tiotropium)	48 hours
Inhaled ICS	12 hours
Inhaled ICS/LABA	24 hours
Inhaled Ultralong ICS/LABA combinations	48 hours

Inhaled and/or nebulized SABAs (eg, salbutamol)	6 hours
Inhaled and/or nebulized SAMAs (eg, ipratropium)	8 hours
SABA/SAMA combination	8 hours
Inhaled and/or nebulized corticosteroid (ICS)	12 hours
Long-acting beta agonists (LABA)	24 hours
Long-acting muscarinic antagonist (LAMA)	48 hours
Inhaled ICS/LABA	24 hours
Systemic corticosteroids (oral, IM, IV)	4 weeks

This will be verified before performing the measurements.

In case of asthma exacerbations treated with systemic corticosteroids, the visits can be postponed up to 1 week to ensure the wash-out period before performing HRCT scan, FeNO, FOT and spirometry. In case this is not possible (eg, a participant experiences an exacerbation shortly before the scheduled visit), the procedures can be performed as planned, but it should be recorded that the participant had recently taken systemic corticosteroids.

For post-bronchodilator FEV_1, the measurement should follow the steps as that at screening test for reversibility validation.

At all visits, spirometry should be performed before IMP administration, in the morning, if possible. 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; afternoon/evening is allowable in the exceptional circumstance when morning spirometry cannot be performed; spirometry should be done at approximately the same time at each visit throughout the study.

Pulmonary function tests will be measured in the sitting position; however, if necessary to undertake the testing with the subject standing or in another position, this should be noted on the spirometry report. For any subject, the position should be consistent throughout the study.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. At least 2 acceptable curves must be obtained.

The largest FEV_1 and largest FVC should be recorded after the data are examined from all of the acceptable curves, even if they do not come from the same curve.

The spirometer must be calibrated following the principles of the ATS/ERS guidelines every day that a study subject is seen, and spirometry is carried out. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (ie, 3-liter syringe) that is used to calibrate the spirometer be subjected to a validated calibration according to the manufacturer's specifications. A participant who is unable to complete a successful spirometry effort as defined by ATS criteria or evaluated by the investigator or did not meet the eligibility criterion for pre-BD FEV_1 at V1 can be retested one additional time during the screening period of the study. The

spirometry will be centrally read. The locally read values of FEV_1 will be considered for the participant qualification into the study at V1 and V2. For the statistical analysis we will use centrally read values. Further details on the procedure will be provided in a separate instructions manual.

Reversibility

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Subjects will receive 2 to up to 4 puffs of albuterol/salbutamol from a primed metered dose inhaler (MDI). Alternatively, and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. Reversibility, which is defined as an increase in absolute FEV_1 of 12% over the baseline value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of bronchodilator administration. If the participant does not meet the eligibility criterion for reversibility at V1, up to 3 attempts may be performed during the screening period. This is only required if a reversibility test meeting eligibility criterion was not performed within 6 months prior to V1.

Asthma Control Questionnaire 7-question version

The ACQ-7 is comprised of 7 items: the first 5 items assess the most common asthma symptoms: 1. frequency in past week awoken by asthma during the night; 2. severity of asthma symptoms in the morning; 3. limitation of daily activities due to asthma; 4. shortness of breath due to asthma; and 5. wheeze; plus question 6. short-acting bronchodilator use; and 7. FEV_1 (% predicted). Participants are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6=maximum impairment).

Clinic staff score for FEV_1% is predicted on a 7-point scale. The details are given in Table 5.

Table 5 - Clinic staff score for FEV_1%

FEV_1% predicted	Score
>95% predicted	0
95%-90%	1
89%-80%	2
79%-70%	3
69%-60%	4
59%-50%	5
<50%	6

Abbreviation: FEV_1 = forced expiratory volume in 1 second

A global score is calculated: the questions are equally weighted and the ACQ-7 score is the mean of the 7 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Participants with a score below 1.0 reflect adequately controlled asthma and participants with scores above 1.0 reflect inadequately

controlled asthma. On the 7-point scale of the ACQ-7, 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.

The participants will complete the ACQ-7 on paper.

Asthma Control Questionnaire items 1 to 6 should be completed by the participant, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The questionnaire should be completed by the participants before the consultation and clinical tests, including spirometry, in a quiet place.

The ACQ-5 (Mean of the responses to the first 5 questions) and ACQ-6 (Mean of the responses to the first 6 questions) will be derived from ACQ-7. For the ACQ-7 scores will be considered the local values of FEV_1 For the statistical analysis we will use the centrally read values.

Asthma Quality of Life Questionnaire with Standardized Activities (Self-Administered)

Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) was designed as a self-administered patient-reported outcome to measure the functional impairments that are most troublesome to adolescents ≥12 years of age and adults as a result of their asthma. 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 (12 items).
- Activity limitation (11 items).
- Emotional function (5 items).
- Environmental Stimuli (4 items).

Individual items are equally weighted. The overall score is the mean of response to each of the 32 questions (ranging from 1 to 7). 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 (participant interviews), and sensitive to change. The MCID for AQLQ(S) is 0.5 (37).

The participants will complete the AQLQ(S) on paper.

Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) should be completed by the participant, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The questionnaire should be completed by the participants before the consultation and clinical tests, including spirometry, in a quiet place.

Forced Oscillometry

Asthma is an inflammatory airway disease affecting the entire bronchial tree, including the small airways, defined as those with an internal diameter of 2 mm or less. Multiple lines of evidence suggest that, within subjects with asthma, the small airways are dysfunctional (38), inflamed (39), and damaged (40), therefore playing an important role in asthma. Forced oscillation technique (FOT) R5 - R20 is a direct measure of anatomical narrowing in the small airways (41). The FOT

determines breathing mechanics by superimposing small external pressure signals on the spontaneous breathing of the subject. It is indicated as a diagnostic method to obtain reliable differentiated tidal breathing analysis. As FOT is performed without closure of a valve connected to the mouthpiece, and without maximal or forced respiratory maneuvers, it is unlikely that FOT itself will alter airways smooth muscle tone.

Forced oscillation technique utilizes the external applied pressure signals and their resultant flows to determine lung mechanical parameters. These pressure-flow relationships are largely distinct from the natural pattern of individual respiratory flows, so that measured FOT results are, for the most part, independent of the underlying respiratory pattern. Therefore, oscillometry minimizes demands on the participant and requires only passive cooperation of the subject: maintenance of an airtight seal of the lips around a mouthpiece and breathing normally through the measuring system with a nose-clip occluding the nares. FOT should be conducted prior to spirometry. The assessment will be done by central reading. Further details on the procedure will be provided in a separate instruction manual.

Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide will be analyzed using a NIOX instrument using a flow rate of 50 mL/s and reported in ppb. This assessment should be conducted prior to spirometry and the participant should refrain from eating and drinking for at least 1 hour prior to the procedure. The test will be performed after a wash out period of bronchodilators according to their action duration as detailed in Table 4 (Section 8.1). Retesting of FeNO can be done one additional time during screening if the eligibility criterion for FeNO was not met at V1. FeNO will be re-checked at randomization visit (V2) for eligibility. Further details on the procedure for measuring exhaled nitric oxide with NIOX will be provided in a separate instruction manual. FeNO assessment will be performed by local reading. The recommendation is to perform the investigations in the following order: FeNO, FOT, spirometry.

Functional Respiratory Imaging

Functional Respiratory Imaging is a non-invasive measurement of the participant specific respiratory system. A set of distinct imaging parameters analyzes exposure, structure and function of the lungs and airways in asthma.

The process starts with the acquisition of low dose, pre-bronchodilator HRCT scans of the participant.

The measurements are performed on the segmented 3-dimensional geometries from these scans. Computational fluid dynamics (CFD) is used to quantify airflow and exposure.

Airway Volume ([s]iVaw)

(s)iVaw is the change of volume of the airways (in mL), taking into account the lung volume changes (in L) as well.

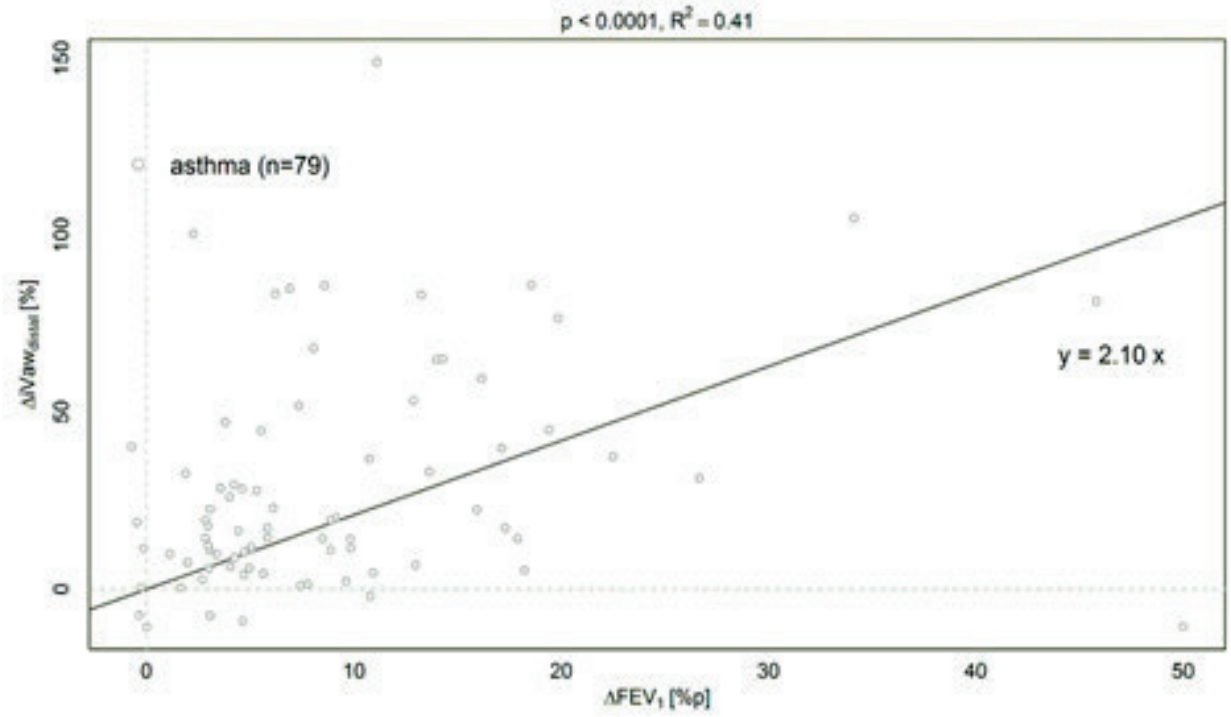
With anti-inflammatory compounds, often the lung volumes reduce (they become less inflamed), while the airway volumes increase, since lower volume increase airway resistance showing a better picture of the true dynamics of the airways versus the lung volumes.

The anti-inflammatory effect of dupilumab can be described in terms of changes in airway caliber such as airway volumes ([s]iVaw).

Airway caliber changes are more sensitive compared to FEV_1 hence can provide additional insights into potential remodeling and additional improvements not described by FEV_1 (eg, between Weeks 4 and 24).

A study to evaluate the use of FI to visualize and quantify airways involvement in asthma and COPD evaluated the correlation between FEV_1 and FRI-based airway volumes, showing that a 10% change in FEV_1 corresponds to a change of 21% in airway volumes (Figure 2) *(Lanclus et al. Respiration in revision)*, indicating that FRI is a more sensitive tool to detect therapeutic effects compared to FEV_1.

Figure 2 - Correlation between FEV_1 and FRI-based airway volumes



Airway Resistance ([s]iRaw)

(s)iRaw is defined as the pressure drop over the flow rate of the fluid. The unit is [kPa/(L/s)]) or [kPa*s/L].

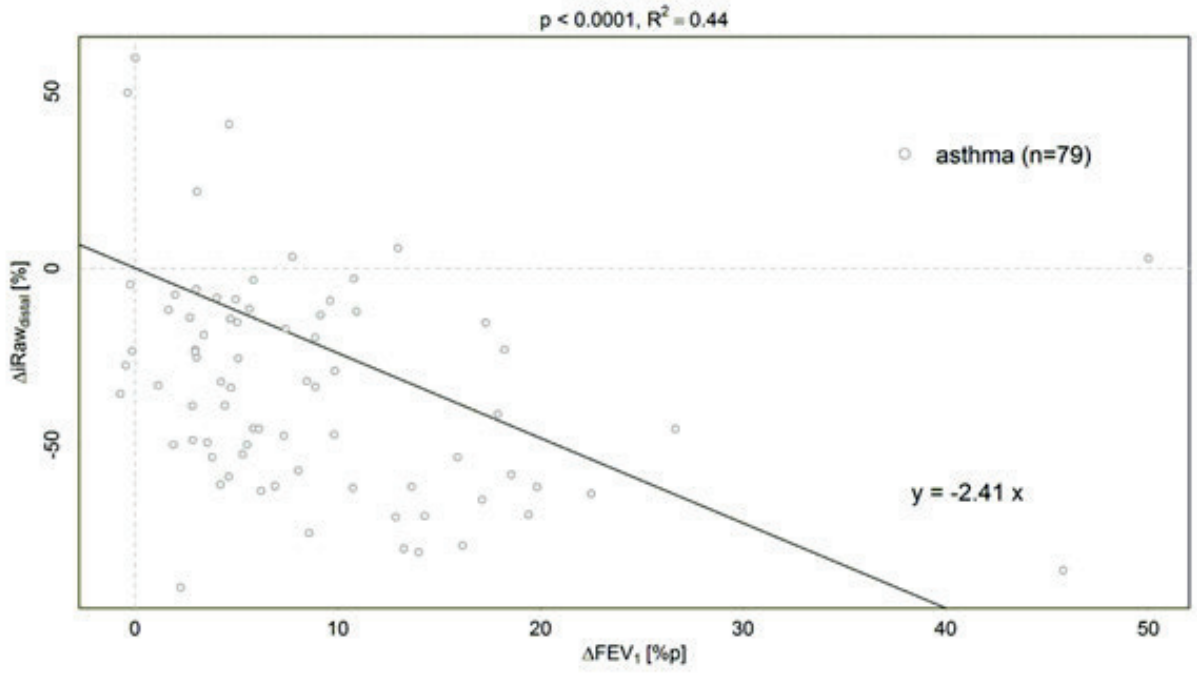
Asthmatic lungs have higher regional resistances due to presence of mucus or airway inflammation.

When the pressure drop over the airways stays the same (force exerted to inhale stays equal) but the airways become smaller (because of eg, obstructions or inflammation), the flow rate will become smaller (there will be less liters of air flowing through these smaller airways in 1 second than when airways are bigger), leading to a higher resistance.

If the lung wants to compensate the higher resistance encountered in the lung, it will need to exert a higher pressure drop. Specific image-based resistance (siRaw) is similar to the image-based resistance (iRaw), but it takes the changes of the lung volume into account.

A study to evaluate the use of functional imaging to visualize and quantify airway involvement in asthma and COPD evaluated the correlation between FEV_1 and FRI-based airway volumes. Evaluated the correlation between FEV_1 and FRI-based airway resistance, in which a 10% change in FEV_1 corresponded to a change of 25% in airway resistance (Figure 3) *(Lanclus et al. Respiration in revision).*

Figure 3 - Correlation between FEV_1 and FRI-based airway resistance



Mucus score

University of California, San Francisco (UCSF researchers (John Fahy's research group) have developed a new method to measure the burden of intraluminal mucus using Multi-detector Computed Tomography (MDCT) by quantifying the number of bronchopulmonary segments that are completely occluded with mucus. This technology has been validated in participants with asthma using CT scans with normal dose radiation protocols (39).

A high mucus score (plugs in ≥4 segments) occurred in 67% of subjects with asthma with FEV_1 of less than 60% of predicted volume, 19% with FEV_1 of 60% to 80%, and 6% with FEV_1 greater than 80% ($P< 0.001$). N=146, among those 96 were severe asthma participants (65%) (39).

Functional Respiratory Imaging can accurately assess the regional airway closures induces by mucus plugs and the re-opening of airways due to intrapulmonary percussive ventilation in COPD participants (40).

Airway wall thickness

Asthmatics have increased airway wall volumes due to inflammation compared to healthy individuals.

The airway wall volume/airway lumen ratio parameter can be derived from the FRI parameters airway wall volume and airway volume. Airway wall thickness can be derived from this as well (and can be shown in discreet locations).

After a treatment with ICS in asthma an increase in airway lumen volume (iVaw) and a reduction in airway wall volume (iVaww) can be observed. The effect size of iVaw is larger than effect size iVaww due to the better resolution of iVaw in HRCT. Similar findings were observed by Haldar et al when studying Mepolizumab (41).

Lobar volumes

By identifying and grouping the voxels that represent the air in the lungs, the lung volume (L) can be determined from the scans at both FRC and TLC. During segmentation, identifying the fissure planes on the CT images and using these surfaces as cutting objects can separate lung lobes. Therefore, not only the total lung volume is determined, but also the volume of each lobe individually, which allows to pick up substantial regional physiological changes of the airways and the lobe volumes.

The HRCT scans assessment will be performed by central reading. Further details on the procedure will be provided in a separate instructions manual. The wash out period of asthma controllers and rescue medication before HRCT scan is detailed in the Table 4 (Section 8.1).

If HRCT scan cannot be performed at D1 due to logistic reasons, it can be scheduled the next day. In this particular situation the investigator should ensure that the IMP loading dose is administered after the HRCT scan, at D1+1 day.

At visits, the HRCT scan can be done before spirometry or before post-BD FEV1 or after spirometry (in the latter case the wash-out period of SABA should be ensured), as per Investigator's decision.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded. Height (cm) will be measured only at the screening visit (V1).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- Temperature (degrees Celsius), heart rate (beats per minute), respiratory rate (breaths per minute), and blood pressure (mmHg) will be assessed.
- Blood pressure and pulse measurements will be assessed in semi-supine or sitting position using the same arm at each visit with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse will be measured prior to receiving investigational product at the clinic visits.
- 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).
- Refer to Section 1.3 for the schedule of vital signs performed throughout this study.

8.2.3 Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes meeting the AE definition (Section 10.3) occurring during the study in the AE section of the e-CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, 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 or medical monitor.
  - 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 assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3).
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the e-CRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described in Section 8.3.4, even if not fulfilling a seriousness criterion, using the screens in the e-CRF.

- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms).
- Anaphylactic reactions.
- Systemic hypersensitivity reactions.
- Helminthic infections.
- Keratitis
- Any severe type of conjunctivitis or blepharitis
- Significant ALT elevation:
  - ALT >5 x ULN in participants with baseline ALT ≤2 x ULN;
    or
  - ALT >8 x ULN if baseline ALT >2 x ULN.
    "Baseline" refers to ALT sampled at baseline visit or, if baseline value is unavailable, to the latest ALT value before the baseline visit
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject 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,
  - 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.
  - Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Symptomatic overdose (serious or nonserious) with IMP/NIMP.
- An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.

An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined according to the drug label. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse event will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the IMP (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3).

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

Investigators are not obligated to actively seek AE or SAE 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

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

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and nonserious AESIs (as defined in Section 8.3) 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 given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the outcome has been determined.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- 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. While the Investigator is not obligated to actively seek this information in former study participants /pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention.

8.3.6 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 TREATMENT OF OVERDOSE

For this study, the overdose of dupilumab is defined as at least twice the intended dose during an interval of less than 11 days.

Symptomatic overdose (serious or nonserious) is an AESI (defined in Section 8.3). No antidote is available for dupilumab.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until dupilumab can no longer be detected systemically.
3. Obtain a plasma sample for pharmacokinetic analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document appropriately in the e-CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

Pharmacokinetic parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamic variables/biomarkers:

- Fractional exhaled nitric oxide (FeNO) levels.

  Fractional exhaled nitric oxide should be conducted prior to spirometry and following a fast of ≥1 hour. Further details on the procedure for measuring FeNO will be provided in a separate instruction manual. Fractional exhaled nitric oxide levels will be measured at the time points mentioned in the SoA (Section 1.3).

8.7 GENETICS

Pharmacogenetic/pharmacogenomic testing is not performed in this study.

8.8 BIOMARKERS

- Whole blood biomarkers: blood eosinophil count.

  Eosinophil counts will be measured at the time points requested mentioned in the SoA (Section 1.3).

8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization and health economics data are not collected in this study.

8.10 USE OF DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data 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.

For participants who consent to the storage and use of their data, data may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions.

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

All study participant data will be coded such that no participant direct identifiers will be linked to them. Coded data 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).

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws.

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

For comparison of dupilumab treatment group to placebo, the following hypotheses of the 2 primary endpoints will be tested.

1. Null hypothesis: 1) the proportion of participants achieving response of FeNo <25 ppb at Week 24 is the same between dupilumab and placebo group; 2) the percentage change from baseline in untrimmed distal [s]iVaw is the same between dupilumab and placebo group.
2. Alternative hypothesis: 1) the proportion of participants achieving response of FeNo <25 ppb at Week 24 is different between dupilumab and placebo group; 2) the percentage change from baseline in untrimmed distal [s]iVaw is different between dupilumab and placebo group.

9.2 SAMPLE SIZE DETERMINATION AND PRESERVATION OF TYPE I ERROR FOR THE PRIMARY ENDPOINTS

To control the type-I error rate for the 2 primary endpoints, a hierarchical testing procedure will be applied at a 2-sided 5% significance level, ie, each hypothesis will be formally tested only if the preceding one is significant at 5% level. The hierarchy of the tests for primary endpoints will be:

1. Proportion of participants achieving response of FeNO <25 ppb at Week 24
2. Percentage change from baseline to Week 24 in untrimmed distal [s]iVaw at TLC

[redacted]

Assumptions for the [s]iVaw parameter were based on extrapolating the limited available data in asthma looking at associations between FEV_1 and lung imaging parameters. Clinically meaningful differences for the imaging parameters have not yet been established. However, expert opinion and literature suggest that they are more sensitive than the lung function parameters, such as pre-BD FEV_1 mentioned above. [redacted]

By replacing FEV_1 change from baseline at Week 24 with proportion of participants achieving response of FeNO <25 ppb at Week 24 as one of the primary endpoints, [redacted]

[redacted]

With the original assumptions for [s]iVaw, 87 evaluable participants will provide approximately 64% power with two-sample t-test at 2-sided 0.05 significance level.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 6):

Table 6 - Populations for analyses

Population	Description
Screened	All participants who sign the informed consent form
Randomized	Randomized participants consist of all participants with a treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered as randomized and will not be included in any efficacy population. Data from these participants will be summarized separately.
Intent-to-treat (ITT)	The analysis population for the efficacy endpoints will be the intent-to-treat population: all randomized participants will be included in the ITT population, and analyzed according to the treatment group allocated by randomization.
Safety	The safety population will include all randomized participants who received at least 1 injection of IMP. For safety analyses, participants will be analyzed according to the treatment actually received.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the Intent-to-treat (ITT) population, unless otherwise noted.

Note that at each scan, images will be taken from each zone of the lung, thus there will be multiple observations per visit for each imaging parameter. Data may be logarithmically transformed prior to analysis if extreme skewness was observed based on blinded data review.

Table 7 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary	
• Proportion of participants achieving FeNO <25 ppb at Week 24	• The primary analysis will be conducted by Cochran-Mantel-Haenszel (CMH) test adjusted by stratification factors. Comparison of the proportions of responders between dupilumab and placebo will be derived, and corresponding odds ratios and 95% CI along with the p-value will be reported. For participants who discontinued the study treatment not due to COVD-19 pandemic, off-treatment data will be used to determine the responder/non-responder status. For any participants discontinue the study treatment due to COVID-19 pandemic, off-treatment data will be set to missing. Missing data at Week 24 will be considered as non-responders.
• Percent change from baseline to Week 24 in untrimmed distal airway volumes corrected for lung volume ((s)iVaw) at total lung capacity (TLC)	• Percent change from baseline to Week 24 in distal [s]iVaw at TLC will be analyzed using a mixed model repeated measures model (MMRM). The model will include percent change from baseline values up to Week 24 as the response variable, and factors for treatment group, region (Eastern Europe/ROW), ICS dose level (medium/high), visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction. An unstructured covariance matrix will be used to model the within participant errors. No imputations for missing values will be carried out. The least square (LS) mean of each treatment group, the LS mean difference between the dupilumab group and placebo, and the corresponding 95% CI of the differences and p-values will be provided. For participants who discontinued the study treatment not due to COVID-19 pandemic, off-treatment imaging data, as available, will be included in the analysis. For any participants who discontinued study treatment due to COVID-19, off-treatment data will be set to missing. Note: baseline value corresponds to the baseline value of the variable being analyzed. In case of variables in the percentage scale, this will be the baseline value on the raw scale.
Secondary	
• Percent change from baseline to Week 24 in untrimmed distal airway volumes corrected for lung volume ((s)iVaw) at functional residual capacity (FRC)	• Same as the primary imaging parameter.
• Percent change from baseline to Week 24 in trimmed distal airway resistance corrected for lung volume ((s)iRaw) at TLC	• Same as above
• Percent change from baseline to Week 24 in trimmed distal airway resistance corrected for lung volume ((s)iRaw) at FRC	• Same as above
• Change from baseline to Week 24 in global lung lobar volumes (iVlobes) at TLC	• Same as above.

Endpoint	Statistical Analysis Methods
• Change from baseline to Week 24 in HRCT-based internal airflow distribution (IAD) for each lung zone	• Same as above.
• Change from baseline to Week 24 in image-based ventilation/perfusion (iV/Q) at TLC for each lung zone	• Same as above.
• Change from baseline to Week 24 in FeNO	• Same as above.
• Change from baseline to Week 24 in pre-bronchodilator FEV_1	• Same as above.
• Change from baseline to Week 24 in post-bronchodilator FEV_1	• Same as above.
• Change from baseline to Week 24 in ACQ-7	• Same as above.
• Change from baseline to Week 24 in global lung mucus scoring (UCSF mucus scoring)	• Same as above.
Exploratory	• Will be described in the statistical analysis plan finalized before database lock. These will include investigating the relationship between key lung function parameters, imaging parameters and biomarker levels.

9.4.2 Safety analyses

All safety analyses will be performed on the safety population and will be presented by treatment group.

The treatment-emergent is defined as the period of time from the date and time of the first dose of IMP through the date of last dose + 12 weeks (or the day before switch to commercialized dupilumab or other biologic treatment, whichever occurs first).

Table 8 - Safety analyses

Endpoint	Statistical Analysis Methods
Secondary	
• Incidence of TEAEs, TESAEs, TEAE leading to study intervention discontinuation and AESI	• Adverse event incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT), the number (n) and percentage (%) of participants experiencing an AE. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages is the safety population within each treatment group. • Proportion of participants with at least one TEAE, serious TEAE, AESI, and TEAE leading to discontinuation of the study intervention will be tabulated by treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the study drug. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

Multiplicity Considerations for the secondary endpoints

A multiplicity control procedure and the selected list of secondary endpoints to be tested in the hierarchical order will be specified in the Statistical Analysis Plan. Regardless of eligibility to be declared significant, results for all comparisons will be presented. Descriptive statistics including number of participants, mean, standard deviation, and LS means will also be provided.

9.4.3 Other analyses

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9). The sensitivity analysis may be conducted, and details will be specified in the Statistical Analysis Plan.

9.5 INTERIM ANALYSES

Not applicable.

9.5.1 Data Monitoring Committee (DMC)

A DMC is not planned for this study.

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, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (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 to the participant or his/her legally authorized representative and answer all questions regarding the study including what happens to the participant when his/her participation ends (posttrial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In 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 the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- The ICF contains 2 separate sections that addresses the use for research of participants' data. 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 are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study be /because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- 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

Study committees: Not applicable

10.1.6 Dissemination of clinical study data and results

Study participants

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

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months, respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

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

Individual 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 e-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 e-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.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the e-CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- 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 entered in the e-CRF 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: Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory reports, notes, memoranda, pharmacy dispensing records, recorded data from automated instruments etc. Data downloaded from the laboratories, spirometry, FeNO measurement, ECG, forced oscillometry, HRCT scans, home dosing diary and asthma background therapy diary, paper questionnaires (ACQ-7, AQLQ[S]) will be considered source data.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site 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 participant screened and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include 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 should 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 investigators 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 9 will be performed by the local laboratories.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing as mentioned in the SoA (Section 1.3).

Table 9 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Eosinophil count
Other screening tests	Highly sensitive (Serum at screening and urine at the other visits) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).
	Hepatitis screening covering hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (total HBcAb) including IgM HBcAb; hepatitis C virus antibodies (HCVAb). In case of results showing HBs Ag (negative), and HBcAb (positive), an HBV DNA testing will be performed to rule out a false positivity if the Investigator believes the participant is a false positive, or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCVAb (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the participant is a false positive.

Laboratory assessments	Parameters
	Human Immunodeficiency Virus (HIV) screening (Anti-HIV-1 and HIV-2 antibodies).
	Tuberculosis testing would only be performed on a country by country basis according to the routine clinical practice and the local guidelines if required by Regulatory Authorities or Ethics Committees.
	The results of each test must be entered into the e-CRF

NOTES :
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 5 (Section 10.5). Although the liver function tests are not requested in the protocol, the routinely done lab tests might identify increased values of ALT, bilirubin. All events related to ALT, bilirubin which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE definition

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

Events meeting the AE definition

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

Events NOT meeting the AE definition

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

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

a) Results in death.

b) Is life-threatening:

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

c) Requires inpatient hospitalization or prolongation of existing hospitalization:

In general, hospitalization signifies that the participant has been detained (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 disability/incapacity

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

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 in the e-CRF.
- 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 AE/SAE e-CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representatives. 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 representatives.
- 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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representatives. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representatives.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a 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 representatives 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's representatives with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed e-CRF.
- The Investigator will submit any updated SAE data to the Sponsor's representatives within 24 hours of receipt of the information.

REPORTING OF SAEs

Serious adverse event reporting to the Sponsor's representatives via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representatives 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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representatives by telephone.
- Contacts for SAE reporting can be found in the CTP.

Serious adverse event reporting to the Sponsor's representatives via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor's representatives.
- 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 CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the CTP.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal 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 level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

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

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

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 follicle-stimulating hormone level in the postmenopausal range [may/should/must] 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.

CONTRACEPTION GUIDANCE

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

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • 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 - oral - intravaginal - transdermal - injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation - 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.

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).

PREGNANCY TESTING:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional urine pregnancy testing should be performed at each visit during the intervention period. In case of positive urinary test during the study, a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. A urine pregnancy test will be performed at home at the end of study visit.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of ≥5 mIU/mL will be performed

COLLECTION OF PREGNANCY INFORMATION:

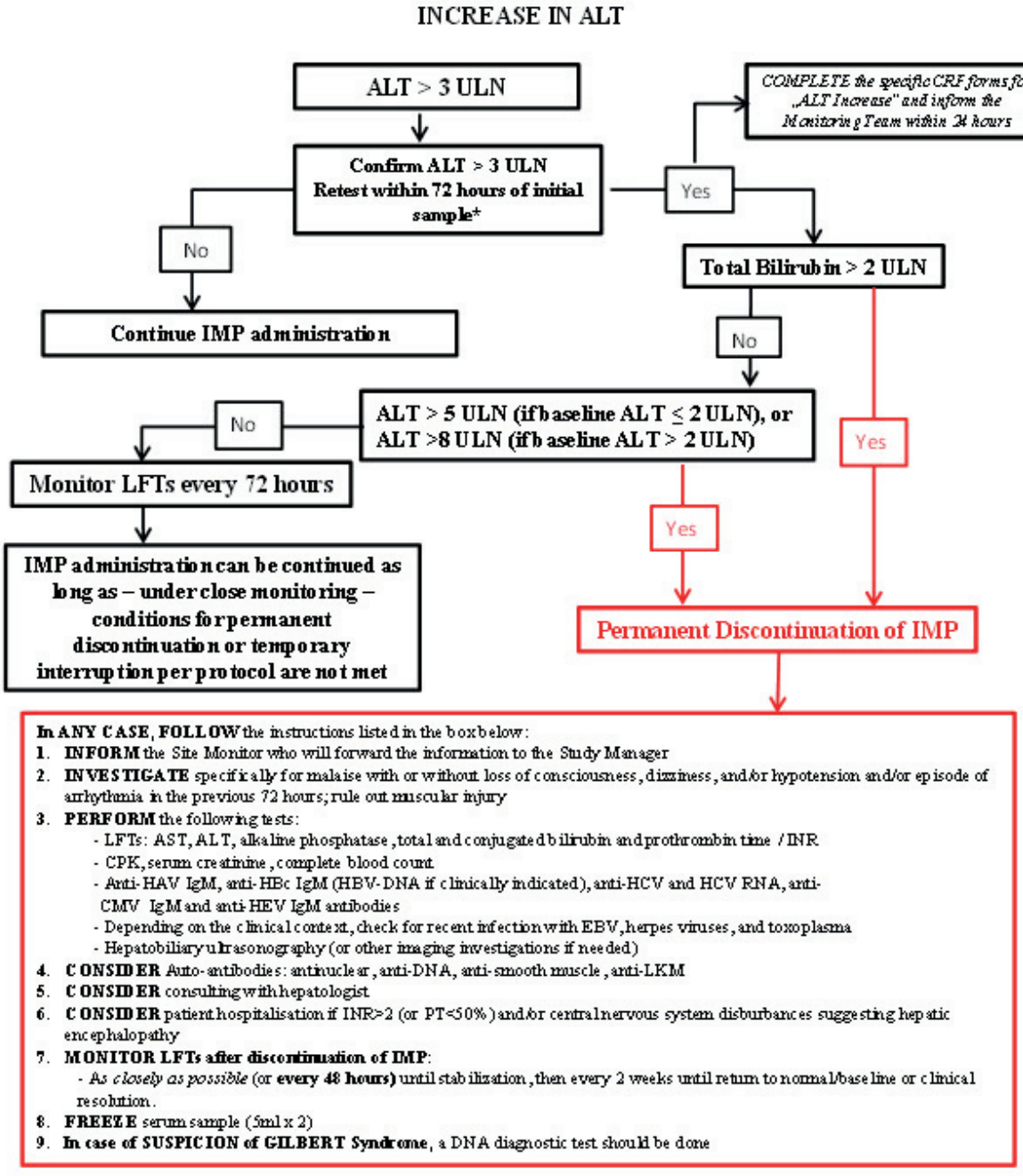
Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

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

10.5 APPENDIX 5: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS



Although the liver function tests are not requested in the protocol, the routinely done lab tests might identify increased values of ALT, bilirubin.
*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note:
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Section 8.3.1 for guidance on safety reporting.
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

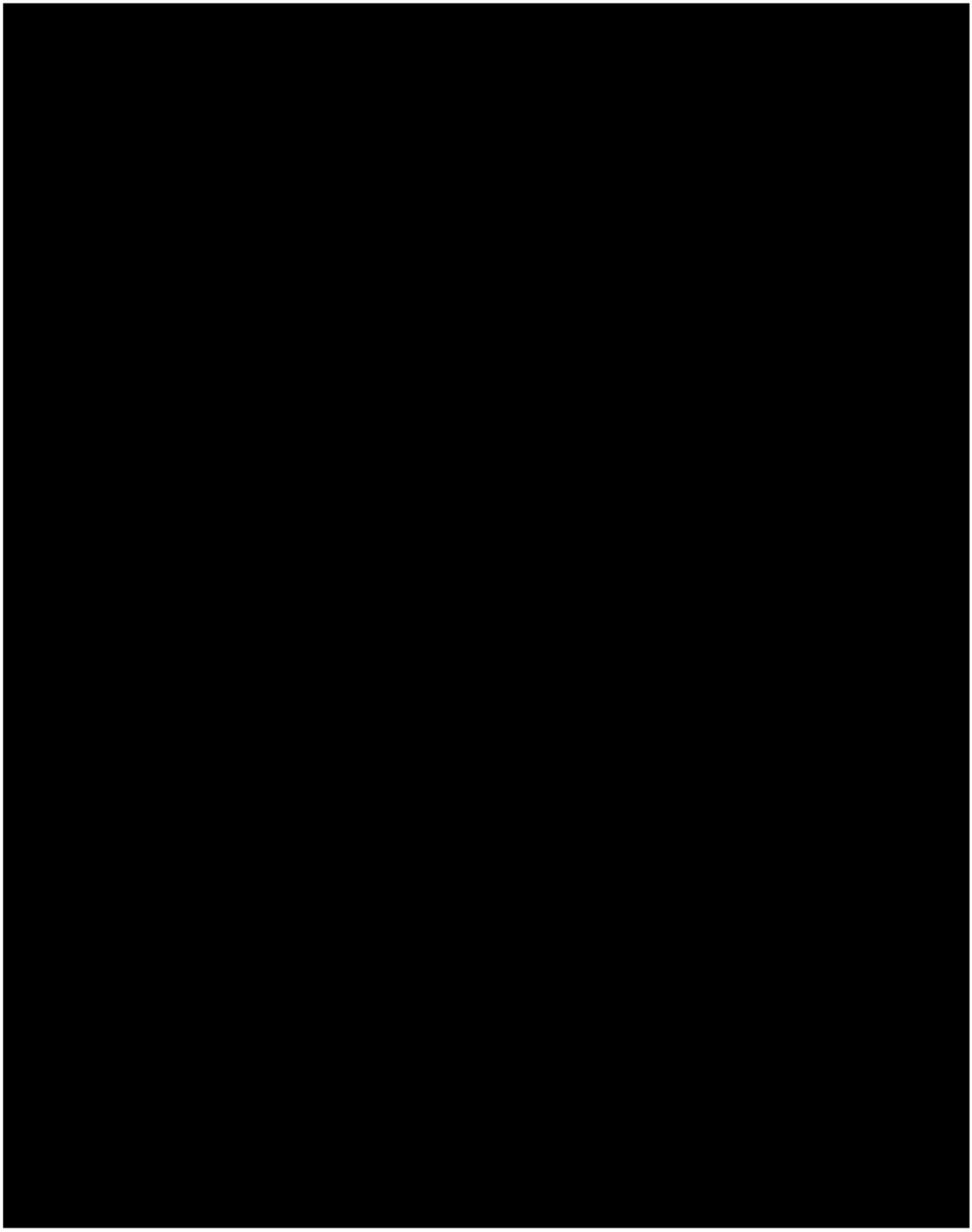
10.6 APPENDIX 6: LIST OF PROHIBITED LIVE ATTENTUATED VACCINES

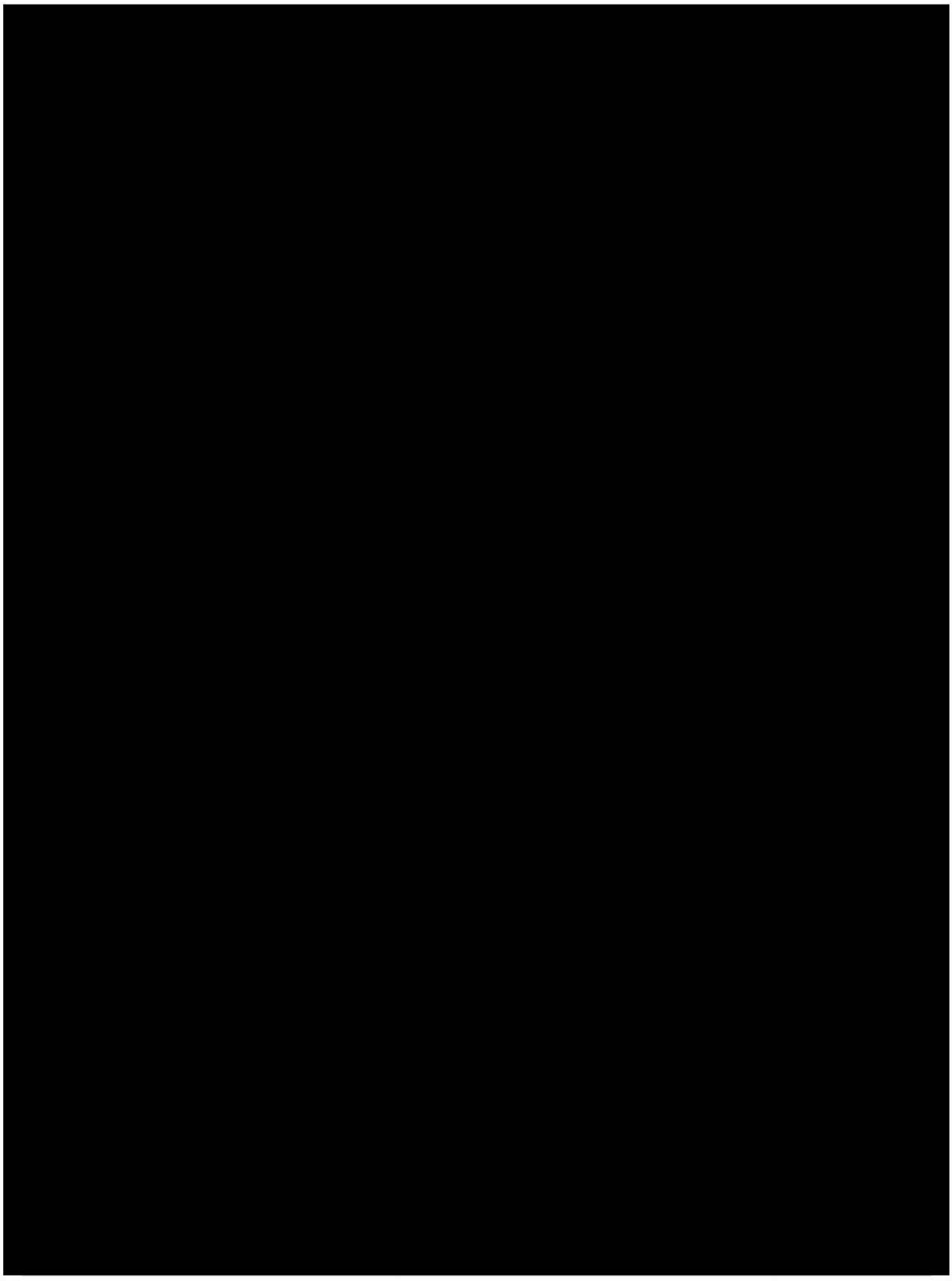
- Bacillus Calmette-Guérin (BCG) antituberculosis vaccine.
- Chickenpox (Varicella).
- Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted.
- Measles (Rubeola).
- Measles-mumps-rubella (MMR) combination.
- Measles-mumps-rubella-varicella (MMRV) combination.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

10.7 APPENDIX 7: 7-ITEM ASTHMA CONTROL QUESTIONNAIRE (ACQ-7) AND ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ[S])

DECEMBER 2002

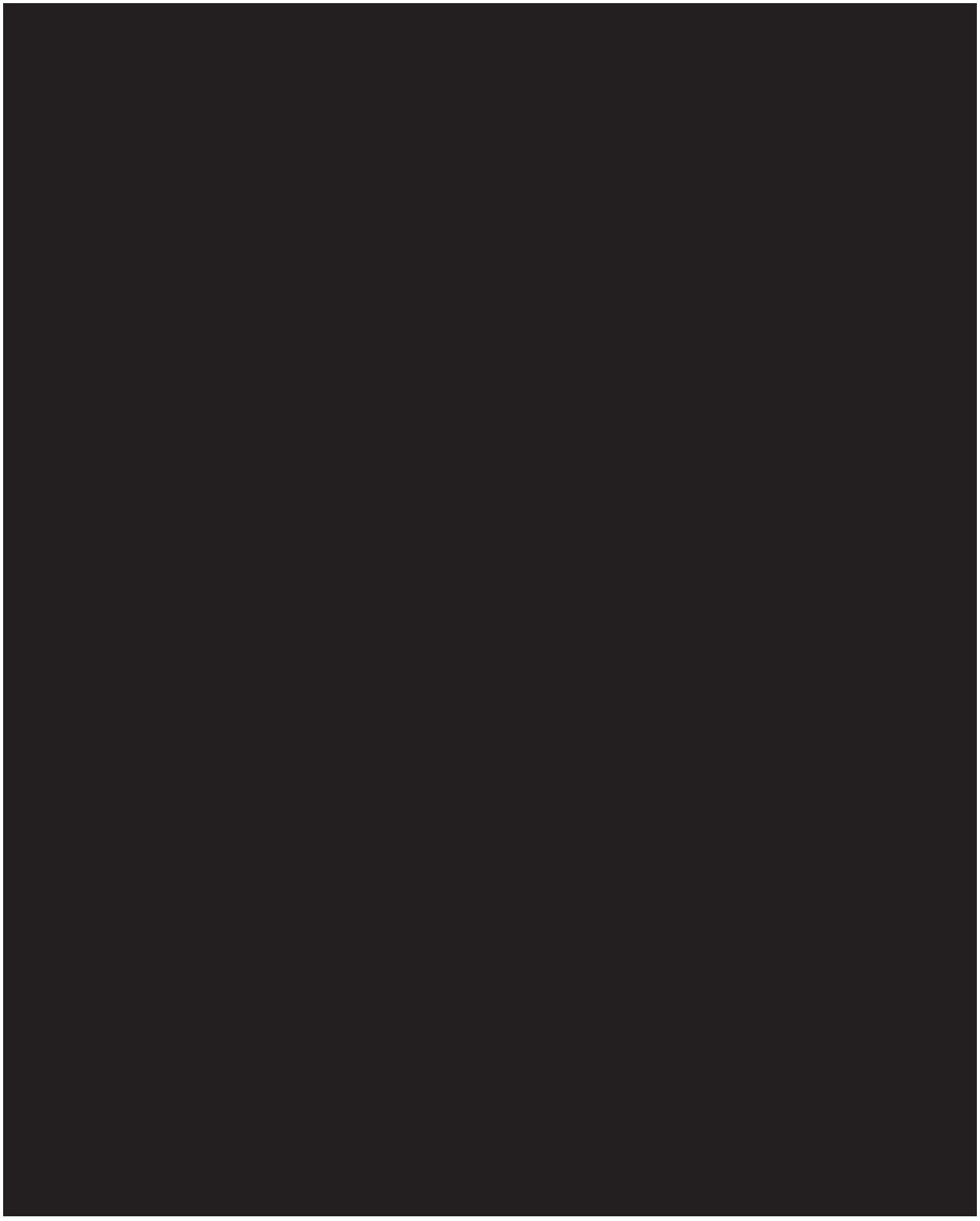
Revised September 2010
ACQ-SA North American English Version

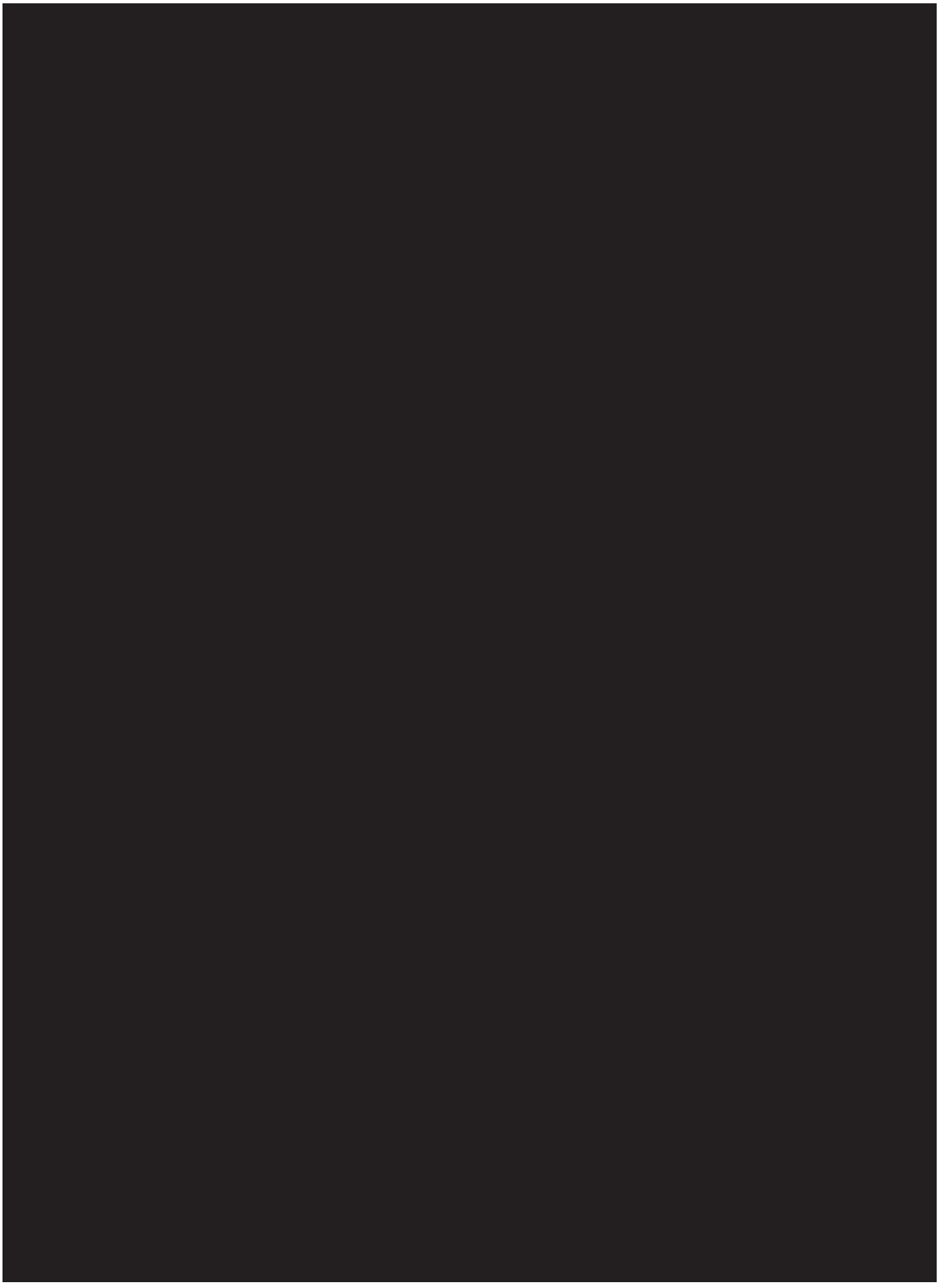


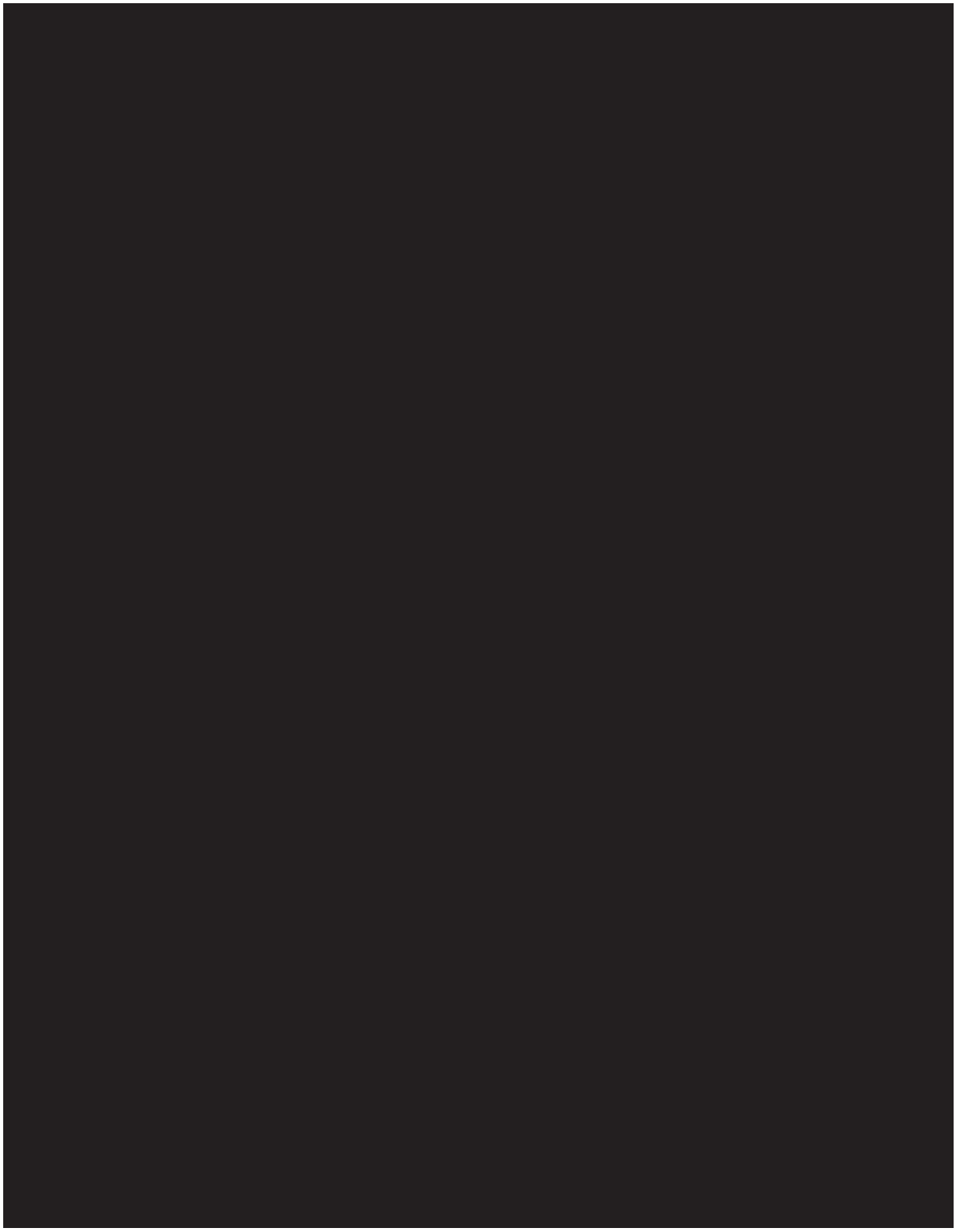


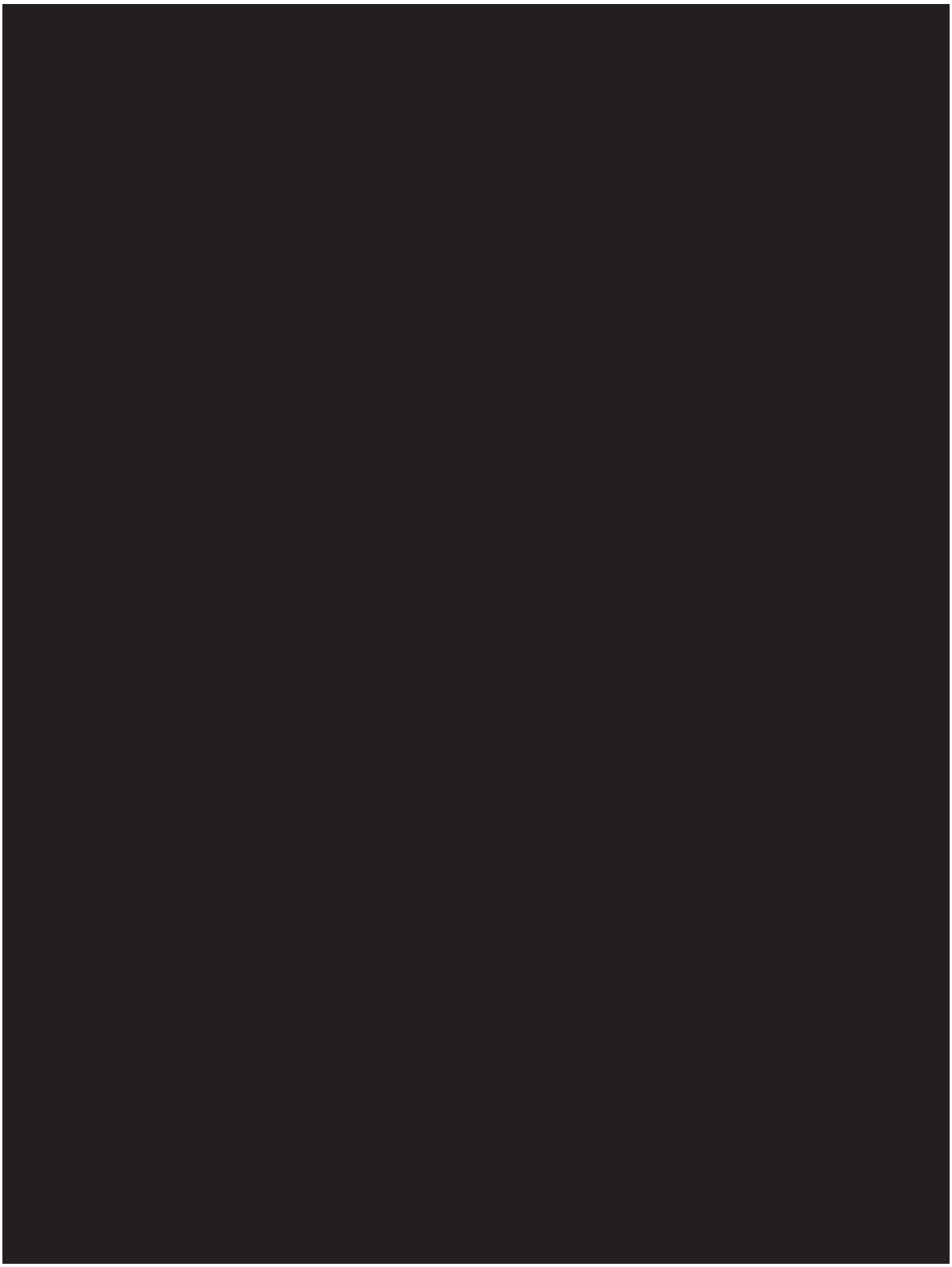
APRIL 2008

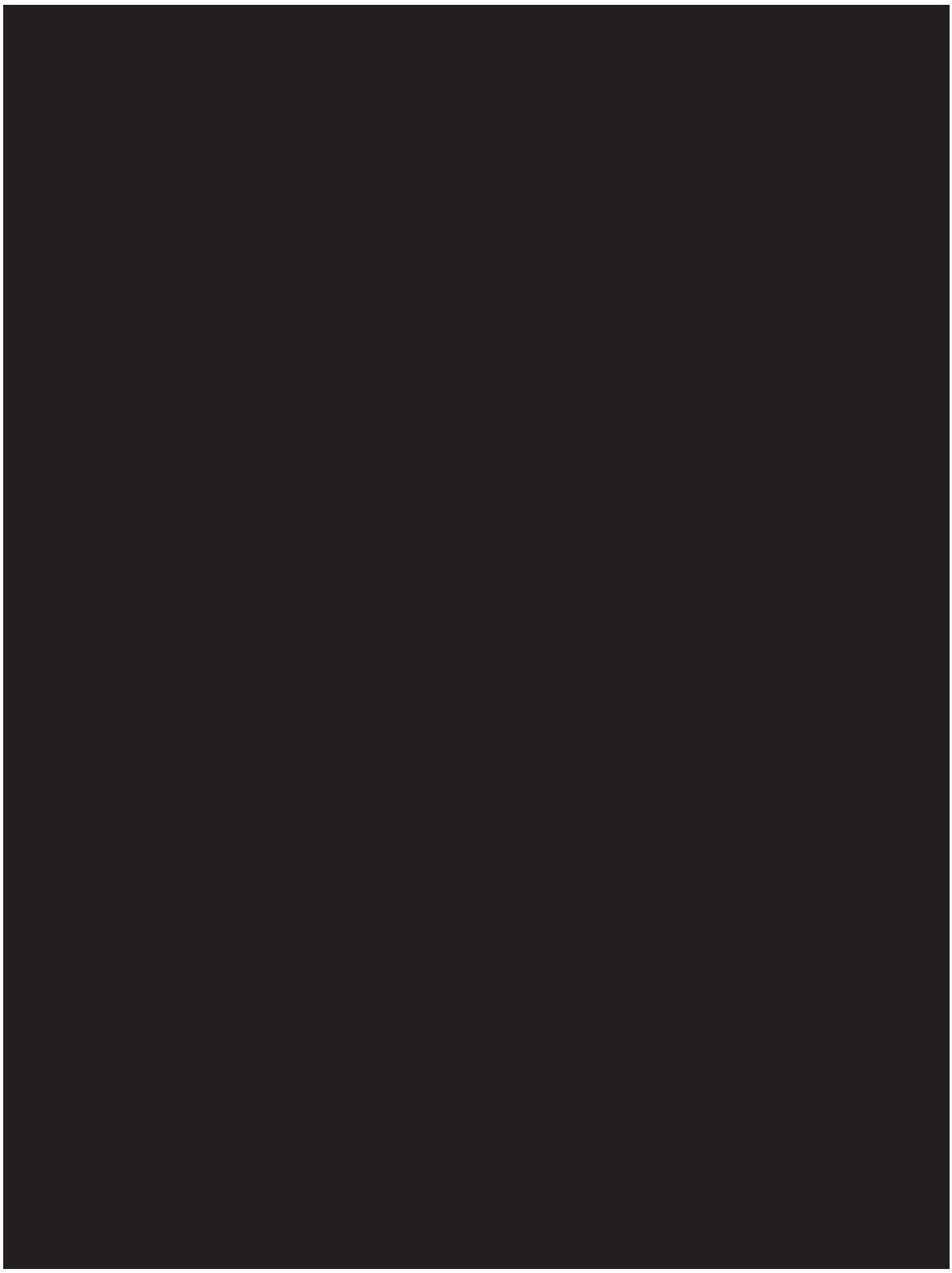
Modified September 2010
AQLQ(S)-SA North American English Version











10.8 APPENDIX 8: COUNTRY SPECIFIC REQUIREMENTS

Guidance on Contraceptive Methods

Highly effective contraceptive method of birth control may be defined according to the local medical practice and regulations.

For Denmark:

Highly effective contraceptive methods of birth control for participants enrolled in Denmark include:

- Intra-uterine devices (IUD).
- Hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release).
- Subjects using a double-barrier contraceptive method (condom used with a diaphragm for example). However, this is limited to exceptional cases or conditions where the participant cannot use other contraceptive methods (ie, hormonal contraceptives or IUD).
- Subject having a sterilized permanent partner may be allowed to participate in the study.

The allowed methods of contraception can be also described in the participant's information (subject information leaflet).

The above methods of contraception must be used in this study by women of childbearing potential throughout the entire trial period and for at least 3 months after the last injection of study medication, covering more than 5 times the terminal half-life of IMP.

Sterilized or infertile subjects (defined as having undergone surgical sterilization ie, vasectomy/bilateral tubectomy, hysterectomy and bilateral ovariectomy or as being postmenopausal defined as at least 12 months of amenorrhea prior enrolment) will be exempted from the requirements to use contraception in this study.

For UK:

Adequate contraceptive measures include:

- Placement of an IUD or intrauterine system (IUS).
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.
- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject.

[Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception].

Age of Majority

For Taiwan: The age of majority is in accordance to the most updated local regulation.

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:

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

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 below and in sections (Section 2.3, Section 5.5, Section 6.1, Section 7.1.2, Section 7.1.2.1, Section 8, Section 9.4.3, 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 Good Clinical Practice 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, screening may be temporarily delayed/halted (see also Section 5.5).

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 an emergency, focus should be given to assessments necessary to ensure the safety of participants and those 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:

- If onsite visits are not possible visit windows may be extended for the assessment of safety and/or efficacy data that cannot be obtained remotely (eg, spirometry, FeNO, FOT, HRCT scan, vital signs).
- Use of local laboratory locations may be allowed.
- Arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) for blood sample collection and study drug administration, if allowed by local regulations and approved by the participant.

As an alternative to the on-site IMP dispensing, IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant.

Rechallenge: In case of missed dose(s), no loading dose of 2 injections will be administered when restarting the treatment, whatever the number of missed doses. The participants should continue their scheduled IMP treatment and visits, even if more than 2 consecutive doses were missed.

Contingencies implemented due to emergency will be documented.

Statistical analysis: a sensitivity analysis may be conducted; details will be specified in the Statistical Analysis Plan.

For a regional or national emergency declared by a governmental agency, contingency procedures

may be implemented for the duration of the emergency. The participants 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 labs).

10.10 APPENDIX 10: RADIATION EXPOSURE

Radiation Expert Affidavit

Eduardo Mortani Barbosa Jr, MD - Independent Clinical Radiation Expert Review

Ref: Research Protocol titled "Randomized, double blind, placebo controlled study to evaluate the effect of dupilumab on airway inflammation through assessments of lung function, mucus plugging and other lung imaging parameters in patients with asthma"

Protocol Number: LPS15834
Compound Number: SAR231893 (dupilumab)

This document aims to address the following issues, which are relevant to the study design and to maximize patient safety:

1. to understand the biological risks of radiation exposure and how these relate to radiation dose;
2. to estimate the risks from a single and multiple CT exposures (up to 6 per patient) at the approximate radiation dose delivered by the average Fluidda LPS15834 CT scanning protocol
3. to understand how the dose of the Fluidda LPS15834 CT protocol compares to other sources of natural radiation exposure and other types of CT scans
4. to assess whether the Fluidda LPS15834 CT protocol can be optimized to decrease the radiation dose delivered to the lowest possible value while still providing diagnostic quality information for the quantitative analytical approach proposed for this research trial (ALARA principle – as low as reasonably achievable)

LPS15834 protocol entails that each patient will receive 3 HRCT scans (at D1, W4 and W24), each comprised by 2 acquisitions, respectively on full inspiration (total lung capacity) and end expiration (functional residual capacity) utilizing respiratory gating. The study protocol indicates that approximately 153 patients will be enrolled, all adults aged 18-70, following informed consent, with uncontrolled moderate to severe asthma, and randomized into 2 arms (placebo and dupilumab). Therefore, each patient will be exposed to a total of 6 HRCT acquisitions.

The effective radiation dose estimated from each research HRCT, assuming an average acquisition protocol in a modern CT scanner (at least 64 slices with radiation reduction options) is approximately 1.8 mSv. This takes into account the following CT acquisition parameters: tube voltage of 100 kV, rotation time of 0.6s, pitch of 1.375, maximum mA of 200, with CTDIvol of 4.5 mGy and DLP of 135 mGy*cm, using a conversion factor for the chest of 0.014 mSv/mGy*cm. The actual dose will vary according to the patient body habitus (with larger patients requiring more radiation dose to achieve similar CT image quality) and patient position in the scanner. Assuming 6 HRCT acquisitions per patient, the average cumulative dose per patient will be approximately 10.8 mSv.

To put that number in perspective, the background radiation exposure from natural sources is approximately 3.0 mSv. A typical, diagnostic chest CT radiation dose ranges from 2-5 mSv, whereas a "low dose" chest CT such as the scans utilized in lung cancer screening is in the 0.7 – 1.5 mSv range.

It is estimated that an additional exposure of 3.4 mSv/year, above background natural exposure, for 30 years decreases life expectancy by 49 days, whereas a lower additional exposure of 1.0 mSv/year for a longer period of 70 years decreases life expectancy by 34 days, on average. This compares favorably to the effect of smoking 20 cigarettes a day for 30 years, which decreases life expectancy by estimated 2370 days (6.5 years) [1]

Radiation-related risks due to HRCT are exclusively stochastic effects, primarily cancer induction, given that current diagnostic doses of less than 10 mSv are well below the threshold for deterministic effects, which generally starts at 2000 mSv (2 Gy) [2, 3]. There is ample literature regarding radiation induced carcinogenesis, particularly at moderate or high exposures (> 100 mSv). However, it must be emphasized that the existing data for lower exposures in the range of the Sanofi LPS15834 study are far less reliable, obtained from linear regression models extrapolating from much higher exposures observed in nuclear accidents and detonations. Moreover, it is difficult and costly to perform high-quality studies to show quantitative causal relationships between low-dose exposures and carcinogenesis, given the long latency of radiation-induced cancers and also the much greater baseline incidence of cancers. The estimated additional relative risk of all cancers from the International Commission of Radiologic Protection published in 2007 [2] is 0.005% per each mSv of radiation dose. This is a very small number in comparison with the baseline incidence of all cancers, which is orders of magnitude higher (it is estimated that the lifetime risk of developing any cancer can be as high as 30%). Therefore, the radiation risk of a single chest CT performed with dose-reduction techniques is considered negligible, particularly for middle-aged and elderly patients. Nonetheless, the risks may become clinically relevant in younger patients (particularly women, because of breast exposure) and also in the setting of repeated studies [4]. Because the typical latency period for radiation induced cancers is at least 10-20 years (earlier for leukemia, later for solid cancers), the risks become more significant the younger the patient is.

The estimation of risks from multiple CT exposures is not straightforward, as the risk is not a linear function of total radiation dose. In other words, the cumulative risk is not just the result of adding all individual exposures to obtain a total exposure. It depends on multiple factors, including the interval of time between each exposure, the gender and age of the patient, the body part scanned, and the survival function. A model of lifetime attributable risk (LAR) of cancer using ICRP 103 data [2, 5] published in 2014 suggested that the LAR for all cancers in a female scanned once at age 20 with a single CT with a dose of approximately 4 mSv is 8.71×10^{-4}, and if 5 CTs (with a radiation dose of 4 mSv each) are performed between age 20-50, 20.05×10^{-4}, whereas for a male scanned with the same parameters it would be 2.21×10^{-4} for a single CT and 10.70×10^{-4} for 5 CTs, respectively. For older patients (especially older than 50), the LAR is significantly smaller.

Therefore, the risk increases non-linearly with increased dose and increased number of exposures. The UK Health Protection Agency suggested the following interpretation of risks based on quantitative estimates falling in these bands, to relay information to physicians and patients:

Negligible: < 1 in a million risk ($<10^{-6}$),
Minimal: 1 in a million–1 in 100,000 risk (10^{-6} - 10^{-5}),

Very Low: 1 in 100,000–1 in 10,000 risk (10^{-5} - 10^{-4}),
Low: 1 in 10,000–1 in 1,000 risk (10^{-4} - 10^{-3}).

Integrating all the data and models described above, my best estimate of lifetime attributable risk (LAR) for the 6 HRCT acquisitions (including inspiratory and expiratory scans) per patient performed by FLUIDDA in this Sanofi LPS15834 protocol is between 5 and 10 x 10^{-4} . This brings the risk to upper range of the "low" band.

While it is probably not realistic to decrease the CT scan dose by 90% (to 1/10 of the current estimated average dose of 1.8 mSv), which would be necessary to bring the risk to the "very low" band, the CT protocol can likely be optimized to decrease the average dose by 50%, for a standard size patient, by taking the following measures:

- reducing maximum mA to 100 (half of the current number, set at 200)
- increasing pitch to 1.5, which should be attainable in most CT scanners – latest scanners would allow up to 3-3.5
- applying iterative reconstruction techniques, in order to decrease image noise and maintain sufficient image quality for quantitative image analysis in spite of the lower radiation dose, provided that the FLUIDDA FRI software will perform adequately

These protocol modifications should be feasible on most modern CT scanners (manufactured in the past 5-8 years). More advanced, recent scanners (past 2-3 years) may allow further reduction of radiation dose via faster gantry rotation, ultra-high pitch, Sn filtration, better detector sensitivity and more sophisticated iterative reconstruction techniques. These may be available at more specialized centers. Furthermore, if feasible according to the expected patient enrollment to raise the minimum age to 25 instead of 18 years old, there would be further decrease in stochastic radiation carcinogenesis LAR, likely by 20-30%, given that a disproportionate amount of risk is connected to youngest ages, and the LAR falls near exponentially with increasing age. Therefore, by combining all of the above strategies (HRCT protocol optimization and adjustment of the minimum patient age), it is conceivable to reduce the LAR by a factor of 10 and bring into the Very Low risk band, accounting for all of the 6 HRCT acquisitions entailed by the LPS15834 protocol.

References:

1. National Academy of Sciences - Biological Effects of Ionizing Radiation (BEIR) series - BEIR V, 1990
2. ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann ICRP 2007; 37:2–4
3. United Nations Scientific Committee on the Effects of Atomic Radiation. Summary of low-dose radiation effects on health. UNSCEAR Website. www.unscear.org/docs/reports/2010/UNSCEAR_2010_Report_M.pdf. Published 2010.
4. Araoz PA, Haramati LB, Mayo JR, Barbosa EJ Jr, Rybicki FJ, Colletti PM: Panel Discussion: Pulmonary Embolism Imaging and Outcomes. AJR(198), 1313-1319, June 2012.
5. V K Ivanov et al 2014 J. Radiol. Prot. 34 825

Health Physics Society-Radiation Exposure Risk-revision 2010.

PS010-2

HEALTH PHYSICS SOCIETY

RADIATION RISK IN PERSPECTIVE

POSITION STATEMENT OF THE HEALTH PHYSICS SOCIETY*

Adopted: January 1996
Revised: July 2010

Contact: Brett Burk
Executive Director
Health Physics Society
Telephone: 703-790-1745
Fax: 703-790-2672
Email: HPS@BurkInc.com
http://www.hps.org

In accordance with current knowledge of radiation health risks, the Health Physics Society recommends against quantitative estimation of health risks below an individual dose[1] of 50 millisievert (mSv) in one year or a lifetime dose of 100 mSv above that received from natural sources. Doses from natural background radiation in the United States average about 3 mSv per year. A dose of 50 mSv will be accumulated in the first 17 years of life and 0.25 Sv in a lifetime of 80 years. Estimation of health risk associated with radiation doses that are of similar magnitude as those received from natural sources should be strictly qualitative and encompass a range of hypothetical health outcomes, including the possibility of no adverse health effects at such low levels.

There is substantial and convincing scientific evidence for health risks following high-dose exposures. However, below 50–100 mSv (which includes occupational and environmental exposures), risks of health effects are either too small to be observed or are nonexistent.

In part because of the insurmountable intrinsic and methodological difficulties in determining if the health effects that are demonstrated at high radiation doses are also present at low doses, current radiation protection standards and practices are based on the premise that any radiation dose, no matter how small, may result in detrimental health effects, such as cancer and hereditary genetic damage. Further, it is assumed that these effects are produced in direct proportion to the dose received, that is, doubling the radiation dose results in a doubling of the effect. These two assumptions lead to a dose-response relationship, often referred to as the linear, no-threshold model, for estimating health effects at radiation dose levels of interest. There is, however, substantial scientific evidence that this model is an oversimplification. It can be rejected for a number of specific cancers, such as bone cancer and chronic lymphocytic leukemia, and heritable genetic damage has not

[1] Dose is a general term used to express (quantify) how much radiation exposure something (a person or other material) has received. The exposure can subsequently be expressed in terms of the absorbed, equivalent, committed, and/or effective dose based on the amount of energy absorbed and in what tissues.

been observed in human studies. However, the effect of biological mechanisms such as DNA repair, bystander effect, and adaptive response on the induction of cancers and genetic mutations are not well understood and are not accounted for by the linear, no-threshold model.

Radiogenic health effects have not been consistently demonstrated below 100 mSv

Radiogenic health effects (primarily cancer) have been demonstrated in humans through epidemiological studies only at doses exceeding 50–100 mSv delivered at high dose rates. Below this dose, estimation of adverse health effect remains speculative. Risk estimates that are used to predict health effects in exposed individuals or populations are based on epidemiological studies of well-defined populations (for example, the Japanese survivors of the atomic bombings in 1945 and medical patients) exposed to relatively high doses delivered at high dose rates. Epidemiological studies have not demonstrated adverse health effects in individuals exposed to small doses (less than 100 mSv) delivered in a period of many years.

Limit quantitative risk assessment to doses at or above 50 mSv per year or 100 mSv lifetime

In view of the above, the Society has concluded that estimates of risk should be limited to individuals receiving a dose of 50 mSv in one year or a lifetime dose of 100 mSv in addition to natural background. In making risk estimates, specific organ doses and age-adjusted and gender-adjusted organ risk factors should be used. Below these doses, risk estimates should not be used. Expressions of risk should only be qualitative, that is, a range based on the uncertainties in estimating risk (NCRP 1997) emphasizing the inability to detect any increased health detriment (that is, zero health effects is a probable outcome).

Impact on radiation protection

Limiting the use of quantitative risk assessment, as described above, has the following implications for radiation protection:

1. The possibility that health effects might occur at small doses should not be entirely discounted. The Health Physics Society also recognizes the practical advantages of the linear, no-threshold hypothesis to the practice of radiation protection. Nonetheless, risk assessment at low doses should focus on establishing a range of health outcomes in the dose range of interest and acknowledge the possibility of zero health effects. These assessments can be used to inform decision making with respect to cleanup of sites contaminated with radioactive material, disposition of slightly radioactive material, transport of radioactive material, etc.

2. Collective dose (the sum of individual doses in a defined exposed population expressed as person-sievert) has been a useful index for quantifying dose in large populations and in comparing the magnitude of exposures from different radiation sources. However, collective dose may aggregate information excessively; for example, a large dose to a small number of people is not equivalent to a small dose to many people, even if the collective doses are the same. Thus, for populations in which almost all individuals are estimated to receive a lifetime dose of less than 100 mSv above background, collective dose is a highly speculative and uncertain measure of risk and should not be used for the purpose of estimating population health risks.

PS010-

Reference

National Council on Radiation Protection and Measurements. Uncertainties in fatal cancer risk estimates used in radiation protection. Bethesda, MD: NCRP; NCRP Report No. 126; 1997.

*The Health Physics Society is a nonprofit scientific professional organization whose mission is excellence in the science and practice of radiation safety. Since its formation in 1956, the Society has represented the largest radiation safety society in the world, with a membership that includes scientists, safety professionals, physicists, engineers, attorneys, and other professionals from academia, industry, medical institutions, state and federal government, the national laboratories, the military, and other organizations. Society activities include encouraging research in radiation science, developing standards, and disseminating radiation safety information. Society members are involved in understanding, evaluating, and controlling the potential risks from radiation relative to the benefits. Official position statements are prepared and adopted in accordance with standard policies and procedures of the Society. The Society may be contacted at 1313 Dolley Madison Blvd., Suite 402, McLean, VA 22101; phone: 703-790-1745; fax: 703-790-2672; email: HPS@BurkInc.com.

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10.11 APPENDIX 11: ABBREVIATIONS

ACQ:	Asthma Control Questionnaire
AD:	atopic dermatitis
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AQLQ(S):	Asthma Quality of Life Questionnaire with Standardized Activities
ATS:	American Thoracic Society
CFR:	Code of Federal Regulations
COPD:	chronic obstructive pulmonary disease
COVID-19:	coronavirus disease 2019
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CT:	computed tomography
ECG:	electrocardiogram
e-CRF:	electronic case report form
EoE:	eosinophilic esophagitis
EOT:	end of treatment
ERS:	European Respiratory Society
ETD:	early treatment discontinuation
FeNO:	fractional exhaled nitric oxide
FEV1:	forced expiratory volume in 1 second
FI:	functional imaging
FOT:	forced oscillation technique
FRC:	functional residual capacity
FRI:	functional respiratory imaging
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
HBcAb:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HCVAb:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
HRCT:	high-resolution computed tomography
HRT:	hormonal replacement therapy
IB:	Investigator’s Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
ICS:	inhaled corticosteroids
IEC:	Independent Ethics Committees
IMP:	investigational medicinal product
IRB:	Institutional Review Boards
IUD:	Intra-uterine device
IVRS:	interactive voice recognition system
IWRS:	interactive web response system

LABA:	long-acting β2 agonists
LTRA:	leukotriene receptor antagonist
MCID:	minimal clinically important difference
MMRM:	mixed model repeated measures model
MoA:	mechanism of action
OCS:	oral corticosteroids
PN:	prurigo nodularis
SABA:	short-acting β2 agonists
SAD:	small airway dysfunction
SAE:	serious adverse event
SoA:	schedule of activities
TB:	tuberculosis
TEAE:	treatment emergent adverse event
UCSF:	University of California, San Francisco
ULN:	upper limit of normal

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).

10.12.1 Amended protocol 02 (15 March 2021)

This amended protocol 02 is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

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

The main reasons for the amended protocol 02 are to introduce some clarifications in the eligibility criteria, to decrease the patient burden and to allow more flexibility for some of the study procedures (eg, FeNO assessment, complete clinical examination, the sequence of the study procedures). We are also taking this opportunity to align the safety reporting (AESI) with the updated IB and to incorporate contingency measures in case of a regional or national emergency. The stratification factor related to regions has been changed to Eastern Europe/ROW. In total, no more than 40% participants should be in "Eastern Europe" strata.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.1 Overall design; 6.3 Measures to minimize bias: randomization and blinding; 9.4.1 Efficacy analyses	The stratification factor related to regions has been changed to Eastern Europe/ROW. In total, no more than 40% participants should be in "Eastern Europe" strata.	Differences in treatment effect of dupilumab 300 mg seen in pivotal Phase 3 study QUEST in EE vs ROW
1.3 Schedule of Activities (SoA); 5.1 Inclusion criteria; 8.1 Efficacy Assessments;	FeNO will be rechecked at randomization.	Ensure FeNO eligibility at V2
Section 1.3 Schedule of Activities (SoA)	Complete physical examinations will be performed at V1, V2, and V5.	The number of complete physical examinations has been reassessed in order to decrease the participants' burden.
	Retesting of FeNO one additional time during screening if the eligibility criterion for FeNO was not met at V1. FeNO will be re-checked at randomization visit (V2) for eligibility.	To allow more flexibility for FeNO assessment during screening; to ensure that the FeNO eligibility criterion should be met at V2 as well.
	ACQ-5 score is the mean of the responses to the first 5 questions.	Correction related to the calculation of ACQ-5 score
	ACQ-6 score is the mean of the responses to the first 6 questions.	Correction related to the calculation of ACQ-6 score
	Clarifications related to HRCT scan at V2	Clarifications related to HRCT scan
	Added provision for retesting of spirometry for patients who did not meet eligibility criterion for pre-BD FEV1 at V1	Clarifications related to the retesting of pre-BD FEV1 during screening

Section # and Name	Description of Change	Brief Rationale
	Updated recommendation related to the sequence of the procedures and HRCT scan	Clarifications related to the sequence of the procedures
	Added provision of administration of IMP loading dose at D1+1 day when HRCT scan is performed the day after D1	Clarifications related to the administration of IMP loading dose, in case that HRCT scan can't be performed at V2
	Added note for contingency measures for a regional or national emergency and reference to the Appendix 9	Contingency measures in case of regional and national emergency
	Clarification added in footnote "r" regarding home dosing diary and asthma background therapy diary	Clarification
Section 2.3 Benefit/Risk Assessment	Updated text related to dupilumab worldwide marketing authorization approval status for all indications Updated numbers of patients exposed to dupilumab in various clinical studies and post-marketing exposure Updated the ADRs list for dupilumab Also updated text on eosinophilia as important potential risk Added benefit/risk assessment related to COVID-19	Regulatory and safety updates related to dupilumab
Section 5.1 Inclusion Criteria	I.06. Added provision for consideration of historical blood eosinophil count, and FeNO assessment at V2 as well.	To clarify in the inclusion criterion I06 that the historical values of blood eosinophil count measured within 6 months prior to V1 in the absence of OCS treatment are allowed; FeNO to be assessed for eligibility at V2 as well
	I.09. Added provision for male contraception duration	Correction related to male contraception duration
Section 5.2 Exclusion Criteria	E.04. Added clarifications related to asthma exacerbation	Clarifications on asthma exacerbation
	E09. Added exclusion provision for hepatic clinically significant disease, as judged by the investigators	Minor update of the criterion
	E14. Updated exclusion criterion for treatment with live (attenuated) vaccine	Clarification of the criterion related to vaccination with live (attenuated) vaccine
	E15. Updated exclusion criterion regarding the treatment with oral corticosteroids (OCS) within 2 weeks prior to V1	To clarify timeframe for OCS treatment
	E18. Updated exclusion criterion regarding the treatment with an investigational drug within 1 month or within 5 half-lives (if known), whichever is longer, prior to V1.	An interdiction of non-antibody investigational drugs for 2 months before V1 is unnecessary.
Section 5.4 Screen Failures	Added provision for retesting of FeNO, spirometry, reversibility test during screening	FeNo retesting allowed one additional time during screening: minor updates on spirometry and reversibility re-test

Section # and Name	Description of Change	Brief Rationale
Section 5.5 Criteria for Temporarily Delaying Screening, Randomization, or Study Intervention Administration	Statement for provisions in case of regional or national emergency added with reference to Appendix 9 (Section 10.9)	Contingency measures in case of regional or national emergency
Section 6.1 Study Intervention(s) Administered	Updates related to IMP administration, patients' instructions on hypersensitivity reactions and self-monitoring after the administration of IMP at home are added; Process in case of missed IMP doses is detailed	Clarifications related to the IMP administration and monitoring after IMP administration To clarify the process in case a participant misses IMP administration(s). The participants will not be prematurely discontinued from treatment in case they miss 2 consecutive doses, to align with the pivotal study QUEST.
Section 6.1 Study Intervention(s) Administered Section 6.5 Concomitant Therapy Section 6.6 Rescue Medicine	Text added allowing systemic corticosteroids for the treatment of asthma exacerbations.	Systemic corticosteroids are allowed for the treatment of asthma exacerbation
Section 7.1.2 Temporary discontinuation	Updated criteria for temporary discontinuation: • treatment with a live (attenuated) vaccine • treatment with immunomodulating biologics (including experimental treatments) • systemic corticotherapy (except the administration in case of asthma exacerbation)	Clarification related to criteria for temporary discontinuation
Section 7.1.2.1 Rechallenge Section 9.4.3 Other analyses	Updates related to regional or national emergency are added	Contingency measures in case of regional and national emergency
Section 7.1.1 Definitive discontinuation	Added definition of baseline ALT value	Clarifications on the definition of baseline ALT value
Section 7.1.2 Temporary Discontinuation	Conditions updated for temporary discontinuation	Temporary intervention discontinuation may be considered by the Investigator also in case of disruption of the clinical trial due to a regional or national emergency declared by a governmental agency; The treatment with systemic corticosteroids in case of asthma exacerbation has been added
Section 8.1 Efficacy Assessments	Updates based on the changes added in the SoA	Clarifications on the study procedures (HRCT scan, FeNO, FOT, spirometry) according to SoA
Section 8.3 Adverse Events and Serious Adverse Events	Updated list of AESI Added definition of baseline ALT value Updated definition of overdose for NIMP	Updated list of AESI based on the new Investigator's Brochure; updated definition of overdose with NIMP
Section 8.3.5 Pregnancy	Clarified instructions related to pregnancy reporting	Clarification
Section 8.4 Treatment of Overdose	Clarifications on the instructions in case of IMP overdose	Clarifications on the instructions

Section # and Name	Description of Change	Brief Rationale
Section 8.10 Use of Data for Future Research	Added new section for provisions and procedures followed in case of participant data use for future research	Clarifications related to participant data used for future research
Section 9.4.2 Safety analyses	Added definition of TE period	Clarification
Section 10.1.1 Regulatory and Ethical Considerations	Added GDPR to be followed Updated procedure to be followed for substantial protocol amendments Updated the Investigator's responsibility	Clarification
Section 10.1.3 Informed consent process	Updated the provisions and procedures of Informed consent process	Clarification
Section 10.1.4 Data protection	Updated data protection section and added subsections - protection of participant data, protection of data related to professionals involved in the study	Clarification
Section 10.1.6 Dissemination of clinical study data	Added subsection - professionals involved in the study or in the drug development program, and updated text	Clarification
Section 10.1.7 Data quality assurance	Updated procedures to be followed for data quality assurance	Clarification on the process of data quality assurance
Section 10.1.8 Source documents	Updated provisions for source documents	Minor changes
Section 10.1.9 Study and site closure	Added subsection - first act of recruitment, and text	Clarification
Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting	Added subsection - definition of unsolicited and solicited AE, and text	Clarification
Section 10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Updated definition of WOCBP and WONCBP, and Contraception Guidance	Updated contraceptive guidance
Section 10.5 Appendix 5: Liver and Other Safety: Suggested Actions and Follow-Up Assessments	Updated algorithm chart for increase in ALT	Updated algorithm
Section 10.8. Appendix 8: Country specific requirements	Majority of age added for Taiwan	Country specific requirement for Taiwan
Section 10.9 Appendix 9: Contingency Measures for a Regional or National Emergency that is Declared by a Governmental Agency	Summary of contingency measures for regional or national emergency declared by a governmental agency	New appendix with the summary of the contingency measures

10.12.2 Amended protocol 01 (12 March 2020)

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

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for the amendment is to meet requirements for Regulatory Agency.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activity 5.2 Exclusion criteria 10.2 Appendix 2: Clinical laboratory tests	Addition of an exclusion criterion E07 related to tuberculosis and tuberculosis testing. Addition of tuberculosis testing and related footnote q. Table 8: Addition of tuberculosis testing	As per Regulatory Agency review, patient with tuberculosis should not be included in the study.

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