1.2 STUDY FLOW CHART

	SCR[a]	Randomized Treatment Period																											Post-treatment Period[d]		
		RND[b]																									EOT[c]			EOS
Week	–4 (±1)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64
Visit[e]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Informed Consent/Assent[f]	x																														
Inclusion/Exclusion Criteria	x	x																													
Patient Demography	x																														
Medical/Surgical History[g], and Reversibility[h]	x																														
Physical Examination	x													x														x			x
Menstruation status[i]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x			x
Vital Signs[j] (including height and weight)	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
Dispense or download electronic diary/ PEF meter[k]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
Health Care Resource Utilization (HCRU)		x						x						x						x						x		x			x
Randomization[b]		x																													
Call IVRS/IWRS	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x			x
Treatment																															
Investigational Product Administration[l]		x	x	x	x	x	x	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]				
Dispense/review of diary for Home Dosing[m] (optional) by parent/caregiver								x		x		x		x		x		x		x		x		x		x		x			
Efficacy Assessments																															
Spirometry[n]	x	x[o]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
Post-bronchodilator FEV1[n]		x	x	x		x		x						x						x								x			x
Patient Reported Outcomes / HRQoL																															
ACQ-IA[p]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x			x
PAQLQ(S)-IA (for patients ≥7 years old at Randomization V2)[p]		x						x						x						x								x			x
PRQLQ-IA [q]		x						x						x						x								x			x

	SCR[a]	Randomized Treatment Period																										Post-treatment Period[d]		
		RND[b]																									EOT[c]			EOS
Week	**–4 (±1)**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**56**	**60**	**64**
Visit[e]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
EQ-5D-Y for children		x												x														x			x
Patient Reported Outcomes (Caregiver)																															
PACQLQ (for caregivers of patients ≥7 years old at Randomization V2)		x						x						x						x								x			x
PK, PD, Pharmacogenetics																															
Blood biomarkers[r]		x						x						x														x			
Total IgE, and antigen-specific IgE[s]		x												x														x			
Antigen-specific IgG4 panel[s]		x												x														x			
Systemic drug concentration[t]		x			x			x						x														x			x
Exhaled NO[u]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
[redacted]																															
Safety Assessments																															
Total IgG, IgG subclasses, IgM, IgA		x												x														x			x
Anti-drug antibodies[w]		x						x						x														x			x
Pregnancy test for girls who are menstruating[x]	x	x		x		x		x		x		x		x		x		x		x		x		x		x		x			x
Prior and concomitant medications	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
AE/SAE recording	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
Clinical lab testing[y] (hematology/biochemistry)	x	x						x						x						x								x			x
Urinalysis	x							x						x						x								x			x
ECG	x																											x			x
[redacted]																															

GSO:	Global Safety Officer
HBc-Ab:	Hepatitis B core antibody
HBs Ab:	Hepatitis B surface antibody
HBs-Ag:	Hepatitis B surface antigen
HBV DNA:	Hepatitis B virus DNA
HCRU:	healthcare resource utilization
HCV-Ab:	Hepatitis C virus antibody
HIV:	Human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
HRQoL:	Health related quality of life
HVC RNA:	Hepatitis C virus RNA
IAF:	Informed assent form
ICF:	Informed consent form
ICH:	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS:	Inhaled corticosteroids
IEC:	Independent Ethics Committee
IgA:	Immunoglobulin A
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
IL:	interleukin
IL-13:	Interleukin-13
IL-4:	Interleukin-4
IMP:	Investigational medicinal product
IRB:	Institutional Review Board
ITT:	intent-to-treat
IVIG:	Intravenous immunoglobulin
IVRS:	Interactive voice response system
IWRS:	Interactive web response system
LABA:	Long-acting β2 agonist
LAMA:	Long acting muscarinic antagonist
LFT:	Liver function tests
LOAC:	Loss of Asthma Control
LTRA:	Leukotriene receptor antagonist
MCID:	Minimal clinically important difference
MDI:	Metered-dose inhaler
MID:	Minimally important difference
MMRM:	Mixed-effect model with repeated measures
NIMP:	Non-investigational medicinal product
NRS:	Numerical Rating Scale
PACQLQ:	Pediatric Asthma Caregiver's Quality of Life Questionnaire
PAQLQ(S)-IA:	Paediatric Asthma Quality of Life Questionnaire with Standardised Activities–Interviewer Administered
PBMC:	Peripheral blood mononuclear cells

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study assessing the effect of dupilumab administered SC for a maximum of 52 weeks in children 6 to <12 years of age with uncontrolled asthma.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study will last up to 68±1 weeks as follows:

- Screening Period (4±1 weeks) to determine a patient's eligibility status and establish level of asthma control before randomization.
- Randomized Treatment Period (up to 52 weeks): treatment with dupilumab or placebo SC injection.
- Post-treatment Period (12 weeks): to monitor a patient's status when off study drug treatment for patients not participating in the 1-year long-term extension study.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur when either:

- The last patient has completed the 12-week post-treatment period or
- The last patient has completed the end-of-treatment (EOT) visit and enrolled in the 1-year long-term extension study.

6.3 INTERIM ANALYSIS

No interim analysis is planned for this study.

6.4 STUDY COMMITTEES

6.4.1 Data Monitoring Committee

A data monitoring committee (DMC) is independent from Sponsor's and is commissioned for the dupilumab clinical development program. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC will review and evaluate the safety data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

The DMC procedures and safety data to be reviewed by the DMC are described in the DMC charter. In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.

at not less than 3 visits followed by a successful IMP administration under close supervision of the investigator or designee at not less than 3 visits.

However, if parent(s)/caregiver(s)/legal guardian(s) do not develop the comfort to inject the IMP at home, or the Investigator determines that injection by parent(s)/caregiver(s)/legal guardian(s) at home is not appropriate, alternative arrangements may be made: for example for qualified site personnel and/or healthcare professionals (eg, visiting nurse service) to administer IMP at these timepoints at the patient's home.

For IMP doses not given at the study site, 'home dosing diary' (paper format) will be provided to record information related to the injections. Such home dosing diaries will be kept as source data in the patient's study file.

Parent(s)/caregiver(s)/legal guardian(s) should be instructed to avoid missing any site visits (ie, IMP doses) or doses of background therapy during the study. For any patient who misses a site-visit (ie, IMP dose) or doses of background therapy, the parent(s)/caregiver(s)/legal guardian(s) should be reminded to be diligent to avoid missed visits and doses of background therapy thereafter.

The patient(s)/parent(s)/caregiver(s)/legal guardian(s) should continue their scheduled visits for IMP treatment (with study procedures, as detailed in Section 1.2), even if more than 2 consecutive doses of IMP are missed, or background medication was not taken by the patient(s) for up to 2-4 days.

The SC injection sites should be alternated among the 4 quadrants of the abdomen (avoiding navel and waist areas), the upper thighs or the upper arms, so that the same site is not injected twice consecutively. For each injection, the anatomic site of administration will be recorded in the electronic-case report form (e-CRF) or, as applicable, the home dosing diary.

Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the patient and parent(s)/caregiver(s)/legal guardian(s). Parent(s)/caregiver(s)/legal guardian(s) will complete a dosing diary to document compliance with injection of IMP.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Inhaled Corticosteroids and Second Controller Medication

The recognized second controller medication for combined use with medium- or high-dose ICS (dose-levels in children 6 to <12 years old, as per Appendix A) as background therapy during this study (only one controller is permitted; see eligibility criterion No. 14 in Section 7.2.2) will include the following classes: LABA, LTRA, LAMA, or methylxanthines. Please refer to Appendix B for an indicative (not exhaustive) list of recognized second controller medications approved for this study. These second controller medications will not be dispensed or supplied by the Sponsor.

- Change from Baseline in other lung function measurements (absolute and relative FEV1, AM/PM peak expiratory flow, FVC, forced expiratory flow (FEF) 25-75%, post-bronchodilator % predicted FEV1) at Weeks 2, 4, 8, 12, 24, 36, 52, and other time points assessed.
- The effect of dupilumab on healthcare resource utilization (HCRU)
- Change from Baseline at Weeks 2, 4, 8, 12, 24, 36, and 52 and other timepoints in:
  - Morning/evening asthma symptom score (electronic diary)
  - PRO:
    - ACQ-IA, for children 6 to <12 years old,
  - Use of reliever medication
  - Number of nocturnal awakenings due to asthma symptoms requiring the use of reliever medication
- Change from Baseline at Weeks 12, 24, 36, 52, 64 in:
  - PRO:
    - Paediatric Asthma Quality of Life Questionnaire with Standardised Activities–Interviewer Administered (PAQLQ(S)-IA) score, for children ≥7 to <12 years old at Randomization Visit 2.

9.2.2.1 Disease-specific Efficacy Measures

9.2.2.1.1 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with the ATS/ ERS guidelines (8). For pre-bronchodilator measured parameters, including FEV1, peak expiratory flow (PEF), FVC and FEF 25-75%, spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.

For post-bronchodilator FEV1, the measure should follow the steps as that at screening test for reversibility validation.

At all visits, spirometry will be performed either in the AM or PM, but preferred in the AM, and the spirometry should be done at approximately the same time at each visit throughout the study. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements.

Pulmonary function tests will be measured in 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, if possible. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable and/or acceptable maneuvers, an explanation should be recorded.

The largest FEV1 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 FEF 25-75% should be obtained from the single curve that meets the acceptability criteria and gives the largest sum of FVC plus FEV1 (best test).

Automated best efforts, which combine FEV1 and FVC are not acceptable.

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.

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

9.2.2.1.2 Reversibility/Post-bronchodilator FEV1

Reversibility is defined as an increase in absolute FEV1 of 10% over the baseline value, demonstrated within 30 minutes of bronchodilator administration.

At the screening test, reversibility is tested after the administration of 200 to 400 mcg (2 to 4 puffs) of albuterol/salbutamol or 45 to 90 mcg of (2 to 4 puffs) levalbuterol/levosalbutamol reliever medication from a primed MDI (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication, if tolerated by the patient). Documented reversibility or positive airway hyperresponsiveness to methacholine within 12 months prior to Visit 1 is considered acceptable.

All reversibility tests will be administered after pulmonary function testing and after asthma medications have been withheld for the appropriate intervals. Patients will receive the albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication as puff inhalations using the respective MDI. Alternatively, and only if it is consistent with usual office practice (to be documented), reversibility testing may be performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication.

The spirometry for measuring absolute FEV1 may be repeated several times within the 30 minutes after administration of bronchodilator.

for the 7 days prior to the first dose of investigational product. Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day1. There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available.

Baseline reliever use will be the mean number of reliever use recorded for the 7 days prior to the first dose of investigational product. Period stability limit is defined as the respective mean AM or PM PFE obtained over the last 7 days prior to Day1. There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available for both measurements.

Information derived from the electronic PEF meter will be evaluated by the Investigator at study visits.

9.2.2.2.2 Asthma Symptom Numerical Rating Scale (NRS) Score

Parent(s)/caregiver(s)/legal guardian(s) will record overall symptom scores in an electronic diary/PEF meter twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Baseline symptom scores will be the mean AM and mean PM scores recorded for the 7 days prior to randomization. The baseline AM/PM symptom score will be computed following the same algorithm used for baseline AM/PM PEF. Scores range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms. There is no global score, just an AM score and a PM score. A Minimal clinically important difference (MCID) of 0.35 is being used (9) (see Appendix E).

9.2.2.2.3 Use of Reliever Medicine

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the parent(s)/caregiver(s)/legal guardian(s) in an electronic diary/PEF meter. Each patient should be reminded that salbutamol/albuterol or levosalbutamol/levalbuterol should be used only as needed for symptoms, not on a regular basis or prophylactically. The baseline number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day will be based on the mean of the 7 days prior to randomization.

9.2.2.3 Health Care Resource Utilization

The HCRU questionnaire (questions on use of reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, school days' loss, etc), as integrated part of the e-CRF, will be administered as shown in Section 1.2, and will additionally be used to asses HCRU in the event of any asthma exacerbation: severe asthma exacerbation event or evidence of LOAC (for detailed definitions see Section 9).

9.2.2.4.1.2 ACQ-5-IA (Asthma Control Questionnaire–Interviewer Administered, 5-question version)

The ACQ-5-IA will be deduced from the responses to the first 5 questions of ACQ-7-IA and will be used for children ≥6 years to <12 years old at Screening.

Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the MCID defined by the developer.

Measurement properties such as reliability and ability to detect change have been documented in the literature (10).

9.2.2.4.2 Pediatric Asthma Quality of Life Questionnaire with Standardized Activities–Interviewer Administered

The PAQLQ(S)–IA was designed as an interviewer-administered PRO to measure the functional impairments that are most troublesome to children ≥7 years old at Randomization Visit 2, as a result of their asthma (see Appendix G). The instrument is comprised of 23 items, each rated on a 7-point Likert scales from 1 to 7.

The PAQLQ(S)-IA has 3 domains. The domains and the number of items in each domain are as follows:

- Symptoms (10 items)
- Activity limitation (5 items)
- Emotional function (8 items)

A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life.

The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The MCID for PAQLQ(S)-IA is 0.5 (11).

9.2.3 Safety and Tolerability Endpoints

The same safety assessments will be applied across both arms. AEs, including serious adverse events (SAEs) and AEs of special interest (AESI), will be collected at any time during study. The Investigator will ask the patient and parents how he/she has felt since the last study visit. To assure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in Section 6.4.1.

Safety observations

- The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow up the outcome of SAEs/AESI until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor.
- Patient height will be recorded at randomization as baseline value and compared with last height available during randomized treatment.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- In case of any SAE/AESI with immediate notification brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor.

9.2.3.1 Adverse Events

Adverse events for each patient will be monitored and documented from the time the subject gives informed consent at Visit 1 until the End of Study (EOS) Visit or till the rollover to the extension study, except for:

- SAEs
- AEs that are ongoing at database lock.

Adverse events, AESIs and SAEs will be reported as described in Section 10.4.

9.2.3.2 Vital Signs

Vital signs blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), and will include height (cm) and body weight (kg), measured at the Screening and Randomization Visits (Visits 1 and 2) and every subsequent visit. Height will be measured with a proper stadiometer at every visit. Stadiometer measurements will be made without patient wearing shoes. Vital signs will be measured at clinic visits, in sitting position, using the same arm at each visit, and prior to administration of investigational product.

Refer to Section 1.2 Study Flow Chart for the schedule of vital signs performed throughout this study.

9.2.3.3 ECG Variables

One recording of a standard 12-lead electrocardiogram (ECG) will be performed at Screening, EOT, and EOS (see Section 1.2).

9.2.3.4 Physical Examination

Physical examinations will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities, including menstruation status (Section 7.2.3). All deviations from normal will be recorded, including those attributable to the patient's disease. Refer to Section 1.2 Study Flow Chart for the schedule of physical examination performed throughout this study.

9.2.3.5 Clinical Laboratory Safety Variables

The clinical laboratory tests will be conducted by an accredited (College of American Pathologists or equivalent) central laboratory with national and regional clinical licenses as required for diagnostic testing and must provide evidence of participation in proficiency testing, as appropriate. After reviewing the laboratory report and evaluating any results that are outside the normal range, the Investigator must sign and date the laboratory report.

Abnormal laboratory values that are considered to be clinically significant by the Investigator should be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of the persistent abnormality is determined.

Refer to Section 1.2 Study Flow Chart for the description of the clinical laboratory evaluations and the schedule of laboratory evaluations performed throughout this study.

The clinical laboratory parameters that will be measured in safety hematology and chemistry blood samples are:

- Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.
- Serum chemistry: To include: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and CPK. Patients' fasting or non-fasting status at blood sample collection will be recorded on the Central Laboratory Requisition Form. Fasting is considered as no intake of food or any drink except for water for at least 8 hours.
- Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- Clinical laboratory testing at Screening Visit 1 will include HBs-Ag, hepatitis B surface antibody (HBs-Ab), HBc-Ab, HCV-Ab, HIV screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA).

Table 2 - Summary of handling procedures for dupilumab

Sample type	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Blood sample volume	2 mL	2 mL
Anticoagulant	None	None
Blood handling procedures	See Operational Manual	See Operational Manual
Serum aliquot split	Two aliquots	Two aliquots
Storage conditions	<6 months: below -20°C <24 months: below -80°C (preferred)	<6 months: below -20°C <24 months: below -80°C (preferred)
Serum shipment condition	In dry ice	In dry ice

9.3.1.1.3 Bioanalytic Method

Serum samples will be assayed using validated methods as described in Table 3.

Table 3 - Summary of bioanalytical methods for dupilumab and anti-dupilumab antibody

Analyte	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	Electrochemiluminescence
Site of bioanalysis	Regeneron	Regeneron

ELISA: enzyme-linked immunosorbent assay

9.3.1.2 Humoral Immune Response to Vaccines

Humoral immune responses to standard vaccines (in this study: any vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza vaccine) occurring during dupilumab treatment will be evaluated for those patients eligible for these vaccinations.

At Screening, parent(s)/caregiver(s)/legal guardian(s) will be asked to provide information on their child's vaccination record and schedule, and assess whether immunizing their children with any vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza (as per local medical practice) will result in vaccination during the study.

Any patient who will receive planned vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza during the study, will be scheduled to receive the respective vaccination(s) and to have blood samples for antibody titers drawn before and after the respective vaccination(s), as detailed below, and as shown in the Study Flow Chart (Section 1.2).

- Pediatric Rhinoconjunctivitis Quality of Life Questionnaire – Interviewer Administered (PRQLQ-IA) score, in children 6 to <12 years old with history of allergic rhinitis)
- EuroQol 5-dimensions questionnaire (EQ-5D-Y) for children

- Change from Baseline in antigen-specific IgE and antigen-specific IgG4, and ratio of IgE:IgG4
- Slope of % predicted FEV1

9.4.2 Pharmacodynamics and Phenotyping

Asthma is a heterogeneous disease comprised of multiple phenotypes and endotypes. To assure optimization of treatment in children, a set of biomarkers related to type 2 inflammation will be assessed at Baseline and after treatment for their association with therapeutic response. In previous asthma trials in adults, treatment with dupilumab significantly suppressed the levels of serum total IgE (a product of immunoglobulin class switching driven by IL-4), antigen-specific IgEs, serum TARC (CCL17; a ligand of CCR4 receptors that attracts Th2 cells), and FeNO (a marker of airway inflammation) baseline values, including blood eosinophil counts from hematology assays were used to phenotype patients. It is feasible that children may differ from adults in their biomarker profile. Therefore, these biomarkers are included in the current study.

In addition, a possible switching in antigen-specific IgE toward the corresponding antigen-specific IgG4 will be assessed in this study to explore the possibility that dupilumab may in part attenuate allergic sensitization.

Assay methodologies are briefly summarized below. More detailed information on the collection, handling, transport and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate laboratory manual.

Patient(s)/parent(s)/caregiver(s)/legal guardian(s), Investigators, and site personnel will be blinded and have no access to any assay results for total IgE, antigen-specific IgEs, antigen-specific IgG4, or TARC, while the study is ongoing, as the related efficacy data are not essential for patient care and have the potential for unblinding the study treatments.

9.4.2.1 Serum Biomarkers

Total IgE will be measured with a quantitative method (eg, ImmunoCAP) approved for diagnostic testing.

Antigen-specific IgE and antigen-specific IgG4 will be detected using panels of antigens appropriate to the location of the clinical site (quantitative ImmunoCAP test; Phadia).

TARC will be assayed with a validated immunoassay.

9.4.2.4 Other Patient Reported Outcomes Including Health Related Quality of Life (Exploratory Endpoints)

9.4.2.4.1 Paediatric Asthma Caregiver's Quality of Life Questionnaire

The PACQLQ was designed as a 13-item questionnaire for the parent(s)/caregiver(s)/legal guardian(s) of children ≥7 years old and <12 years of age at Randomization Visit 2), in order to capture the impact of the child's asthma on their quality of life and which aspects were most troublesome to the parent(s)/caregiver(s)/legal guardian(s) during the time prior to this assessment (see Appendix H).

A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life.

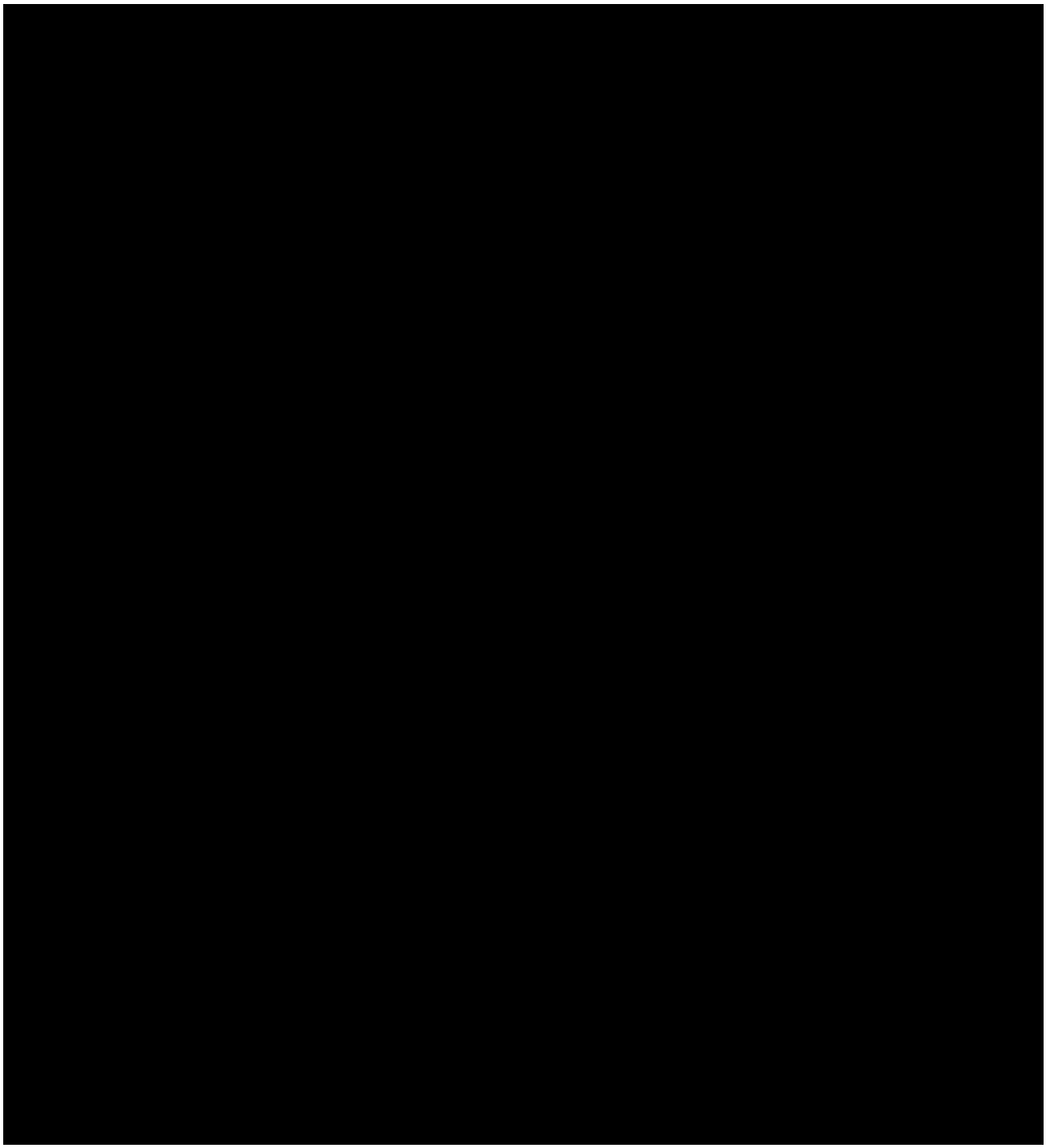
9.4.2.4.2 Pediatric Rhinoconjunctivitis Quality Of Life Questionnaire–Interviewer Administered in patients with comorbid allergic rhinitis.

PRQLQ-IA (see Appendix I) is an interviewer-administered questionnaire developed to measure HRQoL signs and symptoms that are most problematic in children ≥6 years to <12 years old, as a result of perennial or seasonal allergic rhinitis. The 23-item PRQLQ-IA responses are based on 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Higher scores indicated more health-related quality of life impairment (lower scores better). The instrument takes approximately 7 minutes to complete. The minimally important difference (MID) of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (12).

9.4.2.4.3 Euro Qol (EQ-5D-Y) – for Children

The EQ-5D-Y will be completed by children (relates to the quality of life to the child). Those who can read are encouraged to fill the questionnaire by themselves. Those who cannot read, fill it with the help of their adult caregiver (parent/caregiver).

The EQ-5D-Y consists of 2 pages, the EQ-5D-Y descriptive system and the EQ visual analogue scale (VAS; see Appendix J). The descriptive system assesses 5 dimensions but using a child-friendly wording (mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad or unhappy). Each dimension has 3 levels: no problems, some problems, a lot of problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. Also, previously published studies by EuroQol Group members showed preliminary evidence of the instrument's feasibility, reliability and validity.



9.6 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments used in this study are standard for the evaluation of therapy in patients with asthma.

10 STUDY PROCEDURES

The clinical trial consists of three periods, using an add-on therapy approach to inhaled corticosteroid in combination with second controller medications:

- Screening Period (4 [±1] weeks; Visit 1)
- Randomized Treatment Period (52 weeks; Visits 2-28)
- Post-treatment Period (12 weeks; Visits 29-31)

The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within ±3 days for randomized treatment period and ±5 days for post-treatment follow up period.

Spirometry should be performed at all visits as detailed in Section 9.2.2.1.1, in order to have spirometry performed at approximately the same time of the day at each visit throughout the study.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and participate in follow-up assessments according to the visit schedule until the end of the study with a ±5 day window or up to recovery or stabilization of any AE. At the time of permanent treatment discontinuation, patients will perform the early treatment discontinuation (ETD) visit with all the assessments defined for the EOT Visit 28. However, patients who discontinue early from treatment will not be eligible for the 1-year long-term extension study.

For patients who permanently discontinue the study, under exceptional circumstances where there is no possibility for a patient and parent(s)/caregiver(s)/legal guardian(s) to come to the site for the scheduled follow-up visit, a phone contact may be made after Sponsor's approval is given. During that phone contact, at least information about AEs, concomitant medication and asthma exacerbation events must be collected, and the schedule for these calls should still reflect the visit schedule.

Patients should be reminded that sexually active female patients of reproductive potential are required to practice effective contraception during the entire study duration, while taking dupilumab and for 12 weeks post last IMP dose.

Patients who discontinue early from treatment may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall assessment of antibody titers and clinical presentation at the time of discontinuation.

Recommended Order of Assessments: It is recommended that the order of assessments/procedures (as applicable) outlined below will be adhered to by the Investigator and site staff for every patient at each study visit at the investigative site:

1. PROs including HRQoL
2. Procedures:

Sponsor approval and when applicable, document the site's corrective action plan to prevent future occurrences.

At Screening, parent(s)/caregiver(s)/legal guardian(s) will be asked to provide information on their child's vaccination schedule, and assess whether immunizing their children with any vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza (as per local medical practice) will result in vaccination during the study (see Section 9.3.1.2 for more information).

10.1.2 Screening Visit 1 (Week -4 [± 1 week], or between Day -35 and Day -21)

Following a discussion of participation in the clinical trial, written IAF/ICF (as applicable per national requirements) must be obtained and documented, as described in Section 12.2. The IAF/ICF procedure must be completed prior to any screening assessments and procedures.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number and register screening visit.
- Interview to collect patient demographic information, medical history, asthma-specific medical history (ie, family history of atopy & Ig E mediated disease [particularly maternal], premature birth and/or, low birthweight, exposure to tobacco smoke, recurring viral infections in early childhood), surgical history, prior and concomitant medications and menstruation status for female patients of childbearing potential.
- Interview to collect vaccination information and vaccination plan during the treatment period.
- Review entry criteria to assess eligibility, with special attention to assess the following:
  - Prescribed treatment dosage meets the pre-protocol definition of medium to high-dose ICS (see Appendix A) in combination with a second controller (ie, LABA, LTRA, LAMA, or methylxanthines) for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1.
    Note: patients requiring a third controller medication for their asthma are **not** considered eligible for this study.
  - Patient has experienced, within 1 year prior to Visit 1: 1) Treatment with ≥1 SCS (oral or parenteral) bursts for worsening asthma and/or 2) Hospitalization or an emergency/urgent medical care visit for worsening asthma.
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height).
- Perform physical examination.
- Administer ACQ-IA for children (6 to <12 years old).
  - Verify if ACQ-5 score is ≥1.5.
- Measure exhaled nitric oxide.

- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Assess menstruation status and perform urine dipstick pregnancy test for female patients of childbearing potential (who have commenced menstruating)
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - Dispense Home Dosing Diary parent(s)/caregiver(s)/legal guardian(s) willing and trained to perform home-administration of IMP-injection, and provide instructions on preparation, injection and dose. And review the diary for home dosing. Re-check the instructions on home-administration and dosing and dispense Home Dosing Diary, as applicable.
  - For parent(s)/caregiver(s)/legal guardian(s) unable or unwilling to administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct them to record usage in the electronic diary.
- Remind parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and instruct them to record daily usage in the electronic diary.
- Remind parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit 4 weeks later (± 3 days) and ask patient to come in at approximately the same time of this visit

Protocol-defined severe asthma exacerbation events and LOAC (for detailed definitions see Section 9) are collected as efficacy endpoints on the e-CRF. Only asthma exacerbations which fulfill a seriousness criterion should be reported as an AE (as per Section 10.4.1.2).

For this study, asthma exacerbations should be managed by the Investigators based on their medical judgment and applicable national/international asthma management guidelines.

10.4.1.2 Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited 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 patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

- Cancers diagnosed during the study
- Chronic neurodegenerative diseases (newly diagnosed)

10.4.1.3 Adverse Event of Special Interest

An 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.

- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (refer to Appendix L for the definition of anaphylaxis).
- Severe injection site reactions that last longer than 24 hours.
- An infection that meets at least one of the following criteria:
  - Any serious infection (that meet any of the SAE criteria)
  - Requires parenteral (intravenous, intramuscular, SC) antimicrobial therapy.
  - Requires oral antimicrobial therapy for >2 weeks.
  - Is a parasitic infection.
  - Is an opportunistic infection (see list in Appendix M).

  Note: antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.
- Significant elevation of ALT (Appendix K)
  - ALT >5 × ULN in patients with baseline ALT ≤2 × ULN; or
  - ALT >8 × ULN if baseline ALT >2 × ULN
- Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial (It is an unlikely event to happen but for safety concerns, it is imperative to query pregnancy involving a male patient entered in the trial).
  - It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Section 10.4.1.2).
  - 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.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) 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 AE forms.

- An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice of the intended dose within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

  Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.2 Serious Adverse Events Waived From Expedited Regulatory Reporting to Regulatory Authorities

Not applicable.

10.4.3 General Guidelines for Reporting Adverse Events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- When a safety event is categorized as a primary outcome, the event will be reported as an AE but will be waived from reporting to regulatory authorities provided an agreement has been reached with them.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s). In studies that require the use of combined/multiple IMPs/NIMPs, the GSO with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. The GSO must communicate this decision to the study team for inclusion in the protocol and AE CRF.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected. The duration of poststudy follow-up and reporting of AEs will be specified (eg, until recovery).
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - 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

Table 4 summarizes the reporting timelines for select AEs and laboratory abnormalities.

Table 4 - Summary of Adverse Event Reporting Instructions

Adverse event/laboratory abnormality		Reporting timeframe
Serious adverse event		Within 24 hours
Pregnancy		Within 24 hours
Overdose	Symptomatic	Within 24 hours
	Asymptomatic	Routine
ALT elevation	ALT >5 ULN if baseline ALT is ≤2 ULN	Within 24 hours
	ALT >8 ULN if baseline ALT is >2 ULN	Within 24 hours
	ALT >3 ULN plus total bilirubin >2 ULN	Within 24 hours
Anaphylactic reactions or acute allergic reactions that require treatment		Within 24 hours
Severe injection site reactions that last longer than 24 hours		Within 24 hours
Serious infections or infections that are AESI (see Section 10.4.1.3 and Section 10.6.3)		Within 24 hours

AESI: adverse event of special interest; ALT: alanine aminotransaminase; ULN: upper limit of normal;

10.4.4 Instructions for Reporting Serious Adverse Events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.
- Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for Reporting Adverse Events of Special Interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

10.4.6 Guidelines for Management of Specific Laboratory Abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix K.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- ALT increase
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

In addition, on treatment eosinophil counts >3000 cells/µL (3.0 giga/L) are to be reported as AEs.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IEC/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected (eg, wheezing related to asthma).

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

For safety, the treatment code will be unblinded by the Sponsor for reporting to the Health Authority of any SUSAR and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor.

In case of a SUSAR, Sanofi Global Pharmacovigilance and Epidemiology will utilize XGRID to reveal medication assignment for regulatory reporting requirements for the particular case.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

Allergic reaction is a potential risk associated with the administration of most therapeutic monoclonal antibodies.

Allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Anaphylaxis may represent the most severe form of infusion reaction, but these events may also occur via non-IgE mediated mechanisms (eg, anaphylactoid reactions), or may occur via other immune-mediated mechanisms (eg, cytokine-mediated). Refer to Appendix L "Definition of Anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients must be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Furthermore, the patients will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for at least 30 minutes after administration.

Anaphylactic reactions or, systemic allergic reactions that are related to IMP and require treatment must be reported as an AESI (within 24 hours, for further details, see AESI definition in Section 10.4.1.3 and Appendix L) and study medication should be permanently discontinued. Anti-drug antibodies and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

10.6.2 Severe Injection Site Reactions

Based on the SC mode of administration of high doses of protein and on a higher incidence of local injection site reactions observed at the highest IMP dose level evaluated in adults (300 mg weekly dose), severe injection site reactions, are considered as a potential risk. Patients who experience an injection site reaction must be closely monitored for the possibility of a more intense injection site reaction with a future injection. Any severe injection reaction that lasts over

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size of this study was based on a comparison between dupilumab versus placebo with regard to the primary endpoint of annualized rate of severe exacerbations over 52 weeks of treatment for the 3 populations of interest: patients with baseline blood eosinophils ≥300 cells/μL, patients with baseline blood eosinophils ≥150 cells/μL, and patients with type 2 inflammatory phenotype (baseline blood eosinophils ≥150 cells/μL or baseline FeNO ≥20 ppb), with assuming the number of severe exacerbations follows a negative binomial distribution and a randomization ratio of 2:1.

The sample size calculation assumes a linear discontinuation rate (20% at 1 year), thus the average exposure duration for patients is 0.9 year. The assumed relative risk reductions are based on the results in the phase 3 asthma study EFC13579 (QUEST).

To achieve target sample size for each of the populations stated above, approximately 402 patients in the overall population (268 for dupilumab and 134 for placebo) need to be randomized assuming approximately 86% of the randomized patients have type 2 inflammatory phenotype (baseline blood eosinophils ≥150 cells/μL or baseline FeNO ≥20 ppb), approximately 81% of the randomized patients have baseline blood eosinophils ≥150 cells/μL, and approximately 64% of the randomized patients have baseline blood eosinophils ≥300 cells/μL.

Patients will be randomized (2:1 ratio) to receive dupilumab or matching placebo. After a patient is randomly assigned to dupilumab or matching placebo, the dosage of dupilumab or matching placebo for the patient, 200 or 100 mg SC once q2w, will be determined based on baseline body weight >30 kg or ≤30 kg, respectively.

11.4.2.1 Analysis of Primary Efficacy Endpoint(s)

The estimand of the dupilumab treatment effect compares the annualized rate of severe exacerbation for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo. In this primary approach, off-treatment measurements of patients who prematurely discontinue treatment will be included for the analysis. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits. If a patient stays in study till the end of 52-week treatment period, all severe exacerbation events that happen up to Week 52 will be included in the primary analysis, regardless if the patient is on-treatment or not. If a patient withdraws from study prior to the end of 52-week treatment period, all observed severe exacerbation events up to the last contact date will be included in the analysis, and the observation duration is defined as from randomization to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation and up to Week 52.

The annualized rate of severe asthma exacerbation events will be analyzed using a negative binomial regression model to confirm the effectiveness of dupilumab. The analysis for the annualized severe exacerbation rate will be performed in the type 2 inflammatory phenotype, baseline blood eosinophils ≥300 cells/μL, baseline blood eosinophils ≥150 cells/μL, baseline FeNO ≥20 ppb and full ITT populations using appropriate multiplicity control. When performing the primary endpoint analysis in the type 2 inflammatory phenotype, baseline blood eosinophils ≥150 cells/μL or the full ITT populations, the model will include the total number of events of each patient occurring during the 52 weeks as the response variable, with the treatment group, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<300 cells/ μL, ≥300 cells/μL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), and number of severe asthma exacerbation events prior to the study as covariates. When performing the primary endpoint analysis in the baseline blood eosinophils ≥300 cells/μL population, the baseline eosinophil level will be removed from the model covariates. When performing the primary endpoint analysis in the baseline FeNO ≥20 ppb population, the baseline FeNO level will be removed from the model covariates. Severe asthma exacerbation event prior to the study is defined as treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once or hospitalization or emergency medical care visit for worsening asthma (as defined in this protocol). Log transformed observation duration will be the offset variable.

11.4.2.1.1 Sensitivity Analysis

A supportive analysis to assess the treatment effect of dupilumab if patients adhere to the treatment and background asthma medication as directed is also provided. In this approach, the severe exacerbation events reported after the premature treatment discontinuation will be excluded from the analysis. Any measurement obtained after the first permanent stepping-up of background asthma medication will also be excluded from the analysis. The supportive analysis will be performed in the type 2 inflammatory phenotype and baseline blood eosinophils ≥300 cells/μL populations and will use a negative binomial model with the same set of covariates as specified for the primary analysis in the two populations. This model will include severe exacerbation events occurring during the treatment epoch before any permanent stepping-up of background

asthma medication as the response variable and the log transformed duration of the treatment or from randomization to first permanent stepping-up of background asthma medication whichever is shorter will be the offset variable.

If patients withdraw from the study before Week 52 with severe exacerbation events that may occur after study discontinuation will not be observed, these patients are considered as patients with missing data on severe exacerbation. Number, reasons and timing of the missing data will be summarized by treatment groups. In the primary analysis, all observed data will be used regardless of treatment adherence or increase of asthma background medication. No imputation will be conducted for the missing severe exacerbation information after a patient prematurely withdraws from the study up to Week 52. In addition, sensitivity analyses based on pattern mixture model, placebo based pattern mixture model and tipping point analysis based on the same negative binomial model as being used in the primary analysis may be conducted to assess the robustness of the conclusion of the main model. Details of these sensitivity analyses will be described in the SAP.

11.4.2.1.2 Subgroup Analysis

Subgroup analyses will be performed for the primary endpoints, as appropriate, using the same methods by age group, gender, region, race, baseline ICS (medium/high) dose levels, baseline eosinophil level, baseline FeNO level, background controller medication type at randomization, baseline % predicted FEV1, ACQ-7, baseline body weight, atopic medical condition, age of onset of asthma, and number of severe asthma exacerbation events within 1 year prior to the study. Detailed definition of each subgroup category will be provided in the SAP.

The subgroup analyses (except for the baseline eosinophil levels and baseline FeNO levels) will be conducted for both the type 2 inflammatory phenotype population and baseline blood eosinophils ≥300 cells/μL population; and, the subgroup analyses for the baseline blood eosinophil level and baseline FeNO level will be performed in the full ITT population.

11.4.2.2 Analyses of Secondary Efficacy Endpoints

11.4.2.2.1 Analysis of Change from Baseline in Pre-bronchodilator % Predicted FEV1

The key secondary endpoint, change from baseline in pre-bronchodilator % predicted FEV1 at Week 12, will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The analysis for the key secondary endpoint will be performed in the type 2 inflammatory phenotype, baseline blood eosinophils ≥300 cells/μL, baseline blood eosinophils ≥150 cells/μL, baseline FeNO ≥20 ppb, and full ITT populations. When performing the key secondary endpoint analysis in the type 2 inflammatory phenotype, baseline blood eosinophils ≥150 cells/μL, or the full ITT populations, the model will include change from baseline as response variables, and for treatment, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<300 cells/μL, ≥300 cells/μL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline value, and baseline-by-visit interaction as covariates. When performing the analysis in the baseline blood eosinophils ≥300 cells/μL population, the baseline eosinophil level will be removed from the model

covariates. When performing the analysis in the baseline FeNO ≥20 ppb population, the baseline FeNO level will be removed from the model covariates. Sex, height and ethnicity will also be included as covariates in the models for spirometry parameters. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method using the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline at Weeks 12 will be derived from the mixed-effect model with Kenward and Roger degree of freedom adjustment approach. Treatment comparisons at other timepoints, 8, 12, 24, 36 and 52 week and other timepoints in between will also be provided from the mixed-effect model for descriptive purpose. Data up to Week 52 will be included as response variables.

11.4.2.2.2 Analysis of Time-to-event Variables

Time to first severe asthma exacerbation event (and time to first LOAC; for detailed definitions of primary and secondary endpoints, see Section 9.1 and Section 9.2, respectively) will be analyzed using a Cox regression model with time-to-event as the dependent variable, and treatment, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<300 cells/µL, ≥300 cells/µL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of severe asthma events prior to the study as covariates. The estimated hazard ratio (dupilumab versus placebo) along with its 95% confidence interval will be presented. The Kaplan-Meier method will be used to derive the proportion of patients with a severe asthma exacerbation event at Weeks 12, 24, 36, and 52, specific to each treatment group.

11.4.2.2.3 Analysis of Change from Baseline for Other Continuous Variables

The change from baseline for other continuous endpoints will be analyzed using MMRM in the same fashion as for the endpoint of pre-bronchodilator % predicted FEV1. The covariates to be included are treatment, age, weight (≤30kg, >30kg), region, baseline eosinophil (<300 cells/µL, ≥300 cells/µL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment-by-visit interaction, corresponding baseline value and baseline-by-visit interaction. Sex and height will be included as covariates in the models, if the endpoint belongs to spirometry parameters. Descriptive statistics including number of patients, mean, standard error and LS means will be provided for each timepoint. In addition, differences in LS means, the corresponding 95% CI and the p-value will be derived from the MMRM model for comparison of dupilumab against placebo at each timepoint.

11.4.2.2.4 Analysis of Change from Baseline for Other Categorical Variables

Percentage of patients requiring increase in dose or addition of background medication will be analyzed as a categorical variable. Descriptive statistics by treatment group will be provided including the number and the percentage of patients in each category. Time to the first time requiring increase in dose or addition of background medication may also be provided by the Kaplan-Meier method if there are a sufficient number of patients requiring increase in dose or addition of background medication.

11.4.2.2.5 Sensitivity Analyses

Sensitivity analyses will only be conducted for the key secondary endpoint of change from baseline in pre-bronchodilator % predicted FEV1 at Week 12. A supportive analysis will be provided by applying the same model for the primary analysis with only on-treatment measurements obtained before any permanent stepping-up of the asthma background medication.

A sensitivity analysis based on LOCF will also be provided to assess the robustness of the conclusion from the primary analysis on change from baseline in pre-bronchodilator % predicted FEV1 at Week 12 against missing data. Details of the sensitivity analyses will be further provided in the SAP.

11.4.2.2.6 Subgroup Analysis

To assess the consistency in treatment effects across the subgroup levels, subgroup analyses used in the primary efficacy endpoint will also be performed for the key secondary efficacy endpoint of change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.

The sensitivity analysis and subgroup analysis (except for the baseline eosinophil levels and baseline FeNO levels) for the key secondary endpoint of change from baseline in pre-bronchodilator % predicted FEV1 at Week 12 will be conducted in the type 2 inflammatory phenotype and baseline blood eosinophils ≥300 cells/µL population; and, the subgroup analyses for the baseline blood eosinophil level and baseline FeNO level will be performed in the full ITT population.

11.4.2.3 Multiplicity Considerations

The hypothesis testing on the primary endpoint of annualized severe exacerbation rate will be controlled with a two-sided type I error of 0.05 by incorporating a sequential testing procedure as below:

For US and US reference countries:

- 1st : Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with baseline blood eosinophils ≥300 cells/µL.
- 2nd : Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with baseline blood eosinophils ≥150 cells/µL.
- 3rd : Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with type 2 inflammatory phenotype (baseline blood eosinophils ≥150 cells/µL or baseline FeNO ≥20 ppb).

For EU and EU reference countries:

- 1st: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with type 2 inflammatory phenotype (baseline blood eosinophils ≥150 cells/µL or baseline FeNO ≥20 ppb).

- any AESI leading to permanent study drug discontinuation
- any AESI by maximum intensity, corrective treatment, and final outcome
- cumulative incidence at specified time points (K-M estimates at 1 week, 4 weeks, 12 weeks, 24 weeks and 52 weeks)

Definitions of AESIs and the method to identify AESIs will be specified in the SAP.

11.4.3.1.2 Death

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (treatment emergent period, on-study) and reasons for death summarized on the safety population by treatment received
- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Patient data listings will be provided for all AEs, TEAEs, SAE, AEs leading to study discontinuation, AESIs and deaths.

11.4.3.2 Clinical Laboratory Evaluation, Vital Signs and Electrocardiogram Data

Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, SD, median, Q1, Q3, minimum and maximum. The descriptive by visit analysis will be conducted from the baseline up to the scheduled evaluation visit for all patients disregarding the treatment status of the patients at each visit as long as their data is available.

The proportion of patients who had at least one incidence of PCSA at any time during the treatment-emergent period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

Listings will be provided with flags indicating clinically out-of range values, as well as PCSA values.

11.4.3.3 Humoral Immune Response to Vaccines

For patients who receive vaccination, vaccine response parameters will be summarized by treatment groups with descriptive statistics. These parameters will be defined in the SAP.

11.4.4 Analyses of Systemic Drug Concentration, Anti-drug Antibodies, and Pharmacodynamic Variables

11.4.4.1 Drug Concentration Analysis

Concentrations of functional dupilumab in serum will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by treatment per visit.

Concentrations of functional dupilumab in serum will be used for population PK analysis by non-linear mixed effects modeling if warranted. Additional details of the analysis plan and the results will be provided in a separate document.

11.4.4.2 Anti-drug Antibodies Analysis

The incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%), presented by treatment groups. Listing of ADA titer levels will be provided for patients positive in the ADA assay. Samples that are positive in the ADA assay will be further characterized for the presence of anti-dupilumab neutralizing antibodies.

Plots of concentrations of functional dupilumab will be examined and the potential influence of ADA on individual concentration-time profiles will be evaluated. Assessment of the potential impact of ADA on safety and efficacy may be provided.

Anti-drug antibodies at baseline will be summarized by:

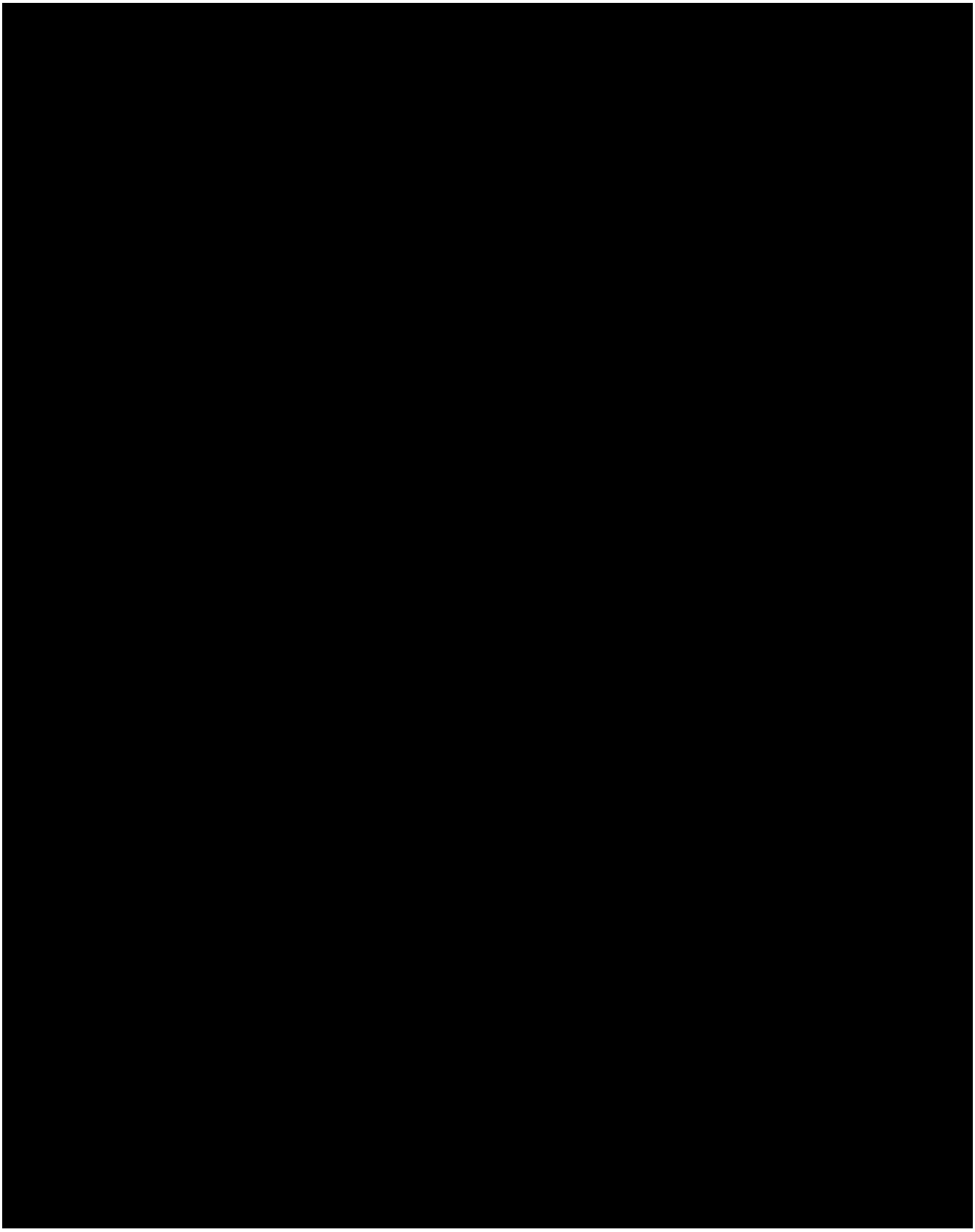
- Number (%) of patients with a baseline sample negative in the ADA assay
- Number (%) of patients with a baseline sample positive in the ADA assay
- The summary statistics (including number, median, Q1, Q3, minimum, and maximum) of the titer for patients positive in the ADA assay at baseline

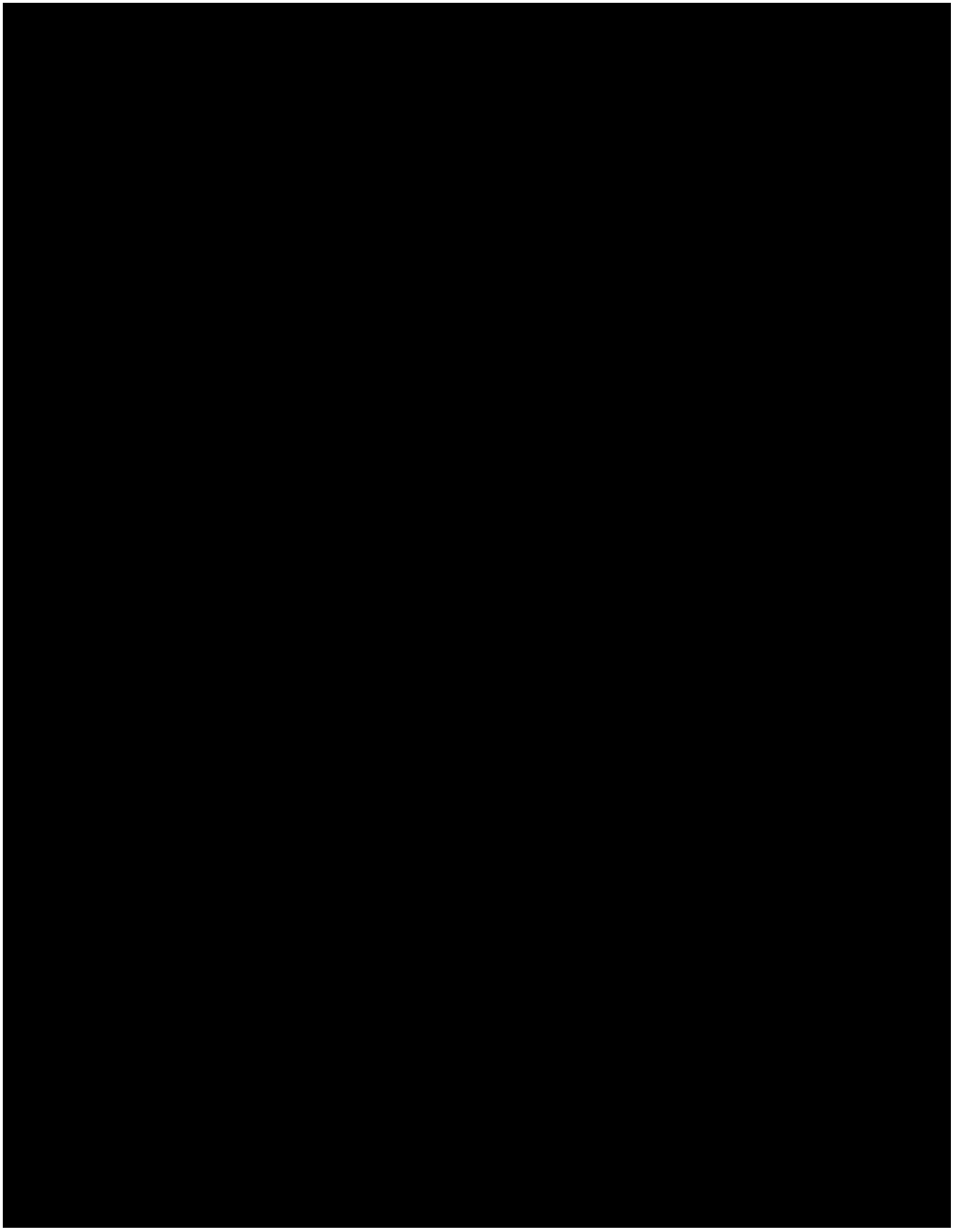
Anti-drug antibody incidence and titer will be provided for the following:

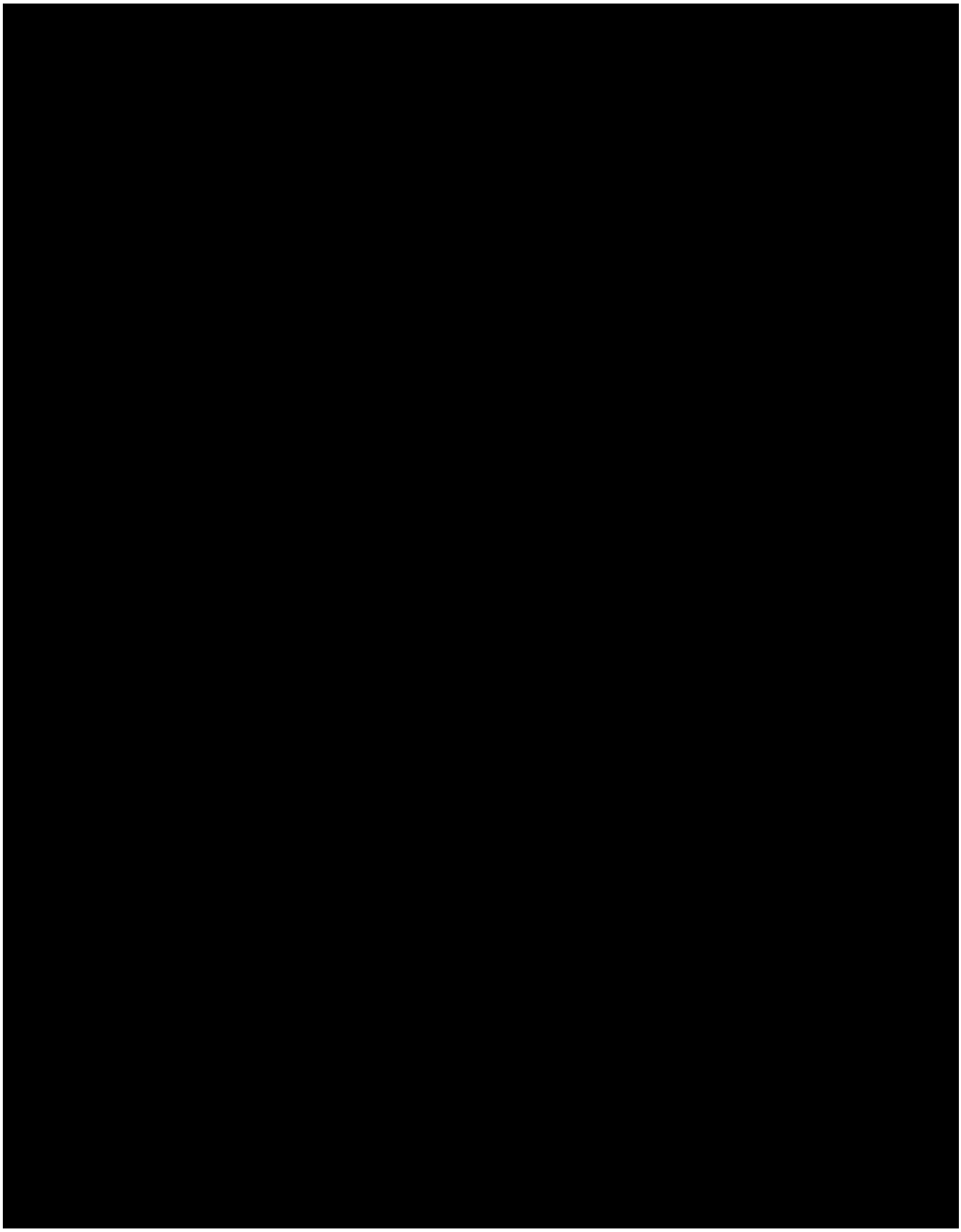
- Number (%) of patients negative in ADA assay at all times
- Number (%) of patients positive in ADA assay at any time
- Number (%) of patients with pre-existing positive response
- Number (%) of patients with treatment-boosted positive response
- Number (%) of patients with treatment-emergent positive response
- Number (%) of patients with transient treatment-emergent positive response
- Number (%) of patients with persistent treatment-emergent positive response
- Number (%) of patients with indeterminate treatment-emergent positive response
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent positive responses

11.6 PLANNED DATABASE LOCK

The database lock is planned based on the time when all randomized patients reach complete week 52 visit or discontinue from the study before week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR (Clinical Study Report). Additional data between database lock and last patient completing last visit will be summarized in a CSR addendum







[redacted]

	SCR[a]	Randomized Treatment Period																											Post-treatment Period[d]		
		RND[b]																										EOT[c]			EOS
Week	**–4 (±1)**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**56**	**60**	**64**
Visit[e]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
Vaccines Record Review / Scheduling[z,aa]	X																														
Any planned vaccination for tetanus, diphtheria, pertussis[z]												<———	X[z]	———>	- - - - - - - - - - - - - - - - - >																
Any planned vaccination for seasonal trivalent / quadrivalent influenza[z]						<———	———	———	———	———	———	———	X[z]	———	———>	- - - - - - - - - - - - - - - - - >															
Blood sample collection[aa] for assessment of IgG response to vaccination					X[aa]			X[aa]						X[aa]						X[aa]								X[aa]			

AE: Adverse event; AESI: Adverse Events of Special Interest ; EQ-5D-Y: EuroQol 5-dimensions questionnaire for children; ETD: early treatment discontinuation visit; FEV1: Forced expiratory volume in 1 second; HRQol: health-related quality of life; IgA: Immunoglobulin A; IgE: IgG: Immunoglobulin E; Immunoglobulin G; IgM: Immunoglobulin M; IVRS: Interactive voice response system; IWRS: Interactive web response system, NO: Nitric oxide; ACQ-IA: Asthma Control Questionnaire–Interviewer Administered; PACQLQ: Pediatric Asthma Caregivers Quality of Life Questionnaire; PAQLQ(S)-IA: Pediatric Asthma Quality of Life Questionnaire With Standardised Activities–Interviewer Administered; PD: Pharmacodynamics; PK: Pharmacokinetics; PRQLQ-IA: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire–Interviewer Administered; PEF: Peak expiratory flow; SAE: Serious adverse event;

a The Screening Period is 4±1 weeks (21-35 days) in duration to collect baseline data on asthma control and assure eligibility criteria. Prior to and during the Screening Period, patients must be on one of the following: stable-dose background therapy of medium-dose inhaled corticosteroid (ICS) with second controller medication (ie, long-acting β2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist (LAMA), or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1.

b Randomization Visit (Visit 2) is defined as Day 1. The randomization will be stratified by eosinophil count (<300 cells/ µL and ≥300 cells/µL) and stable dose-level of ICS (medium/high) at Screening, and by region.

c Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for study visits and participate in assessments according to the visit schedule until the end of the study (EOS) with a ±5 day window or up to recovery or stabilization of any adverse event. At the time of permanent treatment discontinuation, patients will perform the early treatment discontinuation (ETD) visit with all the assessments defined for the end-of-treatment (EOT) Visit 28. However, patients who discontinue early from treatment will not be eligible for the 1-year long-term extension study.
For patients who permanently discontinue the study, under exceptional circumstances where there is no possibility for a patient and parent(s)/caregiver(s)/legal guardian(s) to come to the site for the scheduled follow-up visit, a phone contact may be made after Sponsor's approval is given. During that phone contact, at least information about adverse events (AEs), concomitant medication and asthma exacerbation events must be collected, and the schedule for these calls should still reflect the visit schedule.
Patients who discontinue early from treatment may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall assessment of antibody titers and clinical presentation at the time of discontinuation.

d Eligible patients who complete the Randomized Treatment Period will be offered the opportunity to participate in the 1-year long-term extension study with dupilumab. Patients subsequently enrolled in the 1-year long-term extension study will not participate in the post-treatment period of this trial.

e The visit windows for all subsequent visits post-randomization on Day 1 will be ±3 days during the treatment period and ±5 days during the post-treatment period.

PCSA:	Potentially clinically significant abnormality
PEF:	Peak expiratory flow
ppb:	Parts per billion
PROs:	Patient reported outcomes
PRQLQ-IA:	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire – Interviewer Administered
PT:	Preferred term
q2w:	Once every 2 weeks
q4w:	Once every 4 weeks
SAE:	serious adverse event
SAP:	Statistical analysis plan
SC:	Subcutaneous(ly)
SCS:	Systemic corticosteroids
SD:	Standard deviation
SEM:	Standard error of the mean
SOC:	System Organ Class
TARC:	Thymus and Activation Regulated Chemokine
TBV:	Total blood volume
TEAEs:	Treatment-emergent adverse events
ULN:	Upper Limit of Normal

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Children 6 to <12 years of age, with a physician diagnosis of persistent asthma for ≥12 months prior to screening based on clinical history and examination, pulmonary function parameters according to Global initiative for asthma (GINA) 2015 Guidelines and the following criteria:

- Existing background therapy of medium-dose ICS with second a controller medication (ie, LABA, LTRA), Long acting muscarinic antagonist (LAMA), or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1 (dose levels as per Appendix A).
- Pre-bronchodilator FEV1 ≤95% of predicted normal or pre bronchodilator FEV1/forced vital capacity (FVC) ratio <0.85 at Screening and Baseline Visits.
- Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puffs with metered-dose inhaler [MDI]) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication if tolerated by the patient).

  Note: A maximum of 3 visits to meet the qualifying criterion of reversibility may be made during the screening period and prior to the patient's randomization.

  For patients that will have an additional and last attempt of reversibility testing (for eligibility) at the Baseline Visit 2 before patient's randomization into the interactive response technology (IRT), the post-bronchodilator FEV1 will come from the result of this reversibility test.

  Note: Documented reversibility or positive airway hyper-responsiveness to methacholine within 12 months prior to Screening V1 is considered acceptable.
- Must have experienced, within 1 year prior to Screening Visit 1, defined as any of the following events:
  a) Treatment with a systemic corticosteroid (SCS, oral or parenteral) prescribed by a healthcare professional for worsening asthma at least once or,
  b) Hospitalization or emergency medical care visit for worsening asthma.
- Evidence of uncontrolled asthma, with at least one of the following criteria during the 4 (±1)-week Screening Period:
  c) Asthma Control Questionnaire–Interviewer Administered (ACQ-IA) ACQ-5 score ≥1.5 on at least one day of the Screening Period including V2.
  d) Use of reliever medication (ie, albuterol/salbutamol or levalbuterol/levosalbutamol), other than as a preventive for exercise induced

For patients experiencing a deterioration of asthma during the study, the ICS dose may temporarily be increased up to 4-fold (recorded as LOAC event) for a maximum of 10 days, as indicated and upon recommendation of the physician and/or Investigator. Treatment may then be changed to SCS (severe exacerbation event) or revert back to the original ICS dose depending on the asthma symptoms progression.

If a patient experiences 2 or more severe asthma exacerbation events anytime during the study, a permanent change (ie, step up in medium- to high-dose ICS or addition of second controller for patients on high-dose ICS monotherapy; see Appendix A and Appendix B) on their stable-dose background controller medication may occur, as indicated and upon recommendation of the physician and/or Investigator.

Screening Period

Prior to and during the Screening Period, patients must be on one of the following: stable-dose background therapy of medium-dose ICS with a second controller medication (ie, LABA, LTRA, LAMA, or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months, with a stable dose background treatment for ≥1 month prior to Screening Visit 1.

If patients take 2 different ICS, the total daily dose of ICS should be calculated, to evaluate the eligibility criteria on daily dose of ICS, which will be still considered as one controller. Please refer to medium and high-dose of ICS in Appendix A.

If the Investigator, based on his/her medical judgment, decides to optimize a patients use of asthma reliever and/or background controller medications prior to the Screening Visit, any changes in ongoing asthma medications must occur more than 1 month in advance of the Screening Visit Day 1, in order to maintain a stable dose for at least 1 month prior to Day 1 (Section 7.1). The introduction of new controller medications must occur at least 3 months prior to Screening with a stable dose for at least 1 month (Section 7.1).

Randomized Treatment Period

During this period, patients will continue to take their controller medication(s) used during the Screening Period. The dose of baseline regimen should not be changed, and no adjustments will be made unless the patient experiences 2 or more severe exacerbations events at any time during the study (in which case a step up of controller medication may be allowed). This will be recorded in the eDiary.

Patients may be placed on systemic corticosteroids at any time as clinically indicated based on the presence of symptoms consistent with a severe asthma exacerbation event, as per the Investigator's judgment.

Post-treatment Period

Upon completing the randomized treatment period, patients not continuing with the long-term, open-label extension study will enter the Post Treatment Period and will proceed to be treated

Reversibility is an inclusion criterion, but if the subject does not meet this reversibility criterion at Screening Visit 1, up to 2 additional assessments can be performed at any time between Screening and Baseline Visit 2.

For post-bronchodilator FEV1 at remaining study visits following randomization, the measure should follow the steps as that at screening test for reversibility validation except a maximum of 4 puffs of reliever medication can be used. If other attempt for reversibility test was performed at Baseline Visit 2, then the post-bronchodilator FEV1 will come from the result of this reversibility test.

9.2.2.2 Disease-specific, Daily Efficacy Assessments

9.2.2.2.1 Electronic Diary/PEF meter

On a daily basis throughout the study, the patient uses an electronic diary/PEF meter to:

- Measure morning and evening PEF.
- Respond to the morning and evening asthma symptom scale questions.
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief.
- Record the number of inhalations/day of background product used.
- Record the number of nocturnal awakenings due to asthma symptoms requiring the use of reliever medication.
- Record oral steroids use for exacerbation event.

At Screening (Visit 1), patients and parent(s)/caregiver(s)/legal guardian(s) will be issued an electronic diary/PEF meter. Parent(s)/caregiver(s)/legal guardian(s) will be instructed on the use of the device, and written instructions on the use of the electronic PEF meter will be provided to the parent(s)/caregiver(s)/legal guardian(s). In addition, the Investigator will instruct the parent(s)/caregiver(s)/legal guardian(s) on how to record the following variables in the electronic PEF meter:

- AM PEF performed within 15 minutes after arising (between 5:30 AM and 11:59 AM) prior to taking any albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication)
- PM PEF performed in the evening (between 5:30 PM and 11:59 PM) prior to taking any albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication)
- Patient/Parent(s)/caregiver(s)/legal guardian(s) should try to withhold albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication for at least 6 hours before performing the PEF measurements.
- Three PEF efforts will be performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation

Baseline AM PEF will be the mean AM measurement recorded for the 7 days prior to the first dose of investigational product, and baseline PM PEF will be the mean PM measurement recorded

9.2.2.4 Patient Reported Outcomes, Including Health Related Quality of Life (Secondary Endpoints)

Patients will be administered the following PRO questionnaires by their parent(s)/caregiver(s)/legal guardian(s) or with their help. The interviewer administered versions are only for children: ACQ-IA, paediatric asthma quality of life questionnaire (PAQLQ[S]-IA) and will be administered by an interviewer (clinic staff designated by Investigator).

9.2.2.4.1 Asthma Control Questionnaire–Interviewer Administered

The ACQ-IA was designed to measure both the adequacy of asthma control and change in asthma control, which occurs either spontaneously or as a result of treatment, and will be used for children 6 years to <12 years old at Screening.

9.2.2.4.1.1 ACQ-7-IA (Asthma Control Questionnaire–Interviewer Administered, 7-question version)

The Asthma Control Questionnaire–Interviewer Administered, 7-question version (ACQ-7-IA) has 7 questions, with the first 5 items of ACQ-7 (ACQ-5-IA score) addressing 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. And with 2 questions on overall reliever medication use 6) short-acting bronchodilator use, and – after spirometry assessment – current asthma status: 7) predicted bronchodilator use of FEV1 (pre-bronchodilator use, % and % predicted use).

Patients and/or parent(s)/caregiver(s)/legal guardian(s) are asked to recall how their asthma and/or their child's asthma, respectively, has been during the previous week and to respond to the symptom questions 1) to 6) on a 7-point scale (0 = no impairment, 6 = maximum impairment).

After spirometry assessment, patients and/or parent(s)/caregiver(s)/legal guardian(s) are asked to recall how their asthma and/or their child's asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale (0=no impairment, 6= maximum impairment). Clinic staff scores the % predicted FEV1 on a 7-point scale based on the pre-central reading spirometry result displayed immediately after the testing. Then, the questions are equally weighted and the global ACQ-7 score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled) (see Appendix F).

Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients 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 MCID defined by the developer.

For statistical analysis, ACQ-7 global score is calculated by the sponsor using the BMS post central reading value of the %predicted FEV1 for the question 7 of the questionnaire.

Measurement properties such as reliability and ability to detect change have been documented in the literature.

Table 1 - Eligibility interpretation for hepatitis serology

Hepatitis Serology Result	Protocol Action
HBs Ag positive or indeterminate	Excluded
HBs Ab positive, HBs Ag negative, HBc Ab negative	Eligible
IgM HBc Ab positive	Excluded
Total-HBc Ab positive (with or without HBs Ab positive)	Test for HBV DNA • If HBV DNA positive: excluded • If HBV DNA negative/not detected[a]: eligible
HCV antibody positive	Test for HCV RNA • If HCV RNA positive: excluded • If HCV RNA negative/not detected: eligible

a It is recommended that patients who are receiving potentially immunosuppressive therapy and are IgG HBcAb positive and HBV DNA negative undergo surveillance HBV DNA studies every 1-3 months depending upon the individual potential therapeutic risk and comorbidities. If necessary, a hepatologist should be consulted on a case-by-case basis.
HBc Ab: Hepatitis B core antibody; HBs Ab: HBs Ab: Hepatitis B surface antibody; HBs Ag: Hepatitis B surface antigen; HBV DNA: Hepatitis B virus DNA; HCV RNA: Hepatitis C virus RNA.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix K.

9.2.3.6 Other Safety Laboratory Tests

9.2.3.6.1 Serum Immunoglobulins and Subtypes

Serum immunoglobulins: quantitative immunoassays for total IgG, IgG subclasses 1–4, IgM, and IgA.

Please note that Total IgE, antigen-specific IgE, and antigen-specific IgG4 are assessed as pharmacodynamic parameters (eg, to determine the change from Baseline in IgE/IgG4 ratio; see Section 9.4.2).

As a precaution for maintenance of treatment blinding, results for immunoglobulins will not be released to Investigators during the study, unless required for investigation of other safety findings in individual patients.

9.2.3.7 Pregnancy Test

A urine pregnancy test will be performed at Screening (Visit 1) in female patients of childbearing potential who have commenced menstruating, and a urine dipstick pregnancy test will be performed at Visit 2 prior to randomization and other clinic visits prior to administration of IMP. A negative result must be obtained at Visit 1 and 2 prior to randomization. Refer to Section 1.2 Study Flow Chart for the schedule of pregnancy tests performed throughout this study. Those female patients who commence initial menstruation during the study will be similarly monitored with urine dipstick pregnancy tests and contraception consulting for the duration of the study.

Scheduled blood sample collection for pre- and post-vaccine antibody titers, for both vaccinations (ie, any tetanus, diphtheria and pertussis and/or seasonal trivalent/quadrivalent influenza) should be drawn within 8 weeks prior to vaccination and at 3-4 weeks (up to 6 weeks) after the respective vaccination(s); however, all blood titer samples must be drawn between Week 6 and Week 50 (ie, Visit 5 and Visit 27, respectively).

Depending on patient's vaccination schedule during the course of this study, every effort should be made to draw pre-vaccination titers at either Weeks 6, 12, or 24 (V5, V8, V14) of the Randomized Treatment Period, and to draw post-vaccination titers at either Weeks 12, 24, 36 or 50 (V8, V14, V20, V27) of the Randomized Treatment Period (see Study Flow Chart Section 1.2).

For patient(s) requiring urgent/emergency vaccination with any seasonal trivalent/quadrivalent influenza and/or any tetanus, diphtheria and pertussis vaccine (eg, flu season approaching, animal bite, emergency room standard procedures, etc) between Week 6 and Week 44 (ie, Visit 5 and Visit 24, respectively), the actual vaccination(s) may be given by physicians or qualified caregivers outside the study clinic; however, every effort should be made to obtain blood samples for pre- and post-vaccine antibody titers at scheduled draws as described above. Should vaccination be unable to be planned in accordance with other study blood draws (eg, tetanus vaccination for accidental puncture wounds, etc) as outlined above, at the discretion of the Investigator and with agreement of patient parents or caregiver, additional blood draws may be performed to obtain pre-vaccination and post-vaccination titers.

9.3.1.3 Biomarker endpoints

- Change from baseline in fractional exhaled nitric oxide (FeNO) at Week 12.

Fractional exhaled nitric oxide (FeNO) will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour. Further details on the procedure for measuring exhaled nitric oxide with NIOX will be provided in a separate instruction manual.

9.4 EXPLORATORY ENDPOINTS

9.4.1 Exploratory Endpoints

- Change from baseline in blood biomarkers (TARC and serum total IgE).
- [redacted]
- The proportion of patients requiring a permanent step up in background controller medication after 2 or more severe asthma exacerbation events.
- To evaluate the effect of dupilumab on additional PROs:
  - Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) score, for caregivers of children ≥7 years old at Randomization Visit 2

9.4.2.3 Patients Requiring a Permanent Step Up in Background Controller Medication After 2 or More Severe Asthma Exacerbation Events.

For this study, severe asthma exacerbation events should be managed by the Investigators based on their medical judgment and applicable national/international asthma management guidelines, and as outlined in this protocol:

For patient(s), who experience 2 or more severe asthma exacerbation events anytime during the Treatment Period, a permanent change (step up in medium-to high-dose ICS or addition of second controller for patients on high-dose ICS monotherapy) see Appendix A and Appendix B) on their stable-dose background controller medication may occur, as indicated and according to the respective Investigator's medical judgment and direction.

The proportion of all patients with any of these treatment adjustments will be compared by treatment arm.

a) ECG
b) FeNO levels
c) Spirometry
d) Reversibility/Post-bronchodilator FEV1
e) Electronic diary download

3. Safety and laboratory assessments
4. IMP administration

10.1 VISIT SCHEDULE

10.1.1 Screening Period (Week -5 to Week 0, maximum 35 days prior Day 0)

Prior to all screening assessments, the patient and the parent(s)/caregiver(s)/legal guardian(s) must sign and date the Ethics Committee (EC) approved ICF/IAF. The patient assent should be obtained depending on his/her maturity of understanding study associated information. All patient(s)/parent(s)/caregiver(s)/legal guardian(s) will receive information on the study objective(s) and procedures from the Investigator. [redacted]

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol (see Section 1.2), it is possible for them to be performed over more than 1 site visit if necessary, as long as the screening visit window prior to randomization (Day 1) is respected. 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 to be likely to return to acceptable range for study inclusion within the screening visit window (4 [±1] weeks or 28-35 days) prior to Day 1. In such an event the patient/parent(s)/caregiver(s)/legal guardian(s) do not need to sign a new ICF/IAF and be allocated a new patient number within this same screening window.

Patients that fail the initial screening for exclusion criteria, eg, concomitant medications, may be re-screened for study eligibility one additional time (as described in Section 8.4). For patients re-screened a new ICF/IAF, as applicable, must be signed by patient/parent(s)/caregiver(s)/legal guardian(s), and a new patient number will be allocated. All of the Visit 1 procedures must be repeated (refer to Section 8.4 for further instructions related to re-screening).

Patients that fail the Screening Visit due any unforseen administrative or logistic reason (eg, electronic diary/spirometry equipment malfunction, no IMP, etc), or patient-related/site personnel-related unintentional errors, may be re-screened one time after approval is granted by the Sponsor's clinical study director. In every case of re-screen allowance due to technical equipment malfunction and/or unintentional human error(s), the Study Investigator must document receipt of

  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.

- Perform spirometry.

Entry criteria at Visit 1 include the requirement of a specific FEV1 and demonstration of reversibility as specified in Section 7.1. See below for additional directions.

  - Spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
  - Pre-bronchodilator FEV1 must be ≤95% of predicted normal or pre-bronchodilator FEV1/FVC ratio <0.85.

- Establish reversibility
  - Reversibility must be at least 10% in FEV1 after 200 to 400 mcg (2 to 4 puffs with MDI) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levalbuterol/levosalbutamol reliever medication (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication if tolerated by the patient).
    Note: A total of 3 visits to meet the qualifying criterion of reversibility may be made between the Screening Visit 1 and up to the day of the actual Baseline Visit 2.
    Note: Documented reversibility or positive airway hyperresponsiveness to methacholine within 12 months prior to Screening V1 is considered acceptable.
- Perform 12-lead ECG
- Obtain blood samples for screening clinical laboratory determinations:
  - Hematology (see Section 9.2.3.5 for details)
  - Serum chemistry (see Section 9.2.3.5 for details)
- Obtain blood samples for screening laboratory evaluation of hepatitis screen HBs-Ag, HBs-Ab, HBc Ab, HCV-Ab, HIV screen (Anti-HIV-1 and HIV-2 antibodies) and ANA.
- Obtain urinalysis test (dipstick)
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating)
- Dispense electronic diary/PEF meter, provide instructions for daily use, and remind patient and their parent(s)/caregiver(s)/legal guardian(s) to bring the device to the next visit.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct them and their parent(s)/caregiver(s)/legal guardian(s) to record usage in the electronic diary.

10.1.11 Visit 14 (Week 24 [± 3 days])

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height)
- Perform physical examination
- Urinalysis
- Assess menstruation status and perform urine dipstick pregnancy test for female patients of childbearing potential (who have commenced menstruating)
- Administer ACQ-7
- Administer all additional PROs:
  PAQLQ(S)-IA, PRQLQ-IA, and PACQLQ :
  EQ-5D-Y for children.
- Administer HCRU
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
  - Post-bronchodilator FEV1 should be determined.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Perform blood sampling for the following tests:
  - Clinical laboratory testing (hematology/biochemistry)
  - Serum immunoglobulins (total IgG, IgG subclasses, IgM and IgA)
  - Systemic drug concentration,
  - ADAs
  - Biomarker set, total IgE, and antigen-specific IgE, and antigen-specific IgG4 panel.
  - [redacted]
  - Blood samples for pre-vaccination antibody titers for the patient(s) scheduled to receive vaccination (ie, any tetanus, diphtheria, pertussis and/or seasonal

24 hours will be reported as an AESI with immediate notification. IMP must be temporarily interrupted until the clinical study director (CSD) has evaluated the case. ADA and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

Prophylactic treatment/premedication for an injection site reaction is not permitted.

10.6.3 Infections

Some biologic therapies have been associated with an increased risk of infection, including opportunistic infections. As a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness.

A complete diagnostic work-up should be performed (ie, cultures for fungi and/or mycobacteria other than tuberculosis, histopathological or cytological evaluation, antigen detection and serum antibody titers). Patients should be referred to an infectious disease specialist if deemed necessary for diagnostic work up and appropriate treatment.

Infections or infestations that do not respond to medical treatment should have study drug discontinued until the infection is resolved.

For any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (See Section 10.3.2) patients must be permanently discontinued from study medication.

Infections as defined in Section 10.4.1.3 should be reported as AESIs within 24 hours.

Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 activation of their respective receptors, it inhibits the T-helper 2 (Th2) cytokines production. Infections with a diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte responses. The Th2 response is characterized by production of IL-4, IL-13 and IL-5, subsequently generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a number of helminthic parasitic diseases. The eosinophilic response to helminths is determined both by the host's immune response and by the parasite, including its distribution, migration, and development within the infected host. Therefore, patients treated with dupilumab may potentially have an increased risk of parasitic infection.

In order to minimize this risk, any patient with an active parasitic infection should be excluded from the study (see Section 7.2.3). Similarly, patients with suspected parasitic infection, or those at high risk of parasitic infection are also excluded, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization. During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/or residence in endemic areas, especially when conditions are conducive to infection (eg, extended stay, rural or heavily populated informal settlements, lack of running water, consumption of uncooked, undercooked, or otherwise

Randomization will be stratified by ICS dose (medium-dose versus high-dose) and eosinophil count (<300 cells/µL versus ≥300 cells/µL) at Screening, and by region (Latin America: Argentina, Brazil, Colombia, Chile and Mexico; Eastern Europe: Poland, Hungary, Romania, Lithuania, Turkey, Russia and Ukraine; Western Countries: Australia, Canada, Italy, South Africa, Spain, and USA). The final definition of region may be updated in the SAP, if additional countries are included in the study. If during the study, additional countries are included, necessary changes will be made to the randomization algorithm. These changes will be documented in the SAP.

Note that if any change is made to the definition of stratum in the future, particularly, the definition of region, the changes in the region definition will be included in SAP and the IVRS will be reconfigured to ensure a correct randomization according to the new definition.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and whose parent(s) or legal guardian signed the pediatric informed consent.

Randomized patients consist of all patients with a treatment kit number allocated and recorded in IVRS database, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

The safety experience of patients treated and not randomized will be reported in the safety population according to the actual treatment received.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy Populations

The full intent-to-treat (ITT) population is defined as all randomized patients.

Type 2 inflammatory phenotype population is defined as the randomized patients with baseline blood eosinophils ≥150 cells/µL or baseline FeNO ≥20 ppb.

Baseline blood eosinophils ≥300 cells/µL population is defined as the randomized patients with baseline blood eosinophils ≥300 cells/µL.

Baseline blood eosinophils ≥150 cells/µL population is defined as the randomized patients with baseline blood eosinophils ≥150 cells/µL.

All efficacy endpoints will be analyzed based on both the type 2 inflammatory phenotype population and the population with baseline blood eosinophils ≥300 cells/µL.

- 2nd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with baseline blood eosinophils ≥150 cells/µL.
- 3rd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with baseline blood eosinophils ≥300 cells/µL.

Multiplicity control for any secondary endpoints if considered will be specified in the SAP. Otherwise, nominal p-values will be provided.

11.4.2.4 Handling of Missing Data

If patients withdraw from the study before Week 52 with severe exacerbation events that may occur after study discontinuation (not being observed or without any FEV1 measurements available after withdrawal), these patients are considered as patients with missing data on severe exacerbation or on FEV1 % predicted. Number, reasons and timing of the missing data will be summarized by treatment groups. In the primary analysis for the primary endpoint of severe exacerbation, all observed data will be used regardless of treatment adherence or increase of asthma background medication. No imputation will be conducted for the missing severe exacerbation information after a patient prematurely withdraws from the study up to Week 52. In the primary analysis for the key secondary endpoints of change from baseline in FEV1 % predicted, all data up to Weeks 12 will be included in MMRM model. No additional imputation will be conducted.

In addition, sensitivity analyses for the primary endpoint and the key secondary endpoints may be performed based on a careful examination of the reason and pattern of missing data as described in Section 11.4.2.1.1 and Section 11.4.2.2.5. Further details will be specified in the SAP.

11.4.3 Analyses of Safety Data

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety population according to the following observation period definition.

The observation period will be divided into 4 epochs:

- The screening epoch is defined as the time from the signed informed consent date up to the time prior to first administration of the IMP.
- The treatment epoch is defined as the time from the first administration of the IMP to the last administration of the IMP + 14 days
- The residual treatment epoch is defined as the time from the last administration of the IMP + 15 days to the last administration of the IMP + 98 days.
- The post-treatment epoch is defined as the period of time starting the day after the end of the TEAE period up to the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and AESIs).

The TEAE period will include both treatment and residual treatment epochs.

The minimum titer for samples positive in the ADA assay is based on the minimum required dilution of the assay. It will be classified as

- Low (Titer <1000)
- Moderate (1000≤Titer ≤10 000)
- High (Titer >10 000)

11.4.4.3 Pharmacodynamics and Phenotyping

The values to be used as baselines will be those collected at Visit 2 (Day 1). If any of the scheduled assessments on Day 1 are technically disqualified (eg, insufficient sample), then values determined in any other samples collected prior to the first IMP administration can be used as baseline.

For all parameters, raw data, absolute changes from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point.

Summary plots (mean ± SEM) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment group.

As part of exploratory analysis, correlations between the baseline values for biomarkers and efficacy endpoints will be assessed.

11.4.5 Analyses of Patient Reported Outcomes (Health-related Quality of Life/Health Economics Variables)

Patient reported outcome variables collected in this study include the ACQ-IA questionnaire ACQ-7 score, PAQLQ(S)-IA score, PACQLQ score, and PRQLQ-IA score (in those with history of allergic rhinitis). The change from baseline for these endpoints will be analyzed using MMRM in the same fashion as for the endpoint of pre-bronchodilator % predicted FEV1. The covariates to be included are treatment, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<300 cells/µL, ≥300 cells/µL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment-by-visit interaction, corresponding baseline value and baseline-by-visit interaction. Descriptive statistics including number of patients, mean, standard error and LS means will be provided for each timepoint. In addition, differences in LS means, the corresponding 95% CI and the p-value will be derived from the MMRM model for comparison of dupilumab against placebo at each timepoint. Note that PRQLQ-IA score (in those with history of allergic rhinitis) will only be analyzed for patients with the history of allergic rhinitis.

11.5 INTERIM ANALYSIS

There is no interim analysis planned for this study.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub-investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient who is ≥6 years and his/her parent(s)/caregiver(s)/legal guardian(s) of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All patients/parent(s)/caregiver(s)/legal guardian(s) should be informed to the fullest extent possible about the study, in their language and in terms they are able to understand.

It is the responsibility of the Investigator or designee (if acceptable by local regulations) to obtain written informed assent (IA) from each patient ≥6 years of age (or above an age determined by the IRB/IEC and in according with the local regulations and requirements), and written ICF from each patient's parent(s)/caregiver(s)/legal guardian(s), prior to the patient's participation in the study, and prior to initiating any screening procedures. The written IAF/ICF should be signed and dated by the patient(s) and parent(s)/caregiver(s)/legal guardian(s), respectively.

Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF as determined by the IRB/IEC and in accordance with the local regulations and requirements.

- Patient(s)/parent(s)/caregiver(s)/legal guardian(s) who can write but cannot read will have the assent/consent form read to them before writing their name on the form
- Patient(s)/parent(s)/caregiver(s)/legal guardian(s) who can understand but who can either write nor read will have the informed assent/consent form read to them in presence of an impartial witness, who will sign and date the assent/consent form to confirm that informed consent was given.

The original of each completed informed assent/consent form (IAF/ICF) must be retained by the Investigator as part of the patient's study record and a copy of the signed assent/consent form must be given to the patient/patient's parent(s)/caregiver(s)/legal guardian(s).