AMENDED CLINICAL TRIAL PROTOCOL 06

COMPOUND: DUPILUMAB/SAR231893

One year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study

STUDY NUMBER: LTS14424

STUDY NAME: LIBERTY ASTHMA EXCURSION

VERSION DATE / STATUS: 21-Dec-2021 / APPROVED

Version Number:	1	EudraCT IND Number(s) NCT WHO universal trial number:	2017-003317-25 105379 NCT03560466 U1111-1200-1757
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 06	Japan only	21-Dec-2021, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 05	Japan only	01-Feb-2021, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 04	All	15-Apr-2020, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 03	All	12-Dec-2019, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 02	All	09-Jul-2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01 (br)	Brazil only	14-Mar-2018, version 1 (electronic 1.0)
Protocol Amendment 01 (br)	Brazil only	14-Mar-2018, version 1 (electronic 1.0)
Original protocol		07-Nov-2017, version 1 (electronic 1.0)

Overall Rationale for the Amendment

The purpose of this amendment is to remove the DMC and clarify the use of controller medication in the substudy of Japanese patients outlined in Section 17.7.2 (Country specific requirements for Japan).

Protocol amendment summary of changes table

Section # and Name	Description of change	Brief Rationale
Section 17.7.2.7.2.1 Inhaled corticosteroids alone or in combination with a second controller Section 17.7.2.9 Study procedures / Section 17.7.2.9.1.4 Open-label treatment period (Week 2 to Week 52 [Visits 2-10])	Change in the management of controller medications, to clarify the stability of dose and regimen of asthma background controller medication during the course of the treatment period.	Align the background controller therapy with Phase 3 VOYAGE study. Decrease the impact of medication changes on efficacy outcomes (primary endpoint of substudy is efficacy [Week 12 ppFEV1]).
Section 17.7.2.5.3 data monitoring commitee Section 17.7.2.8.3.1 Long-term safety and tolerability	Removal of the data monitoring committee review	Dupilumab demonstrated an acceptable safety profile in global phase 3 program and is now approved for asthma in this age group in the United States. The open-label study will be monitored by the Sponsor according to the global safety montoring plan.
17.7.2.9.1.3 Enrollment: Visit 1 (Week 0, Day 1)	Change in the visit flow.	Clarification of listing order to ensure appropriate visit flow.

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
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OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

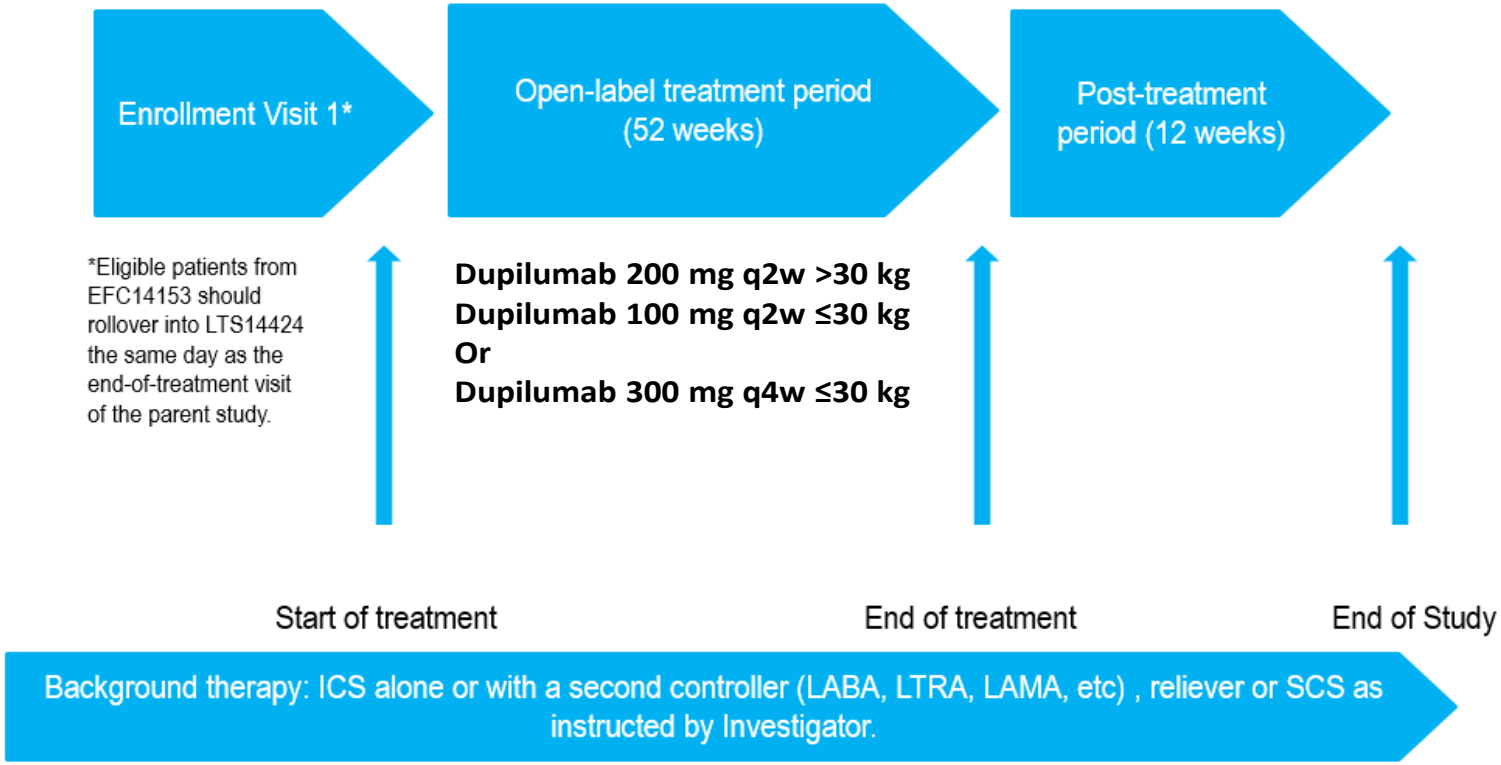
COMPOUND: Dupilumab	**STUDY No.: LTS14424**
TITLE	One year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary objective:** • To evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (EFC14153). **Secondary objective(s):** • To evaluate the long-term efficacy of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study. • To evaluate dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study with regard to: - Systemic exposure, - Anti-drug antibodies (ADAs), - Biomarkers.
STUDY DESIGN	Multinational, multicenter, open-label, single arm, 1-year treatment study evaluating dupilumab given subcutaneously (SC) for a period of 52 weeks. The clinical trial consists of 3 periods: • **Enrollment**: Eligible patients from EFC14153 will rollover into LTS14424 the same day as the end-of-treatment (EOT) visit of the parent study. In the specific situation of COVID-19 pandemic, for those patients that are not able to present to sites for the EOT visit, roll-over into LTS14424 may also be done at the same day as the end of study (EOS) visit of the parent study or up to 12 weeks after EOS visit of Study EFC14153. • **Treatment period**: 52 weeks open-label treatment. • Post-treatment period: 12 weeks. Upon completion of the treatment period (or following early discontinuation of investigational medicinal product [IMP]), patients will continue into the post-treatment period. During the post-treatment period, patients will receive their background controller regimen based on Investigator's judgement.

STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Pediatric patients with asthma who completed the treatment in a dupilumab asthma trial (EFC14153) (specifically for Brazil see Section 17.7.1). Patients who are not able to complete their treatment in Study EFC14153 due to the COVID-19 pandemic will be allowed to enroll into Study LTS14424. Patients who enroll in LTS14424 after completing the EFC14153 EOS visit should have eligibility for LTS14424 reevaluated including background medication check and laboratory assessments (including CBC with differential and basic chemistry) within 1 month prior to LTS14424 Visit 1. I 02. Signed written informed consent/assent. **Main Exclusion criteria:** E 01. Any chronic lung disease other than asthma (for example cystic fibrosis, bronchopulmonary dysplasia) which may impair lung function. E 02. Inability to follow the procedures of the study/noncompliance (for example due to language problems or psychological disorders). E 03. Patients receiving concomitant treatment or required a new concomitant treatment prohibited in the study at Enrollment visit. E 04. Patients who experienced any hypersensitivity reactions to IMP in a previous dupilumab study, which, in the opinion of the Investigator, could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient. E 05. Any abnormalities or adverse events at enrollment that per Investigator's judgment would adversely affect patient's participation in this study or would require permanent IMP discontinuation. Examples: Patients diagnosed with active parasitic infection (helminthes), suspected or high risk of parasitic infection, active tuberculosis (TB), invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidiomycosis, pneumocystocis, aspergillosis), despite infection resolution' or unusually frequent, recurrent or prolonged infections.
Total expected number of patients	Approximately 354
STUDY TREATMENT(s)	
Investigational medicinal product(s)	Dupilumab
Formulation:	**Dupilumab for children ≤30 kg:** 150 mg/mL in prefilled syringe to deliver a dose of 100 mg q2w in a 0.67 mL SC injection. **Or** **Dupilumab for children ≤30 kg:** 150 mg/mL in prefilled syringe to deliver a dose of 300 mg q4w in a 2 mL SC injection.

	Dupilumab for children >30 kg: 175 mg/mL in prefilled syringe to deliver a dose of 200 mg q2w in a 1.14 mL SC injection.
Route(s) of administration:	Subcutaneous injection
Dose regimen:	Dupilumab 200 mg SC q2w for children with body weight >30 kg and 100 mg SC q2w or 300mg q4w for children with body weight ≤30 kg. For children with body weight ≤30 kg receiving 100 mg q2w, the dupilumab dose will be changed to 300 mg q4w at one planned or unscheduled site visit only if the visit occurs more than 8 weeks before the planned end of the treatment period (switch to q4w dose regimen to occur at site visit Week 0 or 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44). Otherwise, they will continue on 100 mg q2w. All newly enrolled children with body weight ≤30 kg will take 300 mg q4w. At the enrollment visit and subsequent visits, patients whose body weight increased from ≤30 kg to >30 kg, can have their dupilumab dose adjusted from 100 mg SC q2w or 300 mg SC q4w to 200 mg SC q2w and then maintained during the remaining treatment period irrespectively of losing weight. Patients will receive the first dose of dupilumab in LTS14424 at Visit 1 which is Week 0 (corresponding to EOT visit at Week 52 of parent study or for patients who will not be able to perform EFC14153 EOT visit onsite due to COVID-19 pandemic, LTS14424 Visit 1 can occur up until 12 weeks after the EFC14153 EOS visit).
Noninvestigational medicinal product(s) **Formulation:**	**Inhaled corticosteroids (ICS)** Alone or in combination with a second controller. **Reliever medication** Patients may receive albuterol/salbutamol or levalbuterol/levosalbutamol metered dose inhaler (MDI) as reliever medication (as needed) during the study. Nebulizer solutions may be used as an alternative delivery method. **Systemic corticosteroids (SCS)** Systemic corticosteroids may be given in case of severe asthma based on Investigator's judgement.
Route(s) of administration:	Oral inhalation via MDI or dry powder inhaler (DPI; for example ICS, ICS combination, albuterol/salbutamol, etc); for other background controllers, relievers, and SCS according to label that is applicable to pediatric patients.
Dose regimen:	Inhaled corticosteroid: ICS alone or in combination with a second controller, dose to be determined by Investigator based on the patient's level of asthma control. Reliever medication, as needed. Systemic corticosteroid (SCS), as prescribed.

ENDPOINT(S)	**Primary endpoint:** • The number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAEs). **Secondary endpoints:** • Efficacy - Annualized rate of severe asthma exacerbation events, during the treatment period, - Change in percentage (%) predicted forced expiratory volume in 1 second (FEV1) and other lung function parameters (absolute FEV1, forced vital capacity, [FVC], forced expiratory flow [FEF] 25% to 75%) from baseline and other time points assessed. • Dupilumab systemic exposure and immunogenicity - Serum dupilumab concentrations, - ADAs. • Biomarkers - Blood: Eosinophil count, - Serum: Total IgE.
ASSESSMENT SCHEDULE	Study onsite visits are performed q2w up to Visit 3 (Week 4) of the study, once every 4 weeks (q4w) up to Visit 8 (Week 24), and approximately every 12-16 weeks up to the end-of-study (EOS) visit.
STATISTICAL CONSIDERATIONS	**Sample size determination:** The study size is predicated on the overall size of the parent study; hence, the maximum number of patients to participate will be the number corresponding to the total randomized in the parent study. The expected number of sample size for LTS14424 study is approximately 354 patients (that is 87% of 408 patients from parent study). **Analysis population:** Safety population: defined as all patients exposed to at least 1 dose or part of 1 dose of dupilumab during LTS14424 study regardless of the amount of treatment administered. Patients will be summarized based on patients receiving dupilumab or placebo treatment in parent study. **Primary analysis:** Incidence of TEAE will be summarized using descriptive statistics. **Analysis of secondary endpoints:** For each variable, descriptive summary and/or inferential statistics that will include: n, within treatment arm point estimate, and confidence intervals will be provided as appropriate. Graphical time course profiles will be provided when appropriate for documentation of outcomes.

DURATION OF STUDY PERIOD (per patient)	• Enrollment: Eligible patients from EFC14153 should rollover into LTS14424 the same day as the EOT visit of the parent study. In the specific situation of COVID-19 pandemic, when patients cannot reach onsite EOT visit, enrolment into LTS14424 may also be done on a site visit on the same day as the EFC14153 end-of-study (EOS) visit or up to 12 weeks after the EFC14153 EOS visit. • Treatment period: Open-label treatment for 52 weeks (1 year). • Post-treatment period: 12 weeks. The total duration, per patient, is a maximum of approximately 64 weeks.



* Due to COVID-19 pandemic, patients may enroll in LTS14424 at or up to 12 weeks after the EFC14153 EOS visit.

Abbreviations: ICS = inhaled corticosteroid; LABA = long acting β2 agonist; LAMA = long acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; q2w = once every 2 weeks; SCS = systemic corticosteroid.

1.2 STUDY FLOW CHART

Study periods	Open-label treatment period (52 weeks)															Post-treatment period (12 weeks)		
	Enrollment[0] SOT[b] (D1)														EOT			EOS
Week (W)	**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[c]**	**W32[c]**	**W36**	**W40[c]**	**W44[c]**	**W48[c]**	**W52**	**W56[c]**	**W60[c]**	**W64**
Onsite visit	1[d]	2	3	4	5	6	7	8	☎	☎	9	☎	☎	☎	10	☎	☎	11
Enrollment																		
Informed consent/assent	X																	
Patient demography	X																	
Medical & surgical history	X																	
Entry criteria	X																	
Treatment																		
Call IVRS/IWRS	X	X[f]	X	X	X	X	X	X			X				X			X
IMP dispense/ administration[e]	X	X[f]	X	X	X	X	X	X			X							
Injection training/technique observation[g]	X																	
Prior & concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																		
Spirometry[h]	X	X		X	X			X							X			X
Safety																		
Vital signs (including height and weight)[i]	X	X	X	X	X	X	X	X			X				X			X
Physical examination	X				X			X							X			X

Study periods	Open-label treatment period (52 weeks)															Post-treatment period (12 weeks)		
	Enrollment[0] / SOT[b] (D1)														EOT			EOS
Week (W)	**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[c]**	**W32[c]**	**W36**	**W40[c]**	**W44[c]**	**W48[c]**	**W52**	**W56[c]**	**W60[c]**	**W64**
Onsite visit	**1[d]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	☎	☎	**9**	☎	☎	☎	**10**	☎	☎	**11**
Menstruation status	X	X	X	X	X	X	X	X			X				X			X
12-lead ECG	X														X			X
Vaccines record review scheduling	X																	
Adverse event reporting	<- ---------- X ----------→																	
Laboratory Testing																		
Clinical laboratories[i]	X		X		X			X			X				X			X
Urine pregnancy test for girls that are menstruating	X	X	X	X	X	X	X	X			X				X			X
Urinalysis[k]	X				X			X							X			X
PK sampling[l]	X				X			X							X			X
ADA[l]	X				X			X							X			X
Serum total IgE and Ag-specific IgE	X							X							X			X
Archival serum sampling[m]	X														X			
Reminder																		
Controller and reliever therapy reminder[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication withhold reminder[c]	X		X	X			X							X			X	

Abbreviations: ADA = anti-drug antibodies; Ag specific IgE = antigen-specific IgE; D1 = Day 1; ECG = electrocardiogram; eCRF = electronic case report form; EOS = end-of-study; EOT = end-of-treatment; IgE = immunoglobulin E; IMP = investigational medicinal product; IVRS/IWRS = Interactive Voice Response System/Interactive Web Response System; ICS = inhaled corticosteroid; LABA = long acting β2-agonist; LAMA = long acting muscarinic antagonist; PK = pharmacokinetic; q2w = once every 2 weeks; q4w = once every 4 weeks; SOT = start-of-treatment; W = (study) week.

a Eligible patients from study EFC14153 should rollover into LTS14424 the same day as the EOT visit of the parent study (which will be Visit 1 of LTS14424 study) or for patients who will not be able to perform EOT visit onsite due to COVID-19 pandemic, Study LTS14424 Visit 1 can occur at EFC14153 EOS visit, or up until and including 12 weeks after Study EFC14153 EOS visit. Patients who enroll after EOS visit in parent study should have laboratory assessments including complete blood count with differential and basic chemistry to evaluate continued eligibility for LTS14424 performed within 1 month prior to LTS14424 Visit 1. (Specifically for Brazil see Section 17.7.1).

b Start-of-treatment/enrollment visit (Visit 1 of present study) for patients after having performed the assessments of EOT or EOS visit in the parent study (due to COVID-19 pandemic). For patients not able to perform EOT or EOS visit onsite due to COVID-19 pandemic, LTS14424 Visit 1 may occur up to 12 weeks after EFC14153 EOS visit. Visit windows for subsequent visits are ±3 days during treatment period and ±1 week for the remainder of the study

c Phone contact to collect safety information + reminders for IMP, controller and reliever therapy, if appropriate reminder for withholding medication at the next visit as described in the individual visit schedules Safety information and date of phone call will be recorded in eCRF.

d Eligible patients in parent study should rollover into LTS14424 the same day as the EOT visit of the parent study. All measurements and procedures of EOT visit of parent study should be done before enrollment to LTS14424 study. If the data can be obtained from EOT visit of parent study, relative procedures of Visit 1 of LTS14424 study can be waivered. New AEs (including worsening AEs) will be reported only in LTS14424 eCRF. For patients who will not be able to perform EOT visit onsite due to COVID-19 pandemic, Study LTS14424 Visit 1 can occur up and until 12 weeks after Study EFC14153 EOS.

e Once every 2 weeks IMP administrations must be separated by at least 11 days. Once every 4 weeks IMP administrations must be separated by at least 25 days. The treatment period visits occur q2w up to Visit 3 (Week 4) of the study, q4w up to Visit 8 (Week 24), and approximately every 12-16 weeks up to the EOS visit. After each IMP administration, patients should be monitored for a minimum of 30 minutes after injections. If the parent(s)/caregiver(s)/legal guardian(s) or the Investigator decides not to administer IMP at home, the injections can be performed at the study site by way of unscheduled visits. The first injection of 300 mg dose must be performed onsite.

f For patients receiving 300 mg q4w, no IMP will be dispensed/administered at Week 2 and no IVRS/IWRS call will occur.

g The injection training is for families who are willing to perform injection administration at home for children receiving q2w doses. The Investigator or delegate should review the patient's administration technique at the Visit 1 (or upcoming onsite visits before permitting IMP administration at home). No IMP administration at home is allowed for patients receiving the 300 mg q4w dose for the first time. Subsequent administrations are encouraged to occur at site wherever possible, if not possible can be done by trained care givers or nurses at home.

h Spirometry should be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). Spirometry will be performed after a washout 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. Also spirometry should be performed prior to IMP administration, as applicable.

i Vital signs: blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), and body weight (kg) will be measured at each visit. Height (cm) will only be measured at the enrollment visit (Visit 1 of present study) and EOT visit. Weight will be measured at each onsite visit. Except height and weight, other vital signs will be measured in the sitting position using the same arm at each visit. All vital signs will be measured prior to dispensation and/or administration of IMP at the clinic visits.

j Clinical laboratories: Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets. Serum chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, albumin, total cholesterol, creatine phosphokinase (CPK), glucose, creatinine, blood urea nitrogen (BUN), bicarbonate, and electrolytes (sodium, potassium, chloride).

k Urinalysis: pH, glucose, ketones, leukocyte esterase blood, protein, nitrate, urobilinogen, and bilirubin (by dipstick).

l Samples will be collected prior to IMP administration, during the treatment period.

m Archival serum sample (optional).

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

ACQ-5-IA:	Asthma Control Questionnaire–Interviewer Administered, 5-question version
ACQ-7-IA:	Asthma Control Questionnaire–Interviewer Administer, 7-question version
ACQ-IA:	Asthma Control Questionnaire–Interviewer Administered
AD:	atopic dermatitis
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATS:	American Thoracic Society
CPK:	creatine phosphokinase
CSR:	clinical study report
CV:	curriculum vitae
CYP:	Cytochrome P450
DMC:	Data Monitoring Committee
DPI:	dry powder inhaler
EC:	Ethics Committee
ECG:	electrocardiogram
eCRF:	electronic case report form
ELISA:	enzyme-linked immunosorbent assay
EOS:	end-of-study
EOT:	end-of-treatment
ERS:	European Respiratory Society
ETD:	early treatment discontinuation
FEF:	forced expiratory flow
FENO:	fractional exhaled nitric oxide
FEV1:	forced expiratory volume in 1 second
FVC:	forced vital capacity
GCP:	Good Clinical Practice
HIV:	Human immunodeficiency virus
HLGT:	high level group term
HLT:	high level term
IAF:	informed assent form
ICF:	informed consent form
ICS:	inhaled corticosteroids
IEC:	Independent Ethics Committee
IgE:	immunoglobulin E
IL:	interleukin
IL-4Rα:	interleukin-4 receptor alpha
IMP:	investigational medicinal product
IRB:	Institutional Review Board
ISR:	injection site reactions

IVRS/IWRS:	Interactive Voice Response System/ Interactive Web Response System
K-M:	Kaplan-Meier
LABA:	long acting β2 agonist
LAMA:	long acting muscarinic antagonist
LFT:	liver function test
LTRA:	leukotriene receptor antagonist
mAb:	monoclonal antibody
MDI:	metered dose inhaler
NIMP:	noninvestigational medicinal product
PD:	pharmacodynamics
PK:	pharmacokinetic
PT:	preferred term
q2w:	once every 2 weeks
q4w:	once every 4 weeks
qw:	every week
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous(ly)
SD:	standard deviation
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
TBV:	total blood volume
TEAEs:	treatment-emergent adverse event
ULN:	upper limit of normal
V:	(study) visit
W:	(study) week

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Asthma is the most common chronic lung disease of childhood that affects >6.6 million children in the United States (US). Asthma is a chronic inflammatory disease of the airways characterized by airway hyper-responsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products. For most asthma patients, a regimen of controller therapy and reliever therapy provides adequate long-term control.

The majority of children with asthma have mild or moderate disease and can obtain adequate asthma control through avoidance of triggering factors and/or with the help of medications, such as short acting inhaled β2-receptor agonists, inhaled corticosteroids (ICS) and, when needed, addition of long acting β2-receptor agonists and leukotriene receptor antagonists (LTRA). However, 2% to 5% of all asthmatic children have uncontrolled asthma despite maximum treatment with conventional medication (1) Children with such severe symptoms are heterogeneous with respect to trigger factors, pulmonary function, inflammatory pattern, and clinical symptoms (2). These children have a reduced quality of life, account for a large proportion of the healthcare costs related to asthma and represent a continuous clinical challenge to the pediatrician. Additionally, the long-term adverse effects of systemic and ICS on bone metabolism, adrenal function, and growth in children lead to attempts to minimize the amount of corticosteroid usage. Lastly, the consequences of unresponsiveness to therapy or lack of compliance with therapy are evidenced by loss of asthma control (LOAC), which can be severe (that is severe asthma exacerbation event) and possibly life-threatening. The poor response of some patients with asthma may reflect the number of cellular and molecular mechanisms operative in asthma. There is increasing interest in distinct phenotypes because targeted therapy is more likely to be successful in patients with similar underlying pathobiologic features (3). Recent therapeutic approaches in asthma have been focused on trying to control type 2 inflammation.

Dupilumab is a human monoclonal antibody (mAb) directed against the interleukin-4 receptor alpha (IL-4Rα) subunit, a component of interleukin (IL)-4 receptors Type I and Type II. The IL-4 receptors mediate the IL-4 signaling (both Type I and Type II) and IL-13 signaling (Type II). As previously mentioned, both IL-4 and IL-13 signaling pathways are thought to play key roles in the pathophysiology of inflammatory allergic diseases. Dupilumab has been recently approved in the US and European Union (EU) for the treatment of adults with moderate to severe atopic dermatitis (AD).

4.2 RATIONALE

An initial demonstration of the efficacy and safety of dupilumab in adults was provided in the randomized, double-blind, placebo-controlled, parallel-group Phase 2a study (ACT11457). This study investigated the effects of dupilumab administered at a dose of 300 mg subcutaneously (SC) once weekly for 12 weeks as compared to placebo on the incidence of asthma exacerbations in

adult patients with persistent moderate to severe eosinophilic asthma. During the first 4 weeks patients continue taking their background medication, consisting of medium to high dose ICS in combination with a long acting β2 agonist (LABA), and then the LABA component was withdrawn and finally the ICS component was removed as well leaving patients treated with either dupilumab or matching placebo. The primary endpoint was the occurrence of an asthma exacerbation; the secondary endpoints included a range of measures of asthma control. The ACT11457 study showed an 87% reduction in asthma exacerbations after 12 weeks of treatment with dupilumab (5.8%) versus placebo (44.2%). A rapid improvement of lung function, as measured by forced expiratory volume in 1 second (FEV1) and reduction of T-helper 2 (Th2) associated biomarkers levels were also observed (4).

In a completed Phase 2b dose ranging study (DRI12544), dupilumab efficacy at 4 dose regimens (300 mg once every 4 weeks [q4w] and once every 2 weeks [q2w], and 200 mg q2w and q4w with a total dose on Day 1 of 600 mg [for the 300 mg regimen] and 400 mg [for the 200 mg regimen]) was evaluated in adult patients with uncontrolled asthma while receiving a stable dose of medium to high-dose ICS/LABA in addition to their study treatment (placebo or dupilumab). Dupilumab demonstrated dose dependent improvement, compared with placebo, in the change from baseline in FEV1 at Week 12. In addition, consistent efficacy results in favor of dupilumab over placebo were observed in the majority of main secondary efficacy endpoints including annualized rate of severe exacerbation events. The maximum treatment effects were observed in the 200 mg and 300 mg q2w regimens. Exposure-response analyses further supported the maximal effect for both endpoints of FEV1 and severe exacerbation rate approached/achieved at the steady-state exposure of the two q2w regimens (mean steady-state trough concentrations of 28.3 and 58.5 mg/L, respectively). Dupilumab was observed to be well tolerated and had an acceptable safety profile across all dose regimens examined. Treatment-emergent adverse events (TEAE) were reported in 79.1% patients in the dupilumab groups (75.3% to 82.8%) and 74.7% patients in the placebo group. The most frequently reported TEAEs included injection site reactions (ISR), respiratory tract infections and related symptoms, headache, and back pain. There was no apparent dose relationship for any particular TEAE except for ISR, majority of which were mild in nature (5).

Study EFC13579 was a Phase 3 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of dupilumab in adolescent and adult patients with persistent asthma. Dupilumab, when added to standard therapies, reduced severe asthma attacks (exacerbations) and improved lung function. At 52 weeks, in the 300 mg dose group, dupilumab reduced severe asthma attacks by 46%. At 12 weeks, in the 300 mg dupilumab dose group, mean improvement in lung function over placebo as assessed by FEV1 was 130 mL (9%) in the overall population, 150 mL (11%) in patients with ≥150 eosinophilic cells/μL, and 240 mL (18%) in patients with ≥300 eosinophilic cells/μL ($p<0.001$ for all groups). The results for the 200 mg and 300 mg dupilumab dose groups were generally comparable on both exacerbations and FEV1. The overall rates of adverse events (AE), deaths, infections, conjunctivitis, herpes, and discontinuations were comparable between the dupilumab and placebo groups. Injection site reactions were more common in the dupilumab groups occurring in 17% of dupilumab patients compared to 8% of placebo patients.

As part of the pediatric program, EFC14153 was designed to establish the efficacy and safety of dupilumab in comparison to placebo in children 6 to 11 years of age with persistent uncontrolled asthma. The dose regimens for this study were selected based on the observed efficacy and safety in the dose ranging study in adult asthma patients (Phase 2b study DRI12544), the pharmacokinetic (PK) characterization and safety observation in pediatric AD study (R668-AD-1412) of 6 to <18 years, as well as the available safety data of EFC13579, the asthma pivotal study being conducted in adults and adolescents. As a result of the collective analysis of the previously mentioned data, the recommended dosing regimens for the pediatric population aged 6 to <12 years were dupilumab 200 mg SC q2w for children >30 kg or 100 mg SC q2w for those with a weight ≤30 kg. Subsequent to the start of LTS14424, the pediatric atopic dermatitis study R668-AD-1652 was completed. In that study, it was identified that the dose 300 mg q4w for patients <30 kg with atopic dermatitis was able to provide acceptable clinical efficacy with an acceptable tolerability and safety profile and it was comparable to other regimens.

Therefore, the Sponsor will introduce this same dose for children with asthma who are ≤30 kg. The Sponsor supports harmonizing the PK across indications where possible. This approach is supported by the similarity in PK that has been demonstrated across healthy individuals as well as patients including those with AD and asthma. Given the high degree of overlap between asthma and AD, especially in younger populations, this simplifies the approach for patients. In addition, q4w dosing has the potential to reduce patient burden and possibly improve overall compliance.

In addition to the safety and efficacy data observed in AD patients, the safety and efficacy of the 300 mg q4w dose is supported by modeling developed from observed data in adults and adolescents with asthma. PK modeling incorporating data from the clinical development program in asthma populations identifies that 300 mg q4w in children 15 to 30 kg is expected to match the adult and adolescent efficacious exposure at 300 mg q2w, within a safe treatment profile and within the desired therapeutic window. The predicted C_{trough} for 300 mg q4w in pediatric patients 15 to 30 kg is similar to the adult and adolescent 300 mg q2w C_{trough}. The predicted C_{max} of 300 mg q4w in pediatric patients 15 to 30 kg does not exceed the adult 300 mg every week (qw) C_{max} in asthma Phase 2/3 studies.

LTS14424 is designed as a 1-year treatment study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma study (EFC14153). In addition, this study will collect PK, safety, and clinical response information on patients with asthma who weigh ≤30 kg and who are treated with dupilumab 300 mg q4w. The doses to be used in this study will include dupilumab 200 mg q2w for children >30 kg; or, for those with a weight ≤30 kg: 100 mg q2w or 300mg q4w. The dosing regimen will be adjusted based on the patient's weight during the study. In Amended Protocol 04, all participants with a weight ≤30 kg who had completed less than 44 weeks of LTS14424 were switched from 100 mg q2w to 300mg q4w at onsite visit.

In Amended Protocol 05, a Japan substudy was added to include pediatric asthma patients aged 6 to <12 years from Japan.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (EFC14153).

5.2 SECONDARY

The secondary objectives of this study are:

- To evaluate the long-term efficacy of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study.
- To evaluate dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study with regard to:
  - Systemic exposure,
  - Anti-drug antibodies (ADAs),
  - Biomarkers.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a multinational, multicenter, open-label, single arm, 1-year treatment study evaluating dupilumab given SC for a period of 52 weeks.

Upon completion of the treatment period (or following early discontinuation of investigational medicinal product [IMP]), patients will continue into the post-treatment period. During the post-treatment period, patients will receive their background controller regimen based on Investigator's judgement.

For a schematic study design, please refer to Section 1.1.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The total duration, per patient, is a maximum of approximately 64 weeks.

For each patient, this includes the following 3 periods:

- **Enrollment:** Eligible patients from EFC14153 will rollover into LTS14424 the same day as the end-of-treatment (EOT) visit of the parent study. In the specific situation of COVID-19 pandemic, when patients cannot reach onsite EOT visit, enrolment into LTS14424 may also be done on a site visit on the same day as the EFC14153 end-of-study (EOS) visit or up to 12 weeks after the EFC14153 EOS visit.
- **Treatment period:** 52 weeks open-label treatment (1 year) with last dosing on Week 50.
- **Post-treatment period:** 12 weeks.

6.2.2 Determination of end of clinical trial (all patients)

The end-of-study (EOS) is defined as the last patient has completed the 12 weeks post-treatment period and completed the EOS visit.

6.3 INTERIM ANALYSIS

This is 1-year treatment safety study. Interim analyses/reports may be prepared to support regulatory submissions of an indication in the dupilumab project or other purposes.

6.4 DATA MONITORING COMMITTEE

The data monitoring committee (DMC) that will monitor safety data during the conduct of the study is independent from Sponsor. This committee is comprised of externally-based individuals with experts in pediatrics, expertise in the diseases under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to 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.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Pediatric patients with asthma who completed the treatment in a dupilumab asthma trial (EFC14153) (Specifically for Brazil see Section 17.7.1).

Patients who are not able to complete their treatment in Study EFC14153 due to the COVID-19 pandemic will be allowed to enroll into Study LTS14424. Patients who enroll in LTS14424 after completing the EFC14153 EOS visit should have eligibility for LTS14424 reevaluated including background medication check and laboratory assessments (including CBC with differential and basic chemistry) within 1 month prior to LTS14424 Visit 1.

I 02. Signed written informed consent/assent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Any chronic lung disease other than asthma (for example cystic fibrosis, bronchopulmonary dysplasia) which may impair lung function.

E 02. Inability to follow the procedures of the study/noncompliance (for example due to language problems or psychological disorders).

E 03. Patients receiving concomitant treatment or required a new concomitant treatment prohibited in the study at enrollment visit (see Section 8.8).

E 04. Patients or his/her parent(s)/caregiver(s)/legal guardian(s) is related to the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff thereof directly involved in the conduct of the study.

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 05. Patients who experienced any hypersensitivity reactions to IMP in a previous dupilumab study, which, in the opinion of the Investigator, could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.

E 06. Any abnormalities or AEs at enrollment that per Investigator's judgment would adversely affect patient's participation in this study or would require permanent IMP discontinuation. Examples: Patients diagnosed with active parasitic infection (helminthes), suspected or high risk of parasitic infection, active tuberculosis (TB), invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidiomycosis, pneumocystocis, aspergillosis), despite infection resolution' or unusually frequent, recurrent or prolonged infections.

E 07. For female patients who have commenced menstruating at any time during the study and are either:

- Found to have a positive urine pregnancy test, or,
- Sexually active, not using an established acceptable contraceptive method:
  - Oral, injected, inserted, or implanted hormonal contraceptive,
  - Intrauterine device or intrauterine system with progesterone,
  - Barrier contraceptive (condom, diaphragm, or cervical/vault caps) used with spermicide (foam, gel, film, cream, or suppository).

E 08. Planned live attenuated vaccinations during the study.

E 09. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, juvenile idiopathic arthritis, inflammatory bowel disease, systemic lupus erythematosus) at enrollment.

8 STUDY TREATMENT

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Dupilumab

Route of administration:

- Dupilumab for children ≤30 kg: 150 mg/mL in prefilled syringe to deliver a dose of 100 mg q2w in a 0.67 mL SC injection.

  OR

- Dupilumab for children ≤30 kg: 150 mg/mL in prefilled syringe to deliver a dose of 300 mg q4w in a 2 mL SC injection.
- Dupilumab for children >30 kg: 175 mg/mL in prefilled syringe to deliver a dose of 200 mg q2w in a 1.14 mL SC injection.

Dose regimen: Dupilumab 200 mg SC q2w for children with body weight >30 kg and 100 mg SC q2w or 300mg q4w for children with body weight ≤30 kg.

For children with body weight ≤30 kg receiving 100 mg q2w, the dupilumab dose will be changed to 300 mg q4w at one planned or unscheduled site visit if they are more than 8 weeks out from completing the treatment period (switch to q4w dose regimen to occur at site visit at Week 0 or 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44). Otherwise, they will continue on 100 mg q2w. All newly enrolled children with body weight ≤30 kg will take 300 mg q4w.

At enrollment visit and subsequent visits, patients whose body weight increased from ≤30 kg to >30 kg, will have their dupilumab dose adjusted from 100 mg SC q2w or 300 mg q4w to 200 mg SC q2w and then maintained during the remaining treatment period irrespectively of losing weight.

Patients will receive their first dose of dupilumab in LTS14424 study at the Visit 1 which is Week 0 (corresponding to EOT visit at Week 52 of parent study or for patients who will not be able to perform EFC14153 EOT visit onsite due to COVID-19 pandemic, Study LTS14424 Visit 1 can occur at the EFC14153 EOS visit or for up to 12 weeks after the Study EFC14153 EOS visit).

8.1.2 Preparation of investigational product

Dupilumab in glass prefilled syringes will be dispensed to the patients. Additional information will be provided in the Pharmacy manual.

8.1.3 Dosing schedule

Dupilumab is administered every 14±3 days q2w or every 28 days ±3 days q4w. The doses of investigational product must be separated by ≥11 days for q2w and ≥25 days for q4w to avoid overdose.

For IMP administrations coinciding with scheduled study site visits (q2w up to Visit 3 [Week 4] for patients receiving q2w doses, q4w up to Visit 8 [Week 24], and approximately every 12-16 weeks up to the EOT visit), the IMP administrations can be performed by the Investigator or designee at site visits following clinic procedures and blood collection (see Section 1.2).

Patients should be monitored for a minimum of 30 minutes at the study site after IMP injections, to assess any ISR (for example for any signs or symptoms of a hypersensitivity reaction). If the parent(s)/caregiver(s)/legal guardian(s) or the Investigator decides not to administrate IMP at home, the other injections can be performed at the study site by way of unscheduled visits. In order to closely monitor the 300 mg dose administration, the first injection must be performed onsite. Subsequent administrations are encouraged to occur at site wherever possible. If this is not possible, administration can be done by trained care givers or nurses at home.

If the parent(s)/caregiver(s)/legal guardian(s) are willing to perform the IMP injection administration at home, these parent(s)/caregiver(s)/legal guardian(s) will be trained by the Investigator or designee to administer IMP, as well as monitoring of ISR, at the Visit 1 or any following visits of present study. After parent(s)/caregiver(s)/legal guardian(s) have successfully administered IMP under close supervision or instruction of the Investigator or designee, the Investigator approves them to perform home administration of IMP at all further IMP doses. Patients should be monitored for 30 minutes after home administration of IMP.

If the Investigator or designee judges that the parent(s)/caregiver(s)/legal guardian(s)'s injection technique is not satisfactory, the further training can be performed in the upcoming 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 time points 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 or IMP doses during the study. For any patient who misses a site visit or IMP dose, the parent(s)/caregiver(s)/legal guardian(s) should be reminded to be diligent to avoid missed visits and IMP doses 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 >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 (eCRF) 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.

Between the protocol-scheduled onsite visits, interim visits may be required for IMP dispensing. As an alternative to these visits, dupilumab may be supplied from the site to the patient/parent(s)/caregiver(s)/legal guardian(s) via a Sponsor-approved courier company where allowed by local regulations and approved by the subject.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Inhaled corticosteroids alone or in combination with a second controller

The recognized second controller medication for combined use with ICS (dose-levels in children 7 to 12 years old) as background therapy during this study will include the following classes: LABA, LTRA, Long acting muscarinic antagonist (LAMA), or methylxanthines. Please refer to Section 17.1 for an indicative (not exhaustive) list of recognized second controller medications approved for this study. These controller medications will not be dispensed or supplied by the Sponsor.

Route of administration:

- Oral inhalation via metered dose inhaler (MDI) or dry powder inhaler (DPI) (for example ICS, ICS combination, albuterol/salbutamol, etc); for other background controllers according to label that is applicable to pediatric patients.

Dose regimen:

- Inhaled corticosteroids: ICS alone or in combination with a second controller as prescribed, as per Investigator's judgement.

For patients experiencing a deterioration of asthma during the study, the ICS with/without second controller dose may temporarily be increased, as indicated and upon recommendation of the physician and/or Investigator. Treatment may then be changed to systemic corticosteroid (SCS) (severe exacerbation event) or reverted back to the original ICS with/without second controller dose or modified ICS with/without second controller dose depending on the asthma symptoms progression.

At enrollment:

At enrollment, patients must be on background therapy (ICS alone or with a second controller) as in EOT visit of parent study. Patients enrolling into Study LTS14424 at a later date due to COVID-19 pandemic, must be on background therapy (High ICS dose alone or with a second controller or Medium ICS dose with a second controller).

If patients take 2 different ICS, the total daily dose of ICS should be calculated, to evaluate the daily dose of ICS.

Open-label treatment period:

During this period, patients will continue to take their controller medication(s). During the course of treatment period, the Investigator, based on his/her medical judgement of the patients' asthma control status, may decide to modify the dose regimen of asthma controller medication(s) to achieve an adequate control of patient's asthma. Background controller medication(s) continuation per prescription will be reminded throughout the course of study to ensure the good compliance of such medication(s). All changes in the background medication regimen should be recorded in the eCRF.

Post-treatment period

Upon completing the treatment period or following early discontinuation of IMP, patients will continue into the post-treatment period. During the post-treatment period, patients will receive their background controller regimen based on Investigator's judgement.

8.2.2 Reliever medication

Patients may use albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

The reliever medication (that is albuterol/salbutamol or levalbuterol/levosalbutamol) will not be dispensed or supplied by the Sponsor.

Route of administration:

- As prescribed.

Dose regimen:

- As prescribed.

The reliever medication will be recorded as number of puffs in eCRF. The conversion factor is shown in the Table 1 and Table 2.

Table 1 - The reliever medication conversion factors

Salbutamol/Albuterol nebulizer solution-total daily dose (mg)	Number of puffs[a]
2.5	4
5.0	8
7.5	12
10	16

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

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

Table 2 - The reliever medication conversion factors

Levosalbutamol/Levalbuterol nebulizer solution-total daily dose (mg)	Number of puffs[a]
0.63	2
1.25	4
2.5	8
3.75	12
5	16

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

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

8.2.3 Systemic corticosteroids

Patients may be placed on SCS at any time as clinically indicated based on the presence of symptoms consistent with a severe asthma, as per the Investigator's judgement. Dose and route of administration will be as prescribed.

8.3 BLINDING PROCEDURES

Not applicable.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The study medication will be administered only to patients included in this study following the procedures described in the clinical study protocol. The 7-digits serialized treatment kit number will be generated centrally by Sanofi clinical supply team. The IMPs are packaged in accordance with this list.

Patients who meet the entry criteria will receive dupilumab either 200 mg q2w or 300 mg q4w SC, based on body weight >30 kg or ≤30 kg at enrollment visit, respectively. Dupilumab dose will be adjusted during the treatment period, from 100 mg q2w or 300 mg q4w to 200 q2w mg SC, if the body weight increased to >30 kg. Once the dose switched to 200 mg q2w SC, the same dose will be maintained during the remaining treatment period. For children with body weight ≤30 kg currently in the treatment period receiving 100 mg q2w, the dupilumab dose will be changed at one planned or unscheduled site visit to 300 mg q4w if they are more than 8 weeks out from completing the treatment period (switch to q4w dose regimen to occur at site visit at Week 0 or 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44). Otherwise, they will continue on 100 mg q2w until EOT. All newly enrolled children with body weight ≤30 kg will take 300 mg q4w.

Patients will be identified with 12-digit patient ID in study LTS14424 whereas 9-digit patient ID may be used in parent study. In that case, mapping rules will be applied to adapt parent study patient ID to LTS14424 12-digit patient ID. The investigational site will enter the patient tracking information for patient identification number, into the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS) during each scheduled protocol visit. Treatment allocation will be performed centrally by IVRS/IWRS. The clinical site coordinator will document the patient number and the treatment kit number in the eCRF and in the patient's source documents, and the patient number on the IMP label prior to dispensing to the patient.

Patients will be considered to be enrolled in the study once a treatment kit number has been assigned by the IVRS/IWRS. Therefore, it is important that all inclusion/exclusion criteria are confirmed and all required procedures are completed prior to the enrollment contact to the IVRS/IWRS. Detailed IVRS/IWRS procedure will be provided in the IVRS/IWRS site manual.

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

Dupilumab is supplied as glass prefilled syringes packed in a patient kit box. Each glass prefilled syringe and the patient kit box is labeled.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

All investigational products should be stored at a temperature between 2°C and 8°C in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (for example pharmacists) in accordance with local regulations, policies, and procedures.

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

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for Duties and Taxes Paid (DTP) shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP dispensed, used and unused, and returned by the parent(s)/caregiver(s)/legal guardian(s) of each patient. The IMP tracking log and inventory form is to be updated each time investigational product is dispensed or returned. Any investigational product not returned (even if considered empty) must be accounted for with a comment in the log. The study monitor will periodically check the supplies of the IMP held by the Investigator or pharmacist to assess accountability.

All medication treatment kits (whether empty or unused) are returned by the parent(s)/caregiver(s)/legal guardian(s) at each visit when a treatment dispensing is planned. The completed patient injection diary (returned diary returned to the site at each visit), returned treatment kit boxes, any unused prefilled syringes, and the remaining volume of solution in each vial or syringe will be used for drug accountability purposes.

Treatment kit number has to be recorded on the appropriate page of the eCRF and also on the IMP tracking log and inventory log form.

The Monitoring Team in charge of the study will have to check eCRF data comparing them with the centralized treatment allocation system information, the IMP kit and IMP tracking log and inventory form.

A q4w phone contact will be planned after Week 24 to remind the parent(s)/caregiver(s)/legal guardian(s) to continue the IMP and the background controller medication (s) of patient as instructed by Investigator.

For noninvestigational medicinal product (NIMP) not provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator and must be captured in standard site documents and records (for example medical notes).

8.7.2 Return and/or destruction of treatments

All partially used or unused treatment kits will be retrieved by the Sponsor or destroyed at study site. All used prefilled syringes should be kept in a sharp container by the parent(s)/caregiver(s)/legal guardian(s) and be returned to sites for destruction. No unused IMP will be destructed at site unless the Sponsor provides written authorization. A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

8.8.1 Prohibited concomitant medication

The following concomitant treatments are not permitted during the study:

- Anti-immunoglobulin E (IgE) therapy (for example omalizumab).
- Biologic therapy.
- Immunosuppressants.
- Intravenous immunoglobulin (IVIG) therapy.
- Live attenuated vaccinations during the study (refer to Section 17.2).
- Asthma relievers other than salbutamol/albuterol or levosalbutamol/levalbuterol: their use is not recommended during the study period. In case of use in exceptional circumstances (for example prescribed by a physician not participating in the study), their use will be documented in the patient's file and reported in the eCRF.
- Other investigational drugs.

8.8.2 Cautioned concomitant medication (Cytochrome P450 enzyme substrates)

The impact of dupilumab on Cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized. However, IL-4 was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (6). Human peripheral blood mononuclear cells (PBMC) incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (6).

The risk of indirect effects of dupilumab, via modulation of IL-4 and IL-13 activities, on the PK of selected CYP substrates (midazolam, omeprazole, warfarin, caffeine, and metoprolol) has been studied in 14 adult patients with moderate to severe AD. The results of this study showed no evidence for a clinically meaningful effect of dupilumab on the activity of CYP3A, CYP2C19, CYP2C9, CYP1A2, or CYP2D6. Some examples of CYP450 substrates with narrow therapeutic index are provided in Section 17.3.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary endpoint for this study is the number (n) and percentage (%) of patients experiencing any TEAE (definition see Section 10.4.1.1) during total study periods.

Additional analyses will describe the number (n) and percentage (%) of patients experiencing any:

- Serious adverse events (SAE) (SAE definition refers to Section 10.4.1.2).
- Adverse events of special interest (AESI) (AESI definition refers to Section 10.4.1.3).
- Adverse events related to IMP.
- Adverse events leading to permanent IMP discontinuation.
- Adverse events other than ISR.

Adverse events, including SAEs and AESI, will be collected at any time during study starting from signed consent form. Any new AEs (including worsening AEs) and ongoing AEs (with onset date before the day of enrollment) at enrollment visit (when done on the same day of EOT or EOS of parent study) will be reported in present 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.

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.

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.

Adverse events for each patient will be monitored and documented from the time the subject gives informed consent/assent at Visit 1 until the EOS visit, except for:

- Serious adverse events.
- Adverse events that are ongoing at database lock.

Adverse events, AESIs, SAEs, AEs leading to IMP discontinuation and deaths will be reported as described in Section 10.4.1 and analyzed as in Section 11.4.3.

Laboratory tests, vital signs, physical examination, or electrocardiogram (ECG) abnormalities are to be recorded as AEs only if they meet the criteria defined in Section 10.4.3, and are assessed as described in Section 9.1.1 to Section 9.1.3. Physical examination will also be performed. In addition to assessment of primary endpoint, below parameters are used on an ongoing basis during the study to monitor safety of participants and will be presented in a descriptive manner.

9.1.1 Vital signs

Vital signs including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), and body temperature (degrees Celsius) will be measured at each onsite visit except for IMP administration only visits.

Vital signs will include height (cm) and body weight (kg). Height will be measured at the enrollment visit (Visit 1 of present study) and EOT visit, while weight at each onsite visit.

Vital signs data for the Visit 1 can be obtained from the EOT visit of the parent study. Refer to Section 1.2 Study Flow Chart for the schedule of vital signs performed throughout this study. For patients not able to perform EOT visit onsite due to COVID-19 pandemic and for whom Visit 1 can be conducted on the same day as EOS visit of the parent study, vital signs can be obtained from EOS. But, in case Visit 1 is done after EOS (up to 12 weeks after EOS), vital signs must be repeated.

9.1.2 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 for girls.

9.1.3 Electrocardiogram (ECG)

Electrocardiogram (ECG) variables will be recorded by a standard 12-lead ECG. Enrollment visit data will be obtained from EOT visit of parent study. One recording will be performed at EOT and EOS (see Section 1.2). For patients not able to perform EOT visit onsite due to COVID-19 pandemic and for whom Visit 1 can be conducted on the same day as EOS visit of the parent study, ECG can be obtained from EOS. But, in case Visit 1 is done after EOS (up to 12 weeks after EOS), ECG must be repeated.

9.1.4 Clinical laboratory tests

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 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 are:

Hematology:

To include blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

Serum chemistry:

To include creatinine, blood urea nitrogen, glucose, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase (CPK). Patients' fasting or nonfasting status at blood sample collection will be recorded on the Central Laboratory Requisition Form.

Urinalysis:

Urinalysis will be conducted by dipstick during onsite visit. The parameters include pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen, and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, further urine test is under Investigator's judgement.

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

Pregnancy test

A urine pregnancy test must be negative at Visit 1 of present study for enrolling girls who have commenced menstruating, and a urine dipstick pregnancy test will be performed at subsequent onsite visits prior to administration of IMP. 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.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Section 17.4.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

The secondary efficacy endpoints of this study are:

- Annualized rate of severe asthma exacerbation events, during the treatment period.
- Change in percentage (%) predicted FEV1 (7) and other lung function parameters (absolute FEV1, forced vital capacity [FVC], forced expiratory flow [FEF] 25% to 75%) from baseline, and other time points assessed.

9.2.1.1 Assessment of severe asthma exacerbation

A severe exacerbation event during the study is defined as a deterioration of asthma requiring:

- Use of SCS for ≥3 days; or,
- Hospitalization or emergency room visit because of asthma, requiring SCS.

Two events will be considered as different if the interval between their start dates is ≥28 days.

The reasons (for example infections including viral and bacterial, allergen exposure, exercise, and others) for any exacerbation event will be recorded in the eCRF.

9.2.1.2 Assessment of lung function by spirometry

Lung function parameters will be assessed by centralized spirometry at enrollment visit (Visit 1 of present study), Visit 2, Visit 4, Visit 5, Visit 8, EOT, and EOS visits. For Visit 1, spirometry parameters prebronchodilators will be obtained directly from EOT of parent study. For those patients that enroll in LTS14424 at the EFC14153 EOS visit or after, lung function assessments will be conducted at the EOS visit or at Visit 1.

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 prebronchodilator measured parameters, including FEV1, peak expiratory flow (PEF), FVC, and FEF 25% to 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours), and withholding the last dose of LAMA for at least 24 hours.

At all related visits, spirometry will be performed either in the AM or PM, but preferably in the AM, and 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 the sitting position; however, if necessary to undertake the testing with the subject standing or in another position, this should be noted on the spirometry report. For any subject, the position should be consistent throughout the study.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, 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% to 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 (that is 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 Other secondary endpoints

9.2.2.1 Dupilumab systemic exposure and immunogenicity

Dupilumab systemic exposure and immunogenicity endpoints of this study are the evolution of:

- Serum dupilumab concentrations.
- Titers for ADAs.

9.2.2.1.1 Sampling time

Predose blood samples will be collected for determination of functional dupilumab concentration in serum and anti-dupilumab antibodies (including neutralizing antibodies) on days designated in the Study Flow Chart (see Section 1.2). The date of collection should be recorded in the patient eCRF. The date and time also will be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

In the event of any SAE or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe ISR lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes. An unscheduled systemic drug concentration page ("PK page") in the eCRF must be completed as well.

Further follow-up of individual patients will be considered based on the overall assessment of antibody titers and clinical presentation.

9.2.2.1.2 Handling procedure

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of systemic drug concentration and ADA is provided in Table 3.

Table 3 - 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

9.2.2.1.3 Bioanalytic method

Serum samples will be assayed using validated methods as described in Table 4.

Table 4 - 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

Abbreviation: ELISA = enzyme-linked immunosorbent assay.

9.2.2.2 Pharmacodynamics and phenotyping

Pharmacodynamics and phenotyping endpoints of this study are the evolution of:

- Blood: Eosinophil count.
- Serum: Total IgE.

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 enrollment, after 24 weeks treatment, at EOT, and at EOS for their association with therapeutic response.

Values of enrollment visit (Visit 1 of present study), will be obtained directly from EOT visit of parent study. For those patients that enroll in LTS14424 at the EFC14153 EOS visit or after, these assessments will be conducted at the EOS visit or at Visit 1.

In previous asthma trials in adults and adolescents, treatment with dupilumab significantly suppressed the levels of serum total IgE (a product of immunoglobulin class switching driven by IL-4) and antigen-specific IgEs enrollment visit 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. These biomarkers have been included in parent study. Therefore, these biomarkers are included in the current study to assess their long-term suppression effect.

Blood eosinophil counts will be captured from hematology assays as describe in Section 1.2.

Biomarkers include total IgE which will be measured with a quantitative method (for example ImmunoCAP) approved for diagnostic testing and antigen-specific IgE which will be detected using panels of antigens appropriate to the location of the clinical site (quantitative ImmunoCAP test; Phadia).

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

9.3 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For patient(s)/parent(s)/caregiver(s)/legal guardian(s) who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes. For subjects who have consented to it, archival blood samples will be collected at enrollment and at EOT visit of present study. Enrollment visit archival sampling will be waivered for patients who have been performed archival serum sampling at EOT visit of parent study.

Archival blood samples will be collected into red-topped tubes with clot activator (5 mL draw), kept at room temperature for 30 minutes and then centrifuged at approximately 1500 g for 10 minutes at room temperature. The serum will then be transferred, in equal portions, into 2 storage tubes, which will be immediately capped and frozen in an upright position at -20°C or colder.

These archived serum samples, and any residual or leftover serum, plasma or blood remaining from planned laboratory work, may be used for research purposes related to asthma (for example exploratory biomarkers of disease or drug effect), additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol. These samples will remain labeled with the same identifiers as the ones used during the study (that is subject ID, sample ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 13.4 and Section 14.5). Any unused samples will be discarded by 5 years after completion of the last visit for the last patient enrolled in this trial.

Globally, guidelines for blood collection volume limits for pediatric studies range between 1% and 5% of total blood volume (TBV) for a single draw (or during a 24-hour period) and up to 10% of TBV over 8 weeks (9). Scheduled collections in the current protocol, for the smallest possible patient (16 kg), remain within this limit for every 3 months. For all scheduled blood collection visits, the total volume does not exceed 1.5 mL/kg for the smallest possible patient.

9.4 APPROPRIATENESS OF MEASUREMENTS

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

10 STUDY PROCEDURES

The clinical trial consists of 3 periods, using an add-on therapy approach to conventional background asthma controller medications:

- Enrollment (Visit 1 of present study).
- Open-label treatment period (52 weeks; Visits 1-10).

  During the open-label treatment period, patients will continue their background therapy dose regimen, as maintained in the parent study or as modified based on Investigator's judgement.
- Post-treatment period (12 weeks; Visit 11).

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 in the treatment period and ±1 week for the remaining study period.

Spirometry should be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). Spirometry should be performed at visits as detailed in Section 9.2.1.2.

Once every 2 weeks IMP administration must be separated by at least 11 days. Once every 4 weeks IMP administration must be separated by at least 25 days. The treatment period visits occur q2w up to Visit 3 (Week 4), q4w up to Visit 8 (Week 24), and approximately every 12-16 weeks up to the EOS visit as detailed in Section 8.1.3.

Investigational medicinal product can be administrated at home from Visit 2 (Week 2) after approval of Investigator. Patients should be monitored for a minimum of 30 minutes after injections at home. Observations should be recorded in a support document by injection giver and provided to Investigator or delegated during onsite visit. However, if the parent(s)/caregiver(s)/legal guardian(s) or the Investigator decides not to administer IMP at home, the injections can be performed at the study site by way of unscheduled visits. Patients should be monitored at the study site for a minimum of 30 minutes after injections.

At the time of permanent treatment discontinuation, patients will perform the early treatment discontinuation (ETD) visits including early EOT visit and early EOS visit. Early EOT will be performed 2 weeks (with a ±3 days window) after last IMP injection whenever possible. If the time of decision taken for permanent IMP discontinuation is >2 weeks after last IMP injection, this early EOT visit should be scheduled as early as possible from permanent discontinuation of IMP decision.

All the assessments defined for the EOT Visit 10 will be performed during this early EOT. Early EOS visit will be performed 12 weeks after early EOT visit with a ±1 week window. All the assessment defined for the EOS Visit 11 will be performed during this early EOS visit.

Patients should be reminded that sexually active 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. Procedures:
    a) Electrocardiogram
    b) Spirometry
2. Safety and laboratory assessments.
3. Investigational medicinal product administration, if planned, IMP dispensation and return.
4. Controller therapy and medication withhold for next spirometry reminder.

10.1 VISIT SCHEDULE

10.1.1 Enrollment: Visit 1 of present study (Start of treatment, Week 0)

Eligible patients from parent study are considered to be candidates for the LTS14424 study. Patients who enroll in LTS14424 after completing the EFC14153 EOS visit should have laboratory assessments including complete blood count with differential and basic chemistry within 1 month prior to LTS14424 Visit 1 to evaluate continued eligibility. Prior to any discussion of participation of LTS14424 study, all the procedures related to EOT visit of parent study should be performed. Then following a discussion of participation in the present clinical trial, the patient and the parent(s)/caregiver(s)/legal guardian(s) must sign and date the Ethics Committee (EC) approved informed consent form (ICF)/informed assent form (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. These steps precede any study procedures.

The below assessments are conducted at Visit 1. These assessments do not need to be repeated if Visit 1 is performed on the same day as EFC14153 EOT or EOS visit.

The following activities are performed at the enrollment visit (Visit 1):

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height); (waiver if data can be obtained from EOT or EOS visit of Study EFC14153 when it is done on the same day as Visit 1 of present study, except for body weight).
- Call IVRS/IWRS to assign patient number and register enrollment visit.

- Interview to collect patient demographic information, medical history, asthma-specific medical history (that is family history of atopy and IgE mediated disease [particularly maternal], premature birth and/or, low birth weight, exposure to tobacco smoke, recurring viral infections in early childhood), surgical history. Data can be obtained from the parent study, if applicable.
- Inquire prior and concomitant medications, including asthma controller and reliever medications.
- Commence AE reporting from the time of the signature of the informed consent/assent for participation in LTS14424 (anticipated to be at the Visit 1).
- Interview to collect vaccination information and vaccination plan during the treatment period. Remind live vaccines are not authorized.
- Review entry criteria to assess eligibility.
- Perform 12-lead ECG (data may be obtained from EOT or EOS visit of parent study when it is done at the same day as Visit 1 of present study).
- Perform physical examination; (waiver if data can be obtained from EOT or EOS visit of parent study when it is done on the same day as Visit 1 of present study).
- Perform spirometry (waiver if data can be obtained from EOT or EOS visit of parent study when it is done on the same day as Visit 1 of present study).
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Menstruation status for female patients of childbearing potential. (Waiver if data can be obtained from EOT or EOS visit of parent study when it is done on the same day as Visit 1 of present study).
- Obtain blood samples for clinical laboratory parameters; (waiver if data can be obtained from EOT or EOS visit of parent study when it is done on the same day as Visit 1 of present study):
  - Hematology (see Section 9.1.4 for details),
  - Serum chemistry (see Section 9.1.4 for details).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating); (waiver if data can be obtained from EOT or EOS visit of parent study when it is done on the same day as Visit 1 of present study).
- Obtain urinalysis test (dipstick); (waiver if data can be obtained from EOT or EOS visit of parent study when it is done on the same day as Visit 1 of present study).

- Systemic drug concentration and ADA; (waiver if data can be obtained from EOT or EOS visit of parent study when it is done on the same day as Visit 1 of present study).
- Total IgE and antigen-specific IgE (refer to Section 9.2.2.2); (waiver if data can be obtained from EOT visit of parent study when it is done on the same day as Visit 1 of present study. For patients enrolling into Study LTS14424 at EOS visit of Study EFC14153 or up to 12 weeks after EOS, an additional blood draw will be done for total and antigen-specific IgE.
- Archival serum for those patients who have signed a specific Future Use of Specimens informed consent/assent of present LTS14424 study (refer to Section 9.3); (waiver if sample is obtained from EOT visit of parent study).
- Note: For patients not able to perform EOT or EOS visit of parent study onsite due to COVID-19 pandemic, all the assessments above must be performed during Visit 1.
- Dispense and administer IMP. Patient whose body weight increased from ≤30 kg to >30 kg during the parent study, their dupilumab dose will be adjusted from 100 mg SC q2w or 300 mg SC q4w to 200 mg SC q2w at the time of enrollment visit (Visit 1 of present study and during treatment period:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection,
  - The injection training is for families who are willing to perform injection administration at home for children receiving q2w doses. The Investigator or delegate will review the patient's administration technique at the Visit 1 (or upcoming onsite visits before permitting IMP administration at home).
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their dose of ICS alone or in combination with a second controller.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Schedule a site visit 2 weeks later (Week 2 ±3 days) at approximately the same time of this visit.

10.1.2 Open-label treatment period (Week 0 to Week 52 [Visits 2-10])

10.1.2.1 Visit 2 (Week 2 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.

- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Perform spirometry:
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Assess menstruation status.
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP for children receiving q2w doses:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if IMP administrated on site.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Schedule a site visit 2 weeks later (Week 4 ±3 days) at approximately the same time of this visit.

10.1.2.2 Visit 3 (Week 4 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Assess menstruation status.
- Obtain blood samples for screening clinical laboratory determinations:
  - Hematology (see Section 9.1.4 for details),
  - Serum chemistry (see Section 9.1.4 for details).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).

- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of at least 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Schedule a site visit 4 weeks later (Week 8 ±3 days) at approximately the same time of this visit.

10.1.2.3 Visit 4 (Week 8 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Perform spirometry
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Assess menstruation status.
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).

- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of at least 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold the IMP dosing to secure an interval of 14 ±3 days prior to next onsite visit (Visit 5) for patients receiving IMP administration at home.
- Schedule a site visit 4 weeks later (Week 12 ±3 days) at approximately the same time of this visit.

10.1.2.4 Visit 5 (Week 12 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Perform spirometry:
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Perform physical examination.
- Assess menstruation status.

- Obtain blood samples for:
  - Hematology (see Section 9.1.4 for details),
  - Serum chemistry (see Section 9.1.4 for details).
- Systemic drug concentration and ADA (see Section 9.2.2.1.1 for details).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Urinalysis (dipstick).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of at least 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Schedule a site visit 4 weeks later (Week 16 ±3 days) at approximately the same time of this visit.

10.1.2.5 Visit 6 (Week 16 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Assess menstruation status.
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of a minimum of 30 minutes after the injections monitored by IMP giver if patients receive IMP at home.

- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Schedule a site visit 4 weeks later (Week 20±3 days) at approximately the same time of this visit.

10.1.2.6 Visit 7 (Week 20 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Assess menstruation status.
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of a minimum of 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold the IMP dosing to secure an interval of 14 ±3 days prior to next onsite visit (Visit 8) for patients receiving IMP administration at home.

- Schedule a site visit 4 weeks later (Week 24±3 days) at approximately the same time of this visit.

10.1.2.7 Visit 8 (Week 24 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Perform physical examination.
- Perform spirometry:
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Assess menstruation status.
- Obtain blood samples for:
  - Hematology (see Section 9.1.4 for details),
  - Serum chemistry (see Section 9.1.4 for details).
- Systemic drug concentration and ADA (see Section 9.2.2.1 for details).
- Total IgE and antigen-specific IgE (refer to Section 9.2.2.2).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Urinalysis (dipstick).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of a minimum of 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.

- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Schedule a site visit 12 weeks later (Week 36 ±3 days) at approximately the same time of this visit.

10.1.2.8 Telephone contact at Week 28 and 32 (±3 days)

- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs; and report in eCRF along with date of phone call.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.

10.1.2.9 Visit 9 (Week 36 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.

  Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Assess menstruation status.
- Obtain blood samples for:
  - Hematology (see Section 9.1.4 for details),
  - Serum chemistry (see Section 9.1.4 for details).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of a minimum of 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.

- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Schedule a site visit 16 weeks later (Week 52 ±3 days) at approximately the same time of this visit.

10.1.2.10 Telephone contact at Weeks 40, 44, and 48 (±3 days)

- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs; and report in eCRF along with date of phone call.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.

For Week 48 only

- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold the IMP dosing to secure an interval of 14 ±3 days prior to next onsite visit (EOT visit) for patients receiving IMP administration q2w at home or 28 ±3 days prior to next onsite visit (EOT visit) for patients receiving IMP administration q4w.

10.1.2.11 Visit 10 (Week 52 [±3 days]), End-of-treatment visit

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height).
- Call IVRS/IWRS to register EOT visit.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Perform spirometry:

  Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.

- Perform physical examination.
- Assess menstruation status.
- Perform 12-lead ECG.
- Obtain blood samples for:
  - Hematology (see Section 9.1.4 for details),
  - Serum chemistry (see Section 9.1.4 for details).
- Systemic drug concentration and ADA (see Section 9.2.2.1 for details).
- Total IgE and antigen-specific IgE (refer to Section 9.2.2.2) .
- Archival serum for those patients who have signed a specific Future Use of Specimens informed consent/assent (refer to Section 9.3).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Urinalysis (dipstick).
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.
- Schedule a site visit 12 weeks later (Week 64 ±1 week) at approximately the same time of this visit.

10.1.3 Post-treatment period (12 weeks)

10.1.3.1 Telephone contact at Weeks 56 and 60 (±1 week)

- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs; and report in eCRF along with date of phone call.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller or as adjusted per Investigator's decision.

For Week 60 only:

- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.

10.1.3.2 Visit 11: (Week 64 [±1 week]), end-of-study visit

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register EOS visit.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Perform physical examination.
- Perform spirometry:

  Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Assess menstruation status.
- Perform 12-lead ECG.
- Obtain blood samples for:
  - Hematology (see Section 9.1.4 for details),
  - Serum chemistry (see Section 9.1.4 for details).
- Systemic drug concentration and ADA (see Section 9.2.2.1 for details).
- Total IgE and antigen-specific IgE (refer to Section 9.2.2.2).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Obtain urinalysis test (dipstick).

10.2 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and

evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

All the data collected in the eCRF should be transcribed directly from source documents. Data downloaded from the study-associated central laboratories, and spirometry will be considered source data.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgement that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2), AE is sufficiently resolved and unlikely to recur after resuming therapy with IMP.

In addition, the following conditions will be causes for temporary treatment discontinuation:

- Infections or infestations that do not respond to medical treatment.
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Section 17.4 on Guidelines for management of specific laboratory abnormalities.
- Any administration of live attenuated vaccines (refer to Section 17.2) during the study period.

Temporary discontinuation may lead to permanent discontinuation after Sponsor's review on a case by case basis.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

In case of permanent treatment discontinuation, the patient follow-up and visits are detailed in Section 10.3.4.

10.3.3 List of criteria for permanent treatment discontinuation

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

Patients must be withdrawn from the study treatment (that is from any further investigational product or study procedure) for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Pregnancy (Note: dupilumab should be stopped but patient should be followed up until the outcome has been determined).
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (see Section 17.6).
- Serum ALT >3 upper limit of normal (ULN) and total bilirubin >2 ULN (see Section 17.4)
- Serum ALT >5 ULN if enrollment visit ALT is <2 ULN or ALT >8 ULN if enrollment visit ALT is >2 ULN (Section 17.4).

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. Study Investigators should continue background therapy after treatment discontinuation, as guided by their medical judgement.

Patients who prematurely discontinue the study medication, at the time of permanent treatment discontinuation, patients will perform:

- Early EOT visit: 2 weeks (with a ±3 days window) after last IMP injection. If the time of decision taken for permanent IMP discontinuation is >2 weeks +3 days after last IMP injection, this early EOT visit should be scheduled as early as possible from permanent discontinuation of IMP decision. All the assessments defined for the EOT Visit 10 will be performed during this early EOT,
- Early EOS visit: 12 weeks after early EOT visit with a ±1 week window. All the assessment defined for the EOS Visit 11 will be performed during this visit.

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.

All cases of permanent treatment discontinuation should be entered by the Investigator in the eCRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may be withdrawn from the study at any time during the course of study if their parent(s)/caregiver(s)/legal guardian(s) decide to do so, and irrespective of the reason without any effect on their care. However, if patients no longer wish to take the IMP, they will be encouraged to remain in the study and perform the procedures planned for the EOT/EOS visit, including spirometry.

The Investigators should discuss with parent(s)/caregiver(s)/legal guardian(s) key visits the patient to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

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

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

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

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator must make the best effort to recontact the patient (for example contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (for example times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who have withdrawn from the study cannot be re-enrolled (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Protocol-defined severe asthma exacerbation events (for detailed definitions see Section 9.2.1.1) are collected as efficacy endpoints on the e-CRF. Only asthma exacerbations which fulfill a seriousness criterion should be reported as an AE (SAE) (as per Section 10.4.1.2).

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 judgement 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 (that is 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 (that is agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc.)

- Development of drug dependence or drug abuse,
- Alanine aminotransferase (ALT) >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN,
- New psychosis,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions,
- Bullous cutaneous eruptions requiring treatment,
- Cancers diagnosed during the study,
- Chronic neurodegenerative diseases (newly diagnosed).

10.4.1.3 Adverse event of special interest

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

- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (refer to Section 17.5 for the definition of anaphylaxis).
- Serious ISRs or severe ISRs that last longer than 24 hours.

  Note: A severe ISR (for AE reporting) is any event that meets one of the following criteria:

  - With a diameter of at least 10 cm,
  - Impacting daily activities,
  - With ulceration or necrosis,
  - For which operative intervention is required.
- An infection that meets at least one of the following criteria:
  - Any severe or serious infection (that meet any of the SAE criteria),
  - Is a parasitic infection,
  - Is an opportunistic infection (see list in Section 17.6).
- Significant elevation of ALT (Section 17.4):
  - Alanine aminotransferase (ALT) >3 x the ULN associated with total bilirubin >2 x ULN; or,
  - Alanine aminotransferase (ALT) >5 × ULN in patients with enrollment visit ALT ≤2 × ULN; or,
  - Alanine aminotransferase (ALT) >8 × ULN if enrollment visit 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 nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP 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 <11 days for q2w or <25 days for q4w. The circumstances (that is 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 (that is 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/assent 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 eCRF.
- 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 Global Safety Officer (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 eCRF.
- Causality will be assessed separately for IMP and NIMP.

- 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. At the prespecified study end-date, patients who experience an ongoing SAE or an AESI should be followed until resolution, stabilization, or death and related data will be collected.
- 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.

Instructions for AE reporting are summarized in Table 5.

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 eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF 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 eCRF 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 case report form [CRF] process) is available and should be used when the eCRF 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 (that is within 24 hours), as per SAE notification guidelines described in Section 10.4.4, even if not fulfilling a seriousness criterion, using the screens in the eCRF.

Instructions for AE reporting are summarized in Table 5.

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Section 17.4.

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

- 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.

Table 5 - 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 enrollment visit ALT is ≤2 ULN	Within 24 hours
	ALT >8 ULN if enrollment visit 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 ISR 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

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; ISR = injection site reaction; ULN = upper limit of normal.

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 (Suspected Unexpected Serious Adverse Reaction [SUSAR]), to the regulatory authorities, Independent Ethics Committee (IEC)/Institutional Review Boards (IRB) 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 (for example 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 judgement 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 (CSR).

10.6 SAFETY INSTRUCTIONS

During the study, all patients will be closely monitored.

In addition, any problems related to dupilumab injection administration should be documented in the patient's home dosing diary and in the specific eCRF pages for local injection reactions recording.

10.6.1 Hypersensitivity

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

Allergic reactions may be defined as an immunologically mediated response to a pharmaceutical and/or formulation agent in a sensitized person. Signs and symptoms are often experienced during or shortly after therapeutic administration. Anaphylaxis may represent the most severe form of allergic reactions; refer to Section 17.5 "Definition of Anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should 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 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 study medication must be permanently discontinued. Anti-drug antibodies and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

In case of suspected anaphylaxis or systemic hypersensitivity reaction, sample for ADA should be obtained as close to the time of the event as possible.

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 ISR observed at the highest dose level (300 mg weekly) severe ISR are considered as a potential risk. Patients who experience an ISR must be closely monitored for the possibility of a more intense ISR with a future injection. Any severe ISR that lasts over 24 hours will be reported as an AESI with immediate notification. Anti-drug antibodies and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

Prophylactic treatment/premedication for an ISR is not permitted.

10.6.3 Infections

Some biologic therapies have been associated with an increased risk of infection, including opportunistic infection. 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.

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. 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. Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 binding, and activation of their respective receptors, it inhibits Th2 cytokine production. 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. 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 enrollment. 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, particularly when conditions are conducive to infection (for example extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers, and vectors, etc). Subsequent medical assessments (for example stool exam, blood tests, etc) must be performed in order to rule out parasitic infection/infestation. Patients with confirmed parasitic infections during the study should be reported as AESI with immediate notification.

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

A complete diagnostic work-up should be performed (that is cultures, 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 IMP 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 17.6), patients must be permanently discontinued from IMP.

10.6.4 Elevated liver function tests

No preclinical or clinical data have suggested any hepatic toxicity of dupilumab; however, as general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity.

In order to closely follow liver function tests (LFT), assessment of total protein, albumin, total bilirubin, ALT, AST, and ALP are measured as part of the clinical laboratory testing.

Guidance for the investigation of elevated LFTs is provided in Section 17.4.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations and included in the final CSR.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The primary objective of the study is to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in previous dupilumab asthma clinical trial. Hence, the maximal number of patients to participate in this 1-year treatment safety study will be the number corresponding to the total randomized in previous dupilumab asthma clinical study.

Based on the observed enrolment rate of 87% from parent study to this study, the expected number of sample size for LTS14424 study is approximately 354 patients (that is around 87% of 408 patients from parent study).

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patients who signed the informed consent/assent.

Enrolled patients consist of all the patients who signed informed consent/assent and had a treatment kit number allocated and recorded in IVRS/IWRS database, and regardless of whether the treatment kit was used or not.

The safety population consists of the patients who actually received at least one dose or part of a dose of dupilumab in the LTS14424 study.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

Efficacy population is the same as the safety population.

11.3.2 Safety population

The primary analysis population is the safety population, which is defined as all patients exposed to at least 1 dose or part of 1 dose of dupilumab during LTS14424 study regardless of the amount of treatment administered.

11.3.3 Pharmacokinetics population

The PK population will consist of all the patients in the safety population with at least one nonmissing and evaluable predose serum concentration value after the first dose of dupilumab in the LTS14424 study.

11.3.4 Anti-drug antibody population

The ADA population will consist of all the patients in the safety population with at least one non-missing ADA result following the first dose of dupilumab in the LTS14424 study.

11.4 STATISTICAL METHODS

For each analysis population defined in Section 11.3, the planned analyses will be conducted in the following two analysis sets, respectively.

The full analysis set for each analysis population will include all data observed in the study.

The modified analysis set for each analysis population will censor the data observed on or after the first dose of 300 mg q4w for the patients in this analysis population who were exposed to the 300 mg q4w regimen. Particularly, the patients who will initiate the treatment on 300 mg q4w regimen since Week 0 of LTS14424 study will be excluded from the modified analysis set.

For each analysis set, the planned analyses will be presented by the group of patients according to their actual treatment groups in the parent study EFC14153, specifically, 'Placebo-Dupilumab', 'Dupilumab-Dupilumab', and 'All'.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be summarized in the two analysis sets for safety population as defined in Section 11.4.

11.4.1.1 Extent of investigational medicinal product exposure

Duration of exposure to IMP is defined as: last dose date – first dose date of dupilumab + dose interval, regardless of unplanned intermittent discontinuations. Duration of exposure will be summarized using descriptive statistics such as mean, standard deviation (SD), median, minimum, and maximum.

11.4.1.2 Compliance

A given administration of IMP will be considered "noncompliant" if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as 100 x (the number of administrations the patient was compliant divided by the total number of administrations the patient was planned to take during the treatment period).

Treatment compliance will be summarized descriptively (N, mean, SD, median, minimum, and maximum). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

All analyses will be done descriptively in the two analysis sets for safety population as defined in Section 11.4 in observed case, as appropriate.

The baseline value for the applicable efficacy parameters is the original baseline from the parent study.

For the continuous efficacy variables, descriptive statistics (mean, SD, median, minimum, and maximum) will be presented for the parameter and its change from baseline over visits. In addition, figure of mean change from baseline (with corresponding standard error) will be presented for the continuous efficacy parameter over visits. The baseline for the primary analyses for change from baseline for continuous efficacy variables will be the baseline in parent study. Supplemental analyses for change from current study baseline will also be provided for selected efficacy variables. The list of these selected variables will be further detailed in Statistical Analysis Plan (SAP).

For the categorical efficacy variables, the number and percentage will be presented over time for all patients who have data available at that time point.

For severe exacerbation events, total number of severe exacerbation events, total patient-years, unadjusted annualized severe exacerbation event rate, and individual patient annualized severe exacerbation event rate (number, mean, SD, median, minimum, maximum) during the treatment period will be summarized. In the modified analysis set, for the patients whose dose regimen switch from 100 mg q2w to 300 mg q4w, the events observed on or after the first injection day of 300 mg q4w regimen will be excluded and the observational period will be censored at the day before the first dose of 300 mg q4w. The time point window for the efficacy analyses will be the same as that defined for safety analyses. More details about the efficacy analysis methods and the time point window can be found in the SAP.

11.4.3 Analyses of safety data

All safety analysis will be performed in two analysis sets for the safety population as defined in Section 11.4. The baseline value for the applicable safety parameters is the original baseline from the parent study.

11.4.3.1 Adverse events

The treatment-emergent period is defined for the two analysis sets separately as follows.

For the full analysis set, the treatment emergent period is from the date of first IMP injection to the date of the last IMP injection +14 weeks for the patients who end the dupilumab treatment on either 100 mg q2w or 200 mg q2w regimen; and, the treatment emergent period is from the date of first IMP injection to the date of the last IMP injection +16 weeks for the patients who end the dupilumab treatment on 300 mg q4w regimen.

For the modified analysis set, the treatment emergent period is from the date of first IMP injection to the date of the last IMP injection +14 weeks for the patients who never expose to the 300 mg q4w regimen; and, the treatment emergent period is from the date of first injection of 100 mg q2w regimen to the date before the first injection of the 300 mg q4w regimen for the patients who uptitrate the dosage from 100 mg q2w to 300 mg q4w during the study.

Adverse event reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi at the time of database lock. Adverse events occurred during the treatment-emergent period will be considered as TEAEs.

11.4.3.1.1 Treatment-emergent adverse events

Treatment-emergent adverse event incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high level group term (HLGT), high level term (HLT), and preferred term (PT) sorted in alphabetical order, the number (n) and percentage (%) of patients experiencing a TEAE. Multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator is based on the total number of patients in the safety population.

Proportion of patients with at least one TEAE, serious TEAE, and TEAE leading to discontinuation of the study will be tabulated. TEAEs will also be described according to maximum intensity and relation to the study drug. Adverse events that are not treatment-emergent will be summarized separately.

11.4.3.1.2 Adverse event of special interest

The following summaries will be generated:

- Incidence of each AESI will be tabulated.
- The time-to-first event analyzed using Kaplan-Meier (K-M) methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. Number of treatment-emergent AESIs per 100 patient-years (total number of events adjusted for the total duration of exposure) will be presented by decreasing incidence of PT.
- An overview summary of the number (%) of patients with:
  - Any TEAE,
  - Any serious AE (regardless of treatment-emergent status),
  - Any treatment-emergent SAE,
  - Any AE leading to death,
  - Any TEAE leading to permanent study drug discontinuation,
  - Any TEAE by maximum intensity, corrective treatment, and final outcome,
  - Cumulative incidence (K-M estimates) up to specified time points.

Adverse event of special interest (AESI) definitions and the method to identify AESIs will be specified in the SAP.

11.4.3.1.3 Death

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population.
- Treatment-emergent adverse event (TEAE) leading to death (death as an outcome on the AE eCRF 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, and AEs leading to study discontinuation, AESIs, and deaths.

11.4.3.1.4 Clinical laboratory evaluation, vital signs, and electrocardiogram data

Results and change from baseline for the parameters will be summarized for baseline and each post baseline time point, endpoint, minimum, and maximum value. Summary statistics will include number of patients, mean, SD, median, first quartile (Q1), the third quartile (Q3), minimum, and maximum.

Listings will be provided with flags indicating clinically out of range values, as well as potentially clinically significant abnormalities (PCSA) values.

11.4.4 Analyses of systemic drug concentration, anti-drug antibodies, and pharmacodynamics variables

11.4.4.1 Pharmacokinetic analysis

The PK analyses will be performed in the two analysis sets for PK population as defined in Section 11.4 by the dose regimen. The baseline value of each applicable PK variable is the original baseline from the parent study. Serum concentrations of functional dupilumab will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation, minimum, maximum, and median.

11.4.4.2 Anti-drug antibodies analysis

The ADA analyses will be performed in the two analysis sets for ADA population as defined in Section 11.4. The baseline value of each applicable ADA variable is the original baseline from the parent study. The incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%). 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, if applicable. Assessment of the potential impact of ADA on safety, efficacy, and PK may be provided. The ADA analyses will be detailed in SAP.

11.4.4.3 Pharmacodynamics

The biomarker analyses will be applied in the two analysis sets for safety population. The baseline value for the applicable pharmacodynamics (PD) variables is the original baseline from the parent study. For all PD parameters, the descriptive statistics (number, mean, median, SD, Q1, Q3, minimum and maximum) will be summarized over time for the raw measurements, the change from baseline, and percentage change from baseline. Summary plots (mean ±SEM) over time on the raw measurements, change from baseline, and percentage change from the baseline will be presented for the PD parameters.

All parameters will be summarized in descriptive statistics.

11.5 INTERIM ANALYSIS

This is 1 year treatment safety study. Interim analyses/reports may be prepared to support regulatory submissions of an indication in the dupilumab project or other purposes. No alpha adjustment is needed for the final CSR.

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 Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation (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 of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the EC (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent/assent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent/assent discussion. A copy of the signed and dated written informed consent/assent form will be provided to the patient.

The informed consent/assent form used by the Investigator for obtaining the patient's informed consent/assent must be reviewed and approved by the Sponsor prior to submission to the appropriate EC (IRB/IEC) for approval/favorable opinion.

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the EC (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the informed consent/assent form should be signed, name filled in and personally dated by the patient’s parent(s) or by the patient’s legally acceptable representative, and by the person who conducted the informed consent/assent discussion. 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 for only 1 parent or guardian’s signature.

In addition, participants will assent as detailed below or will follow the EC (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB's/IEC's or be consistent with the local requirements):

- Participants who can read the assent form will do so before writing their name and dating or signing and dating the form.
- Participants who can write but cannot read will have the assent form read to them before writing their name on the form.
- Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent/assent form and the assent form used by the Investigator for obtaining the Patient's Informed Consent/assent must be reviewed and approved by the Sponsor prior to submission to the appropriate EC (IRB/IEC) for approval/favorable opinion.

In relation with the population of patients exposed in the trial that is pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical, and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title, and version number), the documents reviewed (clinical trial protocol, ICF, Investigator's Brochure, and Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements, and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent/assent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use, and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the preidentified source data directly recorded in the eCRF. The informed consent/assent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the EC (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (for example patient's medical file,

appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the CV describing the experience, qualification, and training of each Investigator and Subinvestigator will be signed, dated, and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents for 25 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the eCRFs, the Investigator's, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the EC (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities (for example on African American population for Food and Drug Administration [FDA]).

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy, and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IRBs/IECs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, good clinical practice, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon 30 days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent/assent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent/assent form prior to implementation of the change and patient signature should be recollected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Nordlund B, Melen E, Schultz ES, Grönlund H, Hedlin G, Kull I. Prevalence of severe childhood asthma according to the WHO. Respir Med. 2014;108(8):1234-7.

2. Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, De Benedictis FM, Melen E, et al. Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. Eur Respir J. 2010;36(1):196-201.

3. Levine SJ, Wenzel SE. Narrative review: The role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. Ann Intern Med. 2010;152(4):232-7.

4. Wenzel SE, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-66.

5. Wenzel SE, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016;388(10039):31-44.

6. Liptrott NJ, Penny M, Bray PG, Sathish J, Khoo SH, Back DJ, et al. The impact of cytokines on the expression of drug transporters, cytochrome P 450 enzymes and chemokine receptors in human PBMC. Br J Pharmacol. 2009;156(3):497-508.

7. Abdel-Razzak Z, Loyer P, Fautrel A, Gautier JC, Corcos L, Turlin B, et al. Cytokines down-regulate expression of major cytochrome p-450 enzymes in adult human hepatocytes in primary culture. Mol. Pharmacol. 1993;44(4):707-15

8. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coateset A, et al. Standardization of spirometry. Series ‘‘ATS/ERS TASK FORCE: Standardization of Lung Function Testing" Edited by Brusasco V, Crapo R, and Viegi G. Eur Resir J. 2005;26(2):319-38.

9. Howie SRC. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89(1):46–53

10. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902-7.

11. Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, De Benedictis FM, Melen E, et al. Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. Eur Respir J. 2010;36(1):196-201.

12. Levine SJ, Wenzel SE. Narrative review: The role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. Ann Intern Med. 2010;152(4):232-7.

13. Wenzel SE, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-66.

14. Wenzel SE, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016;388(10039):31-44.

15. Liptrott NJ, Penny M, Bray PG, Sathish J, Khoo SH, Back DJ, et al. The impact of cytokines on the expression of drug transporters, cytochrome P 450 enzymes and chemokine receptors in human PBMC. Br J Pharmacol. 2009;156(3):497-508.

16. Abdel-Razzak Z, Loyer P, Fautrel A, Gautier JC, Corcos L, Turlin B, et al. Cytokines down-regulate expression of major cytochrome p-450 enzymes in adult human hepatocytes in primary culture. Mol. Pharmacol. 1993;44(4):707-15

17. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coateset A, et al. Standardization of spirometry. Series ‘‘ATS/ERS TASK FORCE: Standardization of Lung Function Testing" Edited by Brusasco V, Crapo R, and Viegi G. Eur Resir J. 2005;26(2):319-38.

18. Howie SRC. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89(1):46–53

19. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902-7.

20. Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, De Benedictis FM, Melen E, et al. Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. Eur Respir J. 2010;36(1):196-201.

21. Levine SJ, Wenzel SE. Narrative review: The role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. Ann Intern Med. 2010;152(4):232-7.

22. Wenzel SE, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-66.

23. Wenzel SE, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016;388(10039):31-44.

24. Liptrott NJ, Penny M, Bray PG, Sathish J, Khoo SH, Back DJ, et al. The impact of cytokines on the expression of drug transporters, cytochrome P 450 enzymes and chemokine receptors in human PBMC. Br J Pharmacol. 2009;156(3):497-508.

25. Abdel-Razzak Z, Loyer P, Fautrel A, Gautier JC, Corcos L, Turlin B, et al. Cytokines down-regulate expression of major cytochrome p-450 enzymes in adult human hepatocytes in primary culture. Mol. Pharmacol. 1993;44(4):707-15

26. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coateset A, et al. Standardization of spirometry. Series ‘‘ATS/ERS TASK FORCE: Standardization of Lung Function Testing" Edited by Brusasco V, Crapo R, and Viegi G. Eur Resir J. 2005;26(2):319-38.

27. Howie SRC. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89(1):46–53

28. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902-7.

29. Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, De Benedictis FM, Melen E, et al. Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. Eur Respir J. 2010;36(1):196-201.

30. Levine SJ, Wenzel SE. Narrative review: The role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. Ann Intern Med. 2010;152(4):232-7.

31. Wenzel SE, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-66.

32. Wenzel SE, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016;388(10039):31-44.

33. Liptrott NJ, Penny M, Bray PG, Sathish J, Khoo SH, Back DJ, et al. The impact of cytokines on the expression of drug transporters, cytochrome P 450 enzymes and chemokine receptors in human PBMC. Br J Pharmacol. 2009;156(3):497-508.

34. Abdel-Razzak Z, Loyer P, Fautrel A, Gautier JC, Corcos L, Turlin B, et al. Cytokines down-regulate expression of major cytochrome p-450 enzymes in adult human hepatocytes in primary culture. Mol. Pharmacol. 1993;44(4):707-15

35. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coateset A, et al. Standardization of spirometry. Series ‘‘ATS/ERS TASK FORCE: Standardization of Lung Function Testing" Edited by Brusasco V, Crapo R, and Viegi G. Eur Resir J. 2005;26(2):319-38.

36. Howie SRC. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89(1):46–53

37. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902-7.

17 APPENDICES

17.1 APPENDIX A: EXAMPLES OF COMMONLY USED ASTHMA CONTROLLER THERAPIES

Controller group	Medications
Inhaled corticosteroids (ICS)	Beclomethasone dipropionate CFC
	Beclomethasone dipropionate HFA
	Budesonide
	Ciclesonide
	Fluticasone propionate
	Mometasone furoate
	Triamcinolone acetonide
	Fluticasone Furoate
ICS/long acting β2 agonist (LABA) combination as metered-dose inhaler (MDI)	
	Fluticasone Propionate/Salmeterol
	Fluticasone Propionate/Formoterol
	Fluticasone Furoate/Vilanterol
	Budesonide/Formoterol
	Mometasone Furoate/Formoterol
	Beclometasone Dipropionate and Formoterol
Long acting β2 agonist (LABA)	
	Salmeterol
	Formoterol
	Bambuterol
	Clenbuterol
	Tulobuterol
	Vilanterol
	Olodaterol
	Indacaterol
Leukotriene receptor antagonists (LTRA) or anti-leukotrienes	
	Montelukast
	Pranlukast
	Zafirlukast
	Zileuton

Controller group	Medications
Long acting muscarinic antagonist (LAMA)	
	Tiotropium
	Glucopyrronium bromide
	Aclidinium bromide
	Umeclidinium
Methylxanthines	
	Aminophylline
	Theophylline
	Dyphylline
	Oxtryphylline
	Diprophylline
	Acebrophylline
	Bamifylline
	Doxofylline

Abbreviations: CFC = chlorofluorocarbon propellant; HFA = hydrofluoroalkane propellant; MDI = metered dose inhaler.

Note: This list is indicative and not exhaustive.

17.2 APPENDIX B: LIST OF PROHIBITED LIVE ATTENUATED VACCINES

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

Note: This list is indicative and not exhaustive.

17.3 APPENDIX C: EXAMPLES OF CYP SUBSTRATES WITH NARROW THERAPEUTIC RANGE

CYP enzymes	Substrates with narrow therapeutic range[1]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A[2]	Alfentanil, astemizole[3], cisapride[3], cyclosporine[4], dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus[4], terfenadine[3]
CYP2D6	Thioridazine

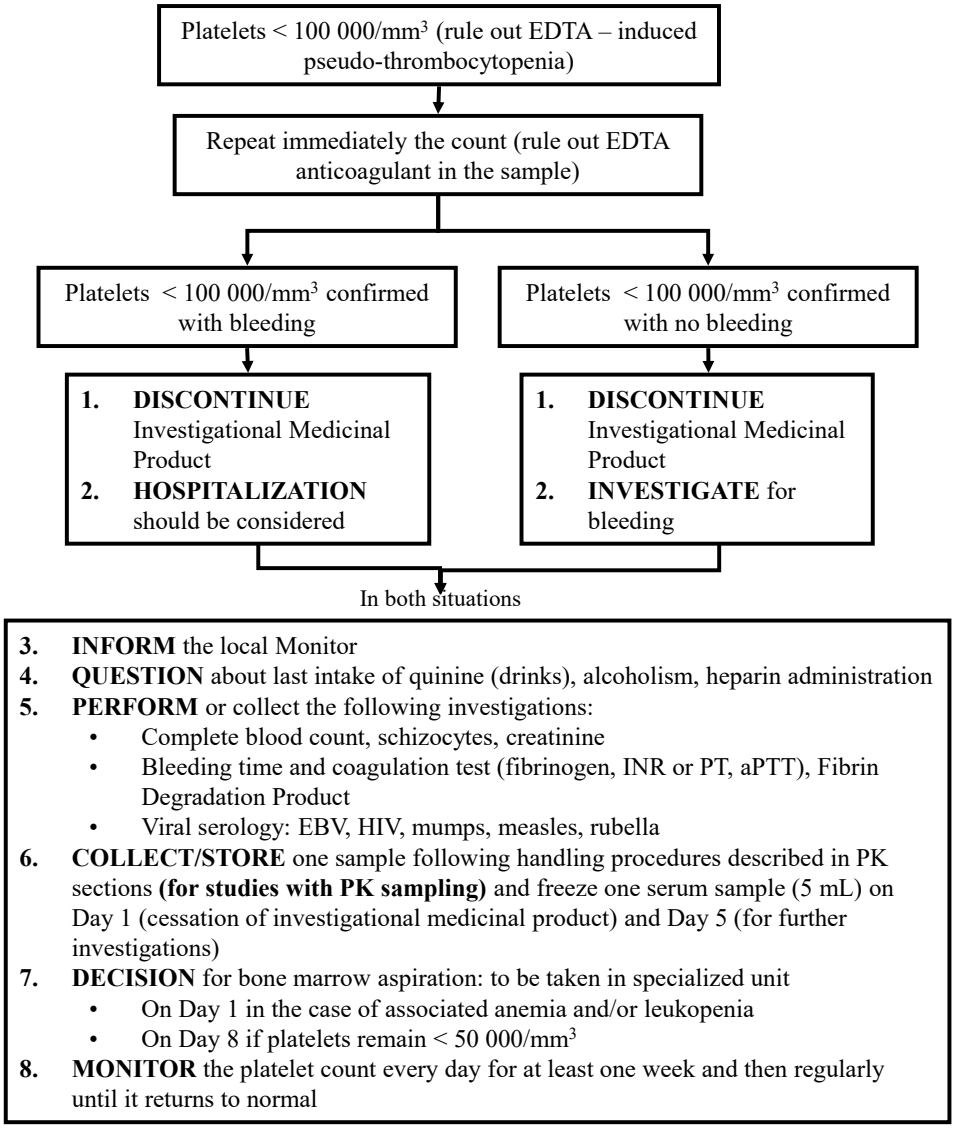
Abbreviation: CYP = Cytochromes P450.

Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

1. CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small changes in their exposure levels by the concomitant use of CYP inhibitors or inducers may lead to either serious safety concerns (for example Torsades de Pointes) or loss of therapeutic effect.
2. Because a number of CYP3A substrates (for example darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
3. Withdrawn from the United States market because of safety reasons.
4. Prohibited medication during the study.

17.4 APPENDIX D: GENERAL GUIDANCE FOR THE FOLLOW-UP OF LABORATORY ABNORMALITIES BY SANOFI

THROMBOCYTOPENIA



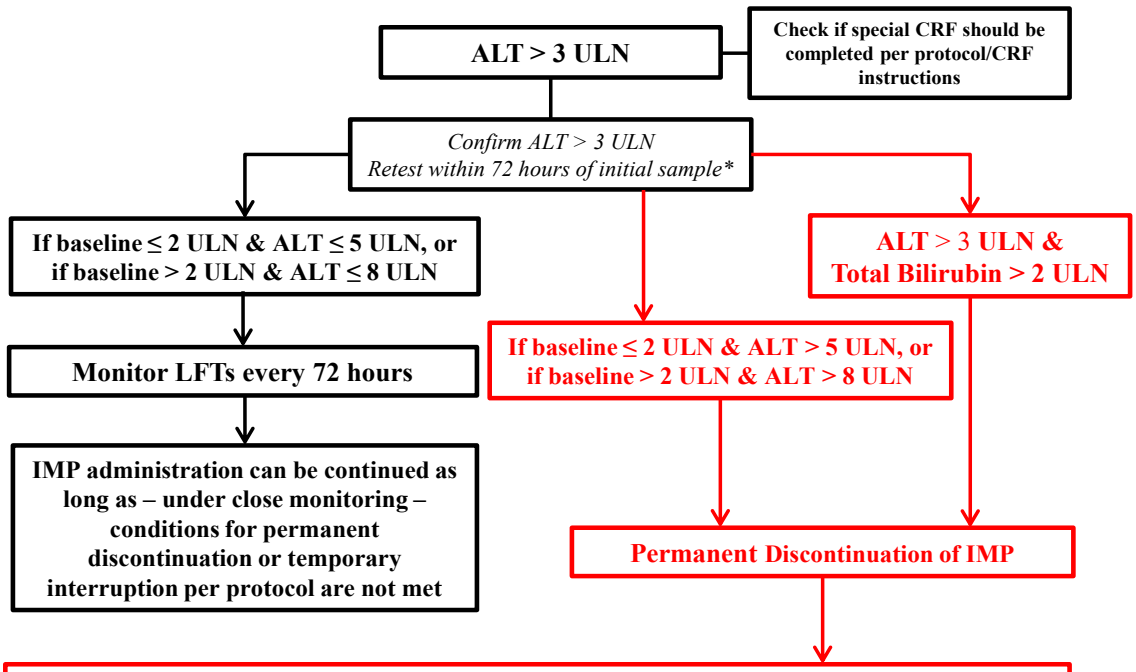
Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Note for PK sampling: For pediatric PK sampling, only 2 mL of blood should be collected to freeze 2 serum samples (0.5 mL each) on Day 1.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.4.3 is met.

Applies to Phase 2, 3, and 4 studies where inclusion is limited to patients with baseline ALT ≤2 x ULN (excluding patients with clinically-relevant hepatic disease)

ALT Increase

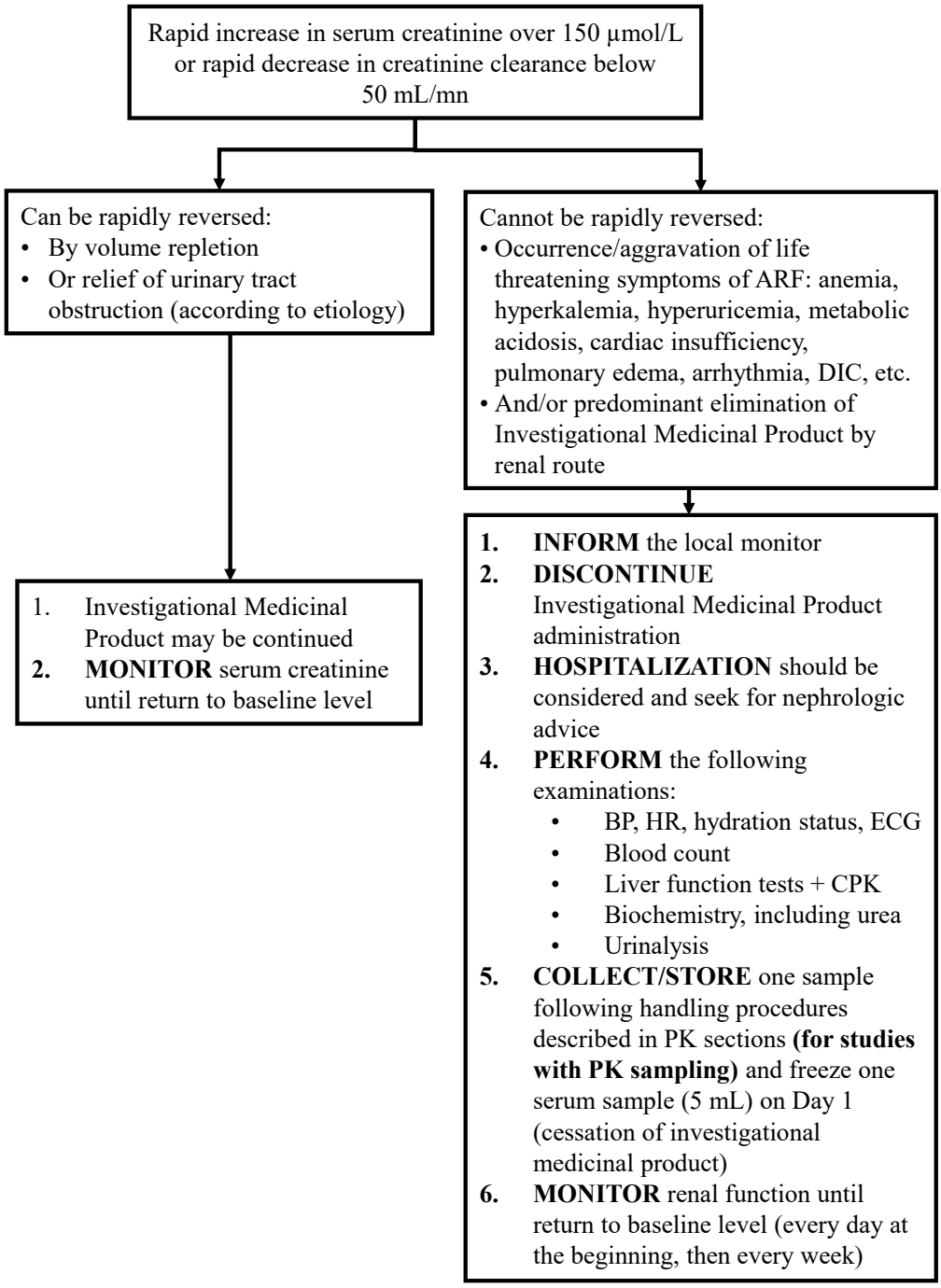


In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **COMPLETE** the CRF for «ALT Increase» for any permanent discontinuations due to liver injury (See protocol/CRF instructions)
3. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
4. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
5. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
6. **CONSIDER** consulting with hepatologist
7. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
8. **MONITOR LFTs after discontinuation of IMP:**
   - A*s closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
9. **FREEZE** serum sample (5ml x 2)
10. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

Note:
Normalization is defined as < ULN or baseline value if baseline value is >ULN.
As soon as seriousness criterion is met or the event leads to permanent treatment discontinuation, the monitoring team should be notified within 24 hours.
*If unable to retest in 72 hours, use original lab results to decide on further monitoring/ discontinuation .

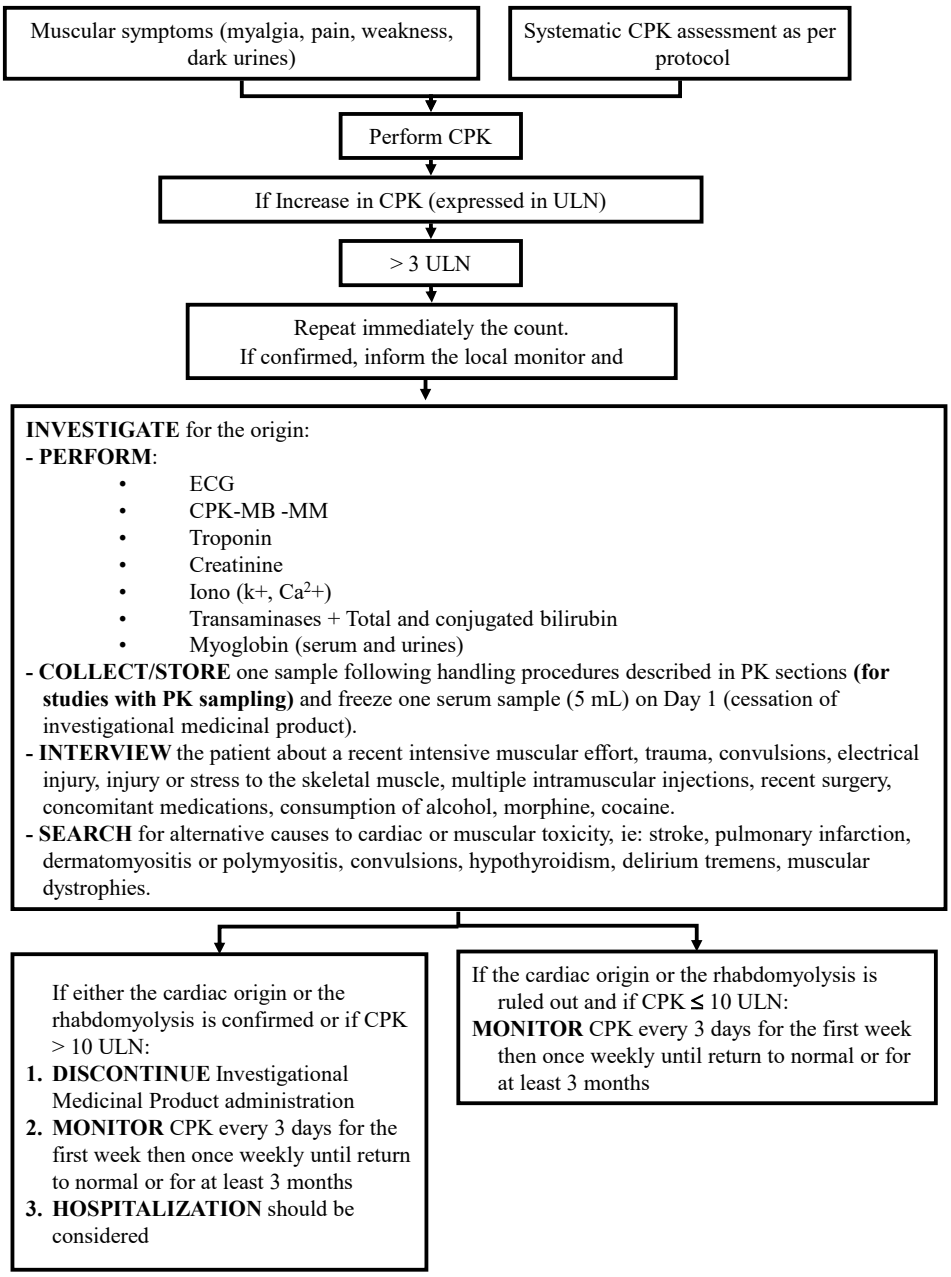
ACUTE RENAL FAILURE



Note for PK sampling: For pediatric PK sampling, only 2 mL of blood should be collected to freeze 2 serum samples (0.5 mL each) on Day 1.

Acute renal failure is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.4.3 is met.

SUSPICION OF RHABDOMYOLYSIS



Note for PK sampling: For pediatric PK sampling, only 2 mL of blood should be collected to freeze 2 serum samples (0.5 mL each) on Day 1.

Suspicion of rhabdomyolysis is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.4.3 is met.

17.5 APPENDIX E: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."

Adapted from:

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA , Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7

Clinical criteria for diagnosing anaphylaxis

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

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

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

17.6 APPENDIX F: LIST OF OPPORTUNISTIC INFECTIONS

- Aspergillosis.
- *Blastomyces dermatitidis* (pathogenic fungus causing blastomycosis; endemic in the south eastern and south-central states of the US and along Mississippi and Ohio Rivers).
- Candidiasis - only systemic or extensive mucosal or cutaneous cases of yeast infection.
- *Coccidioides immitis* (pathogenic fungus causing coccidiosis; endemic south-western US and Central and South America).
- Cryptococcus.
- Cytomegalovirus.
- Herpes Simplex (disseminated).
- Herpes Zoster (disseminated, ophthalmic; or involvement of 2 or more dermatomes).
- Histoplasmosis (pulmonary or disseminated; most common tropical areas [for example Tennessee Ohio-Mississippi river basins]).
- Listeriosis.
- *Non-tuberculous* mycobacteria (NTM), including *Mycobacterium avium* complex (MAC).
- *Pneumocystis pneumoniae* (pathogenic fungus causing pneumocystis pneumonia).

  Note: This list is indicative and not exhaustive.

17.7 APPENDIX G: COUNTRY SPECIFIC REQUIREMENTS

17.7.1 Amended Protocol 01 for Brazil (14 March 2018)

The following text is applicable to Brazil:

Sections: Tabulated Clinical Trial Summary (see I 01) and 7.1 Inclusion Criteria (see I 01, Section 7.1), respectively

I 01. Pediatric patients with asthma who completed the treatment in a dupilumab asthma trial (EFC14153).

Specific for Brazil: EFC14153 patients from Brazil, who prematurely discontinued IMP to receive Yellow Fever vaccine (a live attenuated vaccine) during Yellow Fever outbreak, are allowed to be enrolled in LTS14424 after completing the required procedures in EFC14153 (completion of remaining visits and procedures until EOT V28, considered as V1 for LTS14424).

17.7.2 Country specific requirements for Japan

Japan substudy.

17.7.2.1 Clinical trial summary

COMPOUND: Dupilumab	**STUDY No.: LTS14424**
INVESTIGATOR/TRIAL LOCATION	Japan
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary objective:** • To evaluate the efficacy of dupilumab in children of 6 to <12 years of age with uncontrolled persistent asthma in the Japan substudy. **Secondary objective(s):** • To evaluate the safety and tolerability of dupilumab in pediatric patients with asthma in the Japan substudy. • To evaluate dupilumab in pediatric patients with asthma in the Japan substudy with regard to: - Systemic exposure, - Anti-drug antibodies (ADAs), - Biomarkers.

STUDY DESIGN	The substudy consists of 3 periods: • **Screening period**:4 [±1] weeks. - Prior to and during the screening period, patients must be on stable-dose background therapy of medium-dose inhaled corticosteroids (ICS) with a second controller medication (ie, long acting β2 agonists [LABA], long acting muscarinic antagonists [LAMA], leukotriene receptor antagonists [LTRA], or methylxanthines) or high-dose ICS alone, or high-dose ICS with a second controller medication, for at least 3 months with a stable dose ≥1 month prior to the screening visit (Visit 0). • **Treatment period**: 52 weeks open-label treatment. • **Post-treatment period**: 12 weeks. Upon completion of the treatment period (or following early discontinuation of the investigational medicinal product (IMP]), patients will continue into the post-treatment period. During the post-treatment period, patients will receive their background controller regimen based on Investigator's judgement.
STUDY POPULATION	**Main Inclusion criteria:** I 01. Signed written inform consent/assent. I 02. 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 a second controller medication (ie, LABA, LTRA, LAMA, or methylxanthines) or high-dose ICS alone or high-dose ICS with a second controller, for at least 3 months with a stable dose ≥1 month prior to the screening visit (Visit 0). Fluticasone propionate must be ≥200 mcg daily. - Pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≤95% of predicted normal or pre-bronchodilator FEV1/forced vital capacity (FVC) ratio <0.85 at screening visit (Visit 0) and baseline visit (Visit 1). - Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puff inhalations with metered dose inhaler [MDI]) of salbutamol reliever medication before enrollment (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 between the screening visit (Visit 0) and up to the day of the actual baseline visit (Visit 1). Patients can have the last attempt of reversibility testing (for eligibility) at the baseline visit (Visit 1) before enrollment.

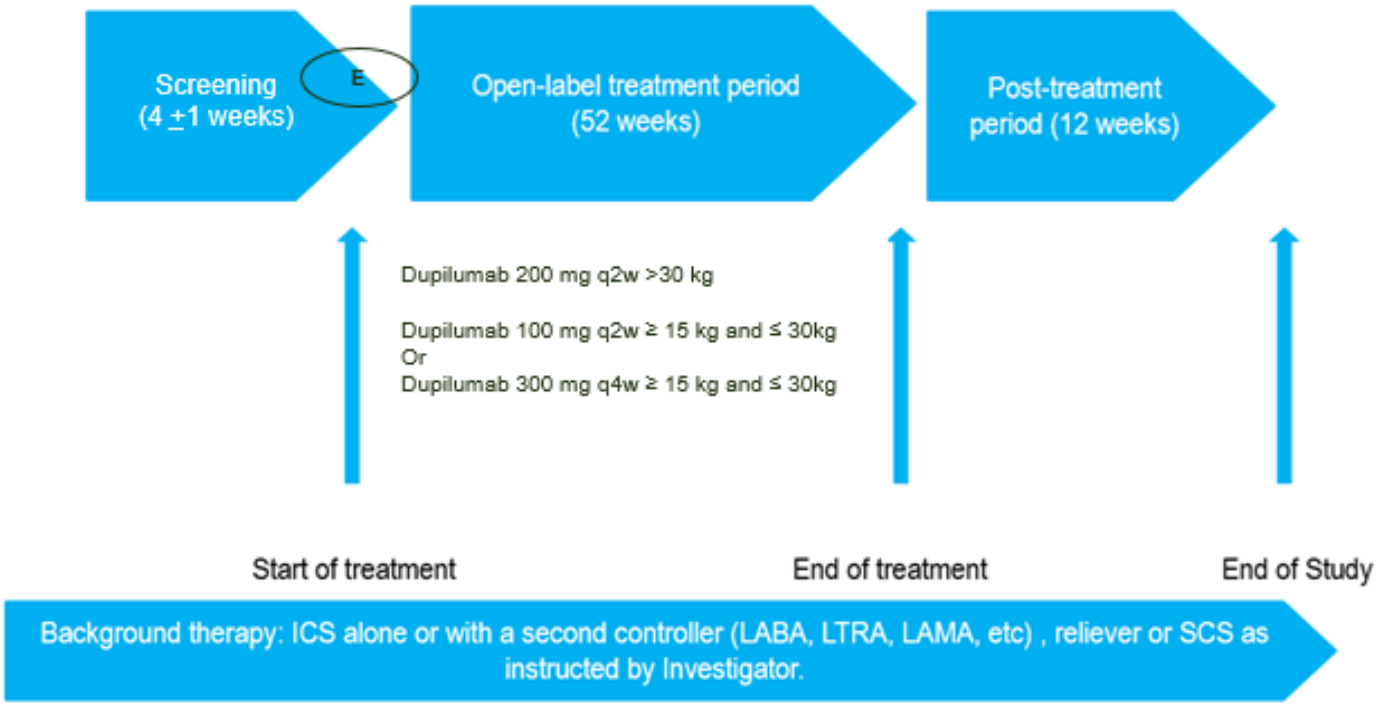
	Note: Documented reversibility or positive airway hyperresponsiveness to methacholine within 12 months prior to screening visit (Visit 0) is considered acceptable. - Must have experienced, within 1 year prior to the screening visit (Visit 0), any of the following events: a) Treatment with a systemic corticosteroid (SCS, oral or parenteral), as prescribed by a healthcare professional for worsening asthma at least once or, b) Hospitalization or emergency room visit for worsening asthma. - Evidence of uncontrolled asthma with Asthma Control Questionnaire–Interviewer Administered (ACQ-IA) ACQ-5 score ≥1.5 at the screening visit (Visit 0) and baseline visit (Visit 1), prior to enrollment. I 03. Blood eosinophil count ≥150 cells/μL or fractional exhaled nitric oxide (FeNO) ≥20 parts per billion (ppb) at screening visit (Visit 0). **Main Exclusion criteria:** E 01. Any chronic lung disease other than asthma (eg, cystic fibrosis, bronchopulmonary dysplasia) which may impair lung function. E 02. Inability to follow the procedures of the study/noncompliance (eg, due to language problems or psychological disorders). E 03. Patients receiving concomitant treatment or required a new concomitant treatment prohibited in the study at the screening and enrollment visits. E 13. Patients who previously have been treated with dupilumab E 14. Diagnosed with active parasitic infection (helminthes); suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization. E 15. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per Investigator's judgment.
Total expected number of patients	Approximately 16 patients
STUDY TREATMENT(s)	
Investigational medicinal product(s)	Dupilumab
Formulation:	**Dupilumab for children ≥15kg and ≤30 kg:** 150 mg/mL in prefilled syringe to deliver a dose of 100 mg once every 2 weeks (q2w) in a 0.67 mL subcutaneous (SC) injection. **Or** **Dupilumab for children ≥15kg and≤30 kg:** 150 mg/mL in prefilled syringe to deliver a dose of 300 mg once every 4 weeks (q4w) in a 2 mL SC injection.

	Dupilumab for children >30 kg: 175 mg/mL in prefilled syringe to deliver a dose of 200 mg q2w in a 1.14 mL SC injection.
Route(s) of administration:	SC injection
Dose regimen:	Dupilumab 200 mg SC q2w for children with body weight >30 kg and 100 mg SC q2w or 300mg q4w for children with body weight ≥15kg and ≤30 kg. Patients with body weight ≤30 kg will receive dupilumab 100 mg q2w or 300 mg q4w in 1:1 ratio at randomization. The same dose regimen determined at baseline will be maintained and will not be adjusted upon weight gain or loss during the treatment period. A minimum of 3 patients assigned to treatment with each of the 3 dose regimens is targeted.
Noninvestigational medicinal product(s) **Formulation:**	**Inhaled corticosteroids (ICS)** Alone or in combination with a second controller. **Reliever medication** Patients may receive salbutamol MDI as reliever medication (as needed) during the study. Nebulizer solutions may be used as an alternative delivery method. **Systemic corticosteroids (SCS)** Systemic corticosteroids may be given in case of severe asthma based on Investigator's judgement.
Route(s) of administration:	Oral inhalation via MDI or dry powder inhaler (DPI; for example ICS, ICS combination, salbutamol, etc.); for background controllers, relievers, and SCS according to label that is applicable to pediatric patients.
Dose regimen:	Inhaled corticosteroid: ICS alone or in combination with a second controller. Reliever medication, as needed. SCS, as prescribed.
ENDPOINT(S)	**Primary endpoint:** • Change from baseline in pre-bronchodilator percentage (%) predicted FEV1 at Week 12. **Secondary endpoints:** • Efficacy - Annualized rate of severe asthma exacerbation events, during the treatment period. - Change from baseline in pre-bronchodilator % predicted FEV1 at Weeks 2, 4, 8, 24, 52, and 64. - Change from baseline in other lung function measurements (absolute FEV1, FVC, FEF 25-75%) at Weeks 2, 4, 8, 12, 24, 52, and 64. - Change from baseline at Week 2, 4, 8, 12, 24, 36, 52, and 64 in ACQ-IA. • Safety - The number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAEs).

	• Dupilumab systemic exposure and immunogenicity - Serum dupilumab concentrations. - ADAs. • Biomarkers - Serum: Total immunoglobulin E (IgE). - FeNO.
ASSESSMENT SCHEDULE	Study onsite visits are performed q2w up to Visit 3 (Week 4) of the study, q4w up to Visit 8 (Week 24), and approximately every 12-16 weeks up to the end-of-study (EOS) visit.
STATISTICAL CONSIDERATIONS	**Sample size determination:** For the Japan substudy, the primary objective is to evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma. Assuming the change from baseline in % predicted FEV1 at Week 12 among the Japan substudy follows a normal distribution with mean of 10.74% and standard deviation of 14.12%, a sample size of 16 for the Japan sub-study will lead to a half-width of the 95% confidence interval being 7.5%. A minimum of 3 patients assigned to treatment with each of the 3 dose regimens is targeted. The sample size calculations were performed using nQuery Advisor. **Analysis population:** Efficacy population: same as safety population, which is defined as all patients exposed to at least 1 dose or part of 1 dose of dupilumab during LTS14424 study regardless of the amount of treatment administered. **Primary analysis:** Change from baseline in percentage (%) predicted FEV1 at Week 12 will be summarized using descriptive statistics. **Analysis of secondary endpoints:** For each variable, descriptive summary will include: n, point estimate, and confidence intervals will be provided as appropriate. Graphical time course profiles will be provided when appropriate for documentation of outcomes. Incidence of TEAE will be summarized using descriptive statistics.
DURATION OF STUDY PERIOD (per patient)	• Screening period: 4 [±1] weeks. • Treatment period: Open-label treatment for 52 weeks (1 year). • Post-treatment period: 12 weeks. The total duration, per patient, is approximately 68 weeks.

17.7.2.2 Flow charts

17.7.2.2.1 Graphical study design



Abbreviations: E = enrollment; ICS = inhaled corticosteroid; LABA = long acting β2 agonist; LAMA = long acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; q2w = once every 2 weeks; q4w=once every 4 weeks; SCS = systemic corticosteroid.

17.7.2.2.2 Study flow chart

Study periods	Screening period (4±1 weeks)[a]	Open-label treatment period (52 weeks)															Post-treatment period (12 weeks)		
		Enrollment SOT (D1)														EOT[b]			EOS
Week (W)	**W-4**	**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[c]**	**W32[c]**	**W36**	**W40[c]**	**W44[c]**	**W48[c]**	**W52**	**W56[c]**	**W60[c]**	**W64**
Onsite visit[d]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	☎	☎	**9**	☎	☎	☎	**10**	☎	☎	**11**
Enrollment																			
Informed consent/assent[e]	X																		
Inclusion /Exclusion criteria	X	X																	
Patient demographics	X																		
Medical & surgical history[f], and reversibility[g]	X																		
Treatment																			
Call IVRS/IWRS	X	X	X[h]	X	X	X	X	X	X			X				X			X
IMP dispense/ administration[i]		X	X[h]	X	X	X	X	X	X			X							
Injection training/technique observation[j]		<- ---------- X ----------→																	
Prior & concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study periods	Screening period (4±1 weeks)[a]	Open-label treatment period (52 weeks)															Post-treatment period (12 weeks)		
		Enrollment SOT (D1)														EOT[b]			EOS
Week (W)	**W-4**	**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[c]**	**W32[c]**	**W36**	**W40[c]**	**W44[c]**	**W48[c]**	**W52**	**W56[c]**	**W60[c]**	**W64**
Onsite visit[d]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	☎	☎	**9**	☎	☎	☎	**10**	☎	☎	**11**
Patient reported outcome(s)																			
ACQ-IA[k]	X	X	X	X	X	X			X			X				X			X
Efficacy																			
Spirometry[l]	X	X	X	X	X	X			X							X			X
Safety																			
Vital signs (including height and weight)[m]	X	X	X	X	X	X	X	X	X			X				X			X
Physical examination	X					X			X							X			X
Menstruation status	X	X	X	X	X	X	X	X	X			X				X			X
Dispense or check diary[n]	X	X																	
12-lead ECG	X															X			X
Vaccines record review scheduling	X																		
Adverse event reporting	<- ---------- X ----------→																		

Study periods	Screening period (4±1 weeks)[a]	Open-label treatment period (52 weeks)															Post-treatment period (12 weeks)		
		Enrollment SOT (D1)														EOT[b]			EOS
Week (W)	**W-4**	**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[c]**	**W32[c]**	**W36**	**W40[c]**	**W44[c]**	**W48[c]**	**W52**	**W56[c]**	**W60[c]**	**W64**
Onsite visit[d]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	☎	☎	**9**	☎	☎	☎	**10**	☎	☎	**11**
Laboratory Testing																			
Clinical laboratories[o]	X	X		X		X			X			X				X			X
Urine pregnancy test for girls that are menstruating[p,r]	X	X	X	X	X	X	X	X	X			X				X			X
Urinalysis[q,r]	X					X			X							X			X
PK sampling[r]		X				X			X							X			X
ADA[r]		X				X			X							X			X
Serum total IgE and Ag-specific IgE[r]		X							X							X			X
FeNO[s]	X	X	X	X	X	X			X							X			X

Study periods	Screening period (4±1 weeks)[a]	Open-label treatment period (52 weeks)															Post-treatment period (12 weeks)		
		Enrollment SOT (D1)														EOT[b]			EOS
Week (W)	W-4	W0	W2	W4	W8	W12	W16	W20	W24	W28[c]	W32[c]	W36	W40[c]	W44[c]	W48[c]	W52	W56[c]	W60[c]	W64
Onsite visit[d]	0	1	2	3	4	5	6	7	8	☎	☎	9	☎	☎	☎	10	☎	☎	11
Reminder																			
Controller and reliever therapy reminder[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication withhold reminder[c]	X	X	X	X	X			X							X			X	

Abbreviations: ADA = anti-drug antibody; ACQ = Asthma Control Questionnaire; Ag specific IgE = antigen-specific IgE; D = (study) day; ECG = electrocardiogram; eCRF = electronic case report form; EOS = end-of-study; EOT = end-of-treatment; FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E; IMP = investigational medicinal product; IVRS/IWRS = Interactive Voice Response System/Interactive Web Response System; ICS = inhaled corticosteroid; LABA = long acting β2-agonist; LAMA = long acting muscarinic antagonist; PK = pharmacokinetic; q2w = once every 2 weeks; q4w = once every 4 weeks; SOT = start-of-treatment; W = (study) week.

a The screening period is 4±1 weeks (21-35 days) in duration to 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 ICS with 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 ≥1 month prior to the screening visit (Visit 0).

b Patients who permanently discontinue IMP will be asked and encouraged to return to the clinic for study visits and participate in assessments according to the visit schedule until the EOS with a ±1 week window or up to recovery or stabilization of any adverse event. At the time of permanent treatment discontinuation, patients will perform the ETD visit with all the assessments defined for the EOT Visit 10.

c Phone contact to collect safety information + reminders for IMP, controller, and reliever therapy, if appropriate reminder for withholding medication at the next visit as described in the individual visit schedules Safety information and date of phone call will be recorded in eCRF.

d The visit windows for all subsequent visits post-enrollment on Day 1 will be ±3 days during the treatment period and ±1 week during the post-treatment period.

e Prior to any screening assessments: all patient ≥6 years of age (or above an age determined by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and in according with the local regulations and requirements) and their parent(s)/caregiver(s)/legal guardian(s) will receive information about the study, on study objective(s) and procedures, to the fullest extent possible, in their language and in terms they are able to understand, and must sign and date the IRB/IEC approved Informed Assent Form (IAF) and Informed Consent Form (ICF), respectively.

f Medical history, asthma- history, atopic and food allergy medical history, surgical history.

g Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puff inhalations with MDI) of salbutamol reliever medication before enrolment (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 hyper-responsiveness to methacholine within 12 months prior to Screening V0 is considered acceptable. If the patient does not meet this reversibility criterion at the screening visit (Visit 0), up to 2 additional assessment attempts can be performed at any time between the screening (Visit 0) and baseline (Visit 1) visits.

h For patients receiving 300 mg q4w, no IMP will be dispensed/administered at Week 2 and no IVRS/IWRS call will occur.

i Once every 2 weeks IMP administrations must be separated by at least 11 days. Once every 4 weeks IMP administrations must be separated by at least 25 days. After each IMP administration, patients should be monitored for a minimum of 30 minutes after injections. If the parent(s)/caregiver(s)/legal guardian(s) or the Investigator decides not to administer IMP at home, the injections can be performed at the study site by way of unscheduled visits.

j The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home. It is possible to start home administration provided parent(s)/caregiver(s)/legal guardian(s) have been trained by the investigator or designee to administer IMP by demonstration at not less than 3 injections (eg, at Week 0, Week 2 and Week 4 for q2w doses and at Week 0, Week 4 and Week 8 for q4w doses) followed by a successful IMP administration under close supervision of the investigator or designee at not less than 3 injections (eg, at Week 6, Week 8, Week 10, and Week 12 for q2w doses and Week 12, Week 16 and Week 20 for q4w doses). Subsequent administrations are encouraged to occur at site wherever possible,

k Asthma Control Questionnaire–Interviewer Administered (ACQ-IA, for children 6 to <12 years), ACQ-7 and ACQ-5 scores are administered by the interviewer during the study visits at the clinical site. The ACQ-7 score will be used to follow up evaluations in all patients. The ACQ-5 (the first 5 items of the ACQ-7) score is used for eligibility evaluation at Screening V0 and Baseline V1 for all patients.

l Spirometry should be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). Spirometry will be performed after a washout period of bronchodilators according to their action duration (for example withholding the last dose of salbutamol for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. Also spirometry should be performed prior to IMP administration, as applicable.

m Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), and body weight (kg) will be measured at each on site visit except for IMP administration only visit. Height will be measured at each onsite visit except for the IMP administration only visit and Visit 9 (Week 36).Except for height and weight, other vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

n Paper diary is used for daily recording of asthma controller drug use during the screening period to calculate controller treatment compliance. The diary is dispensed at Visit 0.

o Clinical laboratories: Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets. Serum chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, albumin, total cholesterol, creatine phosphokinase (CPK), glucose, creatinine, blood urea nitrogen (BUN), bicarbonate, and electrolytes (sodium, potassium, chloride). Clinical laboratory testing only at Visit 0 will include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). For details, please refer to Section 17.7.2.8.3.5.

p For female patients who have commenced menstruating (ie, are of child-bearing potential) at Screening, a urine pregnancy test is mandatory at the screening visit (Visit 0) with negative result obtained prior to enrolment at Visit 1 (Week 0) and at every subsequent visits defined in the flowchart. For female patients who happen to commence menstruating after Screening, a negative urine dipstick pregnancy test will be obtained prior to administration of IMP. In case of positive urine test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible.

q Urinalysis: pH, glucose, ketones, leukocyte esterase blood, protein, nitrate, urobilinogen, and bilirubin (by dipstick). For details, please refer to Section 17.7.2.8.3.5.

r Samples will be collected prior to IMP administration.

s FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.

17.7.2.3 Rationale

Patients in Japan were not included in Study EFC14153. A substudy is added with Japanese patients aged 6 to <12 years with uncontrolled persistent asthma. The primary objective of the substudy is to evaluate efficacy of dupilumab in this population, which will be evaluated in a separate analysis. The details of the substudy including patient characteristics, evaluations, statistical analysis, and database lock are outlined below.

17.7.2.4 Study objectives

17.7.2.4.1 Primary

The primary objective of this Japan substudy is to evaluate the efficacy of dupilumab in children from Japan who are 6 to <12 years of age with uncontrolled, persistent asthma.

17.7.2.4.2 Secondary

The secondary objectives of this study are:

- To evaluate the safety and tolerability of dupilumab in Japanese pediatric patients with asthma.
- To evaluate dupilumab in Japanese pediatric patients with asthma with regard to:
  - Systemic exposure,
  - ADAs,
  - Biomarkers.

17.7.2.5 Study design

17.7.2.5.1 Description of the study

This substudy is a multicenter, open-label, single arm, 1-year treatment study evaluating dupilumab given SC for a period of 52 weeks among pediatric patients in Japan. Dose regimen will be 200 mg q2w for patients with body weight >30 kg, 100 mg q2w or 300 mg q4w in 1:1 ratio for patients with body weight ≥15 kg and ≤30 kg.

Upon completion of the treatment period (or following early discontinuation of IMP), patients will continue into the post-treatment period. During the post-treatment period, patients will receive their background controller regimen based on Investigator's judgement.

For a schematic study design, please refer to Section 17.7.2.2.1.

17.7.2.5.2 Duration of study participation

17.7.2.5.2.1 Duration of study participation for each patient

The total duration, per patient, is of approximately 68 weeks.

For each patient, this includes the following 3 periods:

- **Screening period**: 4 ±1 weeks.
- **Treatment period**: 52 weeks open-label treatment (1 year) with last dosing at Week 50 for q2w and at Week 48 for q4w.
- **Post-treatment period**: 12 weeks.

17.7.2.5.2.2 Determination of end of clinical trial (all patients)

See Section 6.2.2.

17.7.2.5.3 Data monitoring committee

Not applicable.

17.7.2.6 Selection of patients

17.7.2.6.1 Inclusion criteria

I 01. Signed written inform consent/assent.

I 02. 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 GINA 2015 Guidelines, and the following criteria:

- Existing 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 ≥1 month prior to screening visit (Visit 0) (dose levels as per Section 17.7.2.14). Fluticasone propionate must be ≥200 mcg daily,
- Pre-bronchodilator FEV1 ≤95% of predicted normal or pre bronchodilator FEV1/FVC ratio <0.85 at screening visit (Visit 0) and baseline visit (Visit 1),
- Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puffs with MDI) of salbutamol reliever medication before enrollment (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 between the screening visit (Visit 0) and up to the day of the actual baseline visit (Visit 1). Patients can have the last attempt of reversibility testing (for eligibility) at the

baseline visit (Visit 1) before enrollment.
Note: Documented reversibility or positive airway hyper-responsiveness to methacholine within 12 months prior to screening visit (Visit 0) is considered acceptable.

- Must have experienced, within 1 year prior to screening visit (Visit 0), defined as any of the following events:
  a) Treatment with a 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 Asthma Control Questionnaire–Interviewer Administered (ACQ-IA) ACQ-5 score ≥1.5 at the screening visit (Visit 0) and the baseline visit (Visit 1), prior to enrollment.

I 03. Blood eosinophil count ≥150 cells/µL or FeNO ≥20 parts per billion (ppb) at screening visit (Visit 0).

I 04. Willing and able to comply with clinic visits and study-related procedures.

I 05. With parent(s)/caregiver(s)/legal guardian(s) able to understand the study requirements.

I 06. Patients/parent(s)/caregiver(s)/legal guardian(s), as appropriate, must be able to understand and complete study-related questionnaires.

17.7.2.6.2 Exclusion criteria

Exclusion criteria related to study methodology

E 01. Any chronic lung disease other than asthma (eg, cystic fibrosis, bronchopulmonary dysplasia) which may impair lung function.

E 02. Inability to follow the procedures of the study/noncompliance (eg, due to language problems or psychological disorders).

E 03. Patients receiving concomitant treatment or required a new concomitant treatment prohibited in the study at the screening and enrollment visits (see Section 17.7.2.7.8).

E 04. Patients or his/her parent(s)/caregiver(s)/legal guardian(s) is related to the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff thereof directly involved in the conduct of the study.

E 05. Patients <6 or ≥12 years of age.

E 06. Patients <15 kg body weight at baseline.

E 07. A patient with any history of life-threatening asthma (eg, requiring intubation).

E 08. Co-morbid disease that might interfere with the evaluation of IMP.

E 09. History of malignancy of any kind.

E 10. Anti-immunoglobulin E therapy (omalizumab) within 130 days or interleukin-5 antagonist (mepolizumab) within 110 days prior to Visit 0, or any other biologic therapy/immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus as well as other diseases) within 2 months or 5 half-lives prior to Visit 0, whichever is longer.

E 11. Initiation of allergen immunotherapy within 3 months prior to Visit 0 or dose change from 1 month prior to Visit 0 or a plan to begin allergen immunotherapy or to change its dose during the screening period or the open-label treatment period.

E 12. Exposure to another investigative antibody within a time period prior to Visit 0 that is less than 5 half-lives of the antibody. In case the half-life is not known, then the minimum interval since exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 0.

E 13. Patients who previously have been treated with dupilumab.

Exclusion criteria related to the current knowledge of Sanofi compound

E 14. Diagnosed with active parasitic infection (helminthes); suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.

E 15. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per Investigator's judgment.

E 16. For female patients who have commenced menstruating at any time during the study and are either:

- Found to have a positive urine pregnancy test, confirmed by a serum pregnancy test in case of a positive urine test, or
- Sexually active, not using an established acceptable contraceptive method:
  - Oral, injected, inserted, or implanted hormonal contraceptive.
  - Intrauterine device or intrauterine system with progesterone.
  - Barrier contraceptive (condom, diaphragm, or cervical/vault caps) used with spermicide (foam, gel, film, cream, or suppository).

E 17. Planned live (attenuated) vaccinations during the study and receiving live (attenuated) vaccines within 4 weeks before the enrollment visit (Visit 1).

E 18. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, juvenile idiopathic arthritis, inflammatory bowel disease, systemic lupus erythematosus). Those with high titer autoantibodies at screening who are suspected of having high risk for developing autoimmune disease at the discretion of the Investigator or the Sponsor.

Exclusion criteria related to the current knowledge of Sanofi compound

E 19. History of human immunodeficiency virus (HIV) infection or positive HIV serology at Visit 0.

E 20. Evidence of acute or chronic infection requiring systemic treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 0 or during the screening period, significant viral infections within 4 weeks before Visit 0 or during the screening period that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).

E 21. Patient with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

E 22. At the screening: Patients with positive (or indeterminate) test for hepatitis B surface antigen (HBs-Ag) or positive immunoglobulin M (IgM) hepatitis B core antibody or positive total hepatitis B core antibody (HBc-Ab) confirmed by positive hepatitis B virus DNA (HBV DNA) or positive hepatitis C virus antibody (HCV-Ab) confirmed by positive hepatitis C virus RNA (HCV RNA).

E 23. Liver injury related criteria:

- Clinically significant/active hepatobiliary disease, or,
- Elevated transaminases (ALT and/or AST) >3 ULN at screening.

E 24. Abnormal lab values at Screening:

- CPK >3 ULN, or,
- Platelets <100 000 cells/mm^3, or,
- Eosinophils >1500 cells/mm^3.

Exclusion Criteria Related to the Active Comparator and/or Mandatory Background Therapies

E 25. Non-compliance with use of the mandatory background therapy (ie, medium-dose ICS with a second controller medication [eg, LABA, LTRA, LAMA, or methylxanthines] or high-dose ICS alone or high-dose ICS with a second controller), during the screening period, as defined as <80% of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient diary during the screening period.

E 26. Patient treated with SCS for diagnoses other than severe exacerbation of asthma, and/or high-potency topical steroids within 30 days before screening visit (Visit 0), during the screening period, and/or during the treatment phase of this study.

E 27. Patient with history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, or other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to uncontrolled diabetes, active hepatitis, active or latent untreated tuberculosis, bronchiectasis. Patients with active tuberculosis, latent untreated tuberculosis or a history of incompletely treated tuberculosis will be excluded from the study unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing will be performed in every country according to their local guidelines as required by regulatory authorities and/or ethic committees. Other conditions that are well controlled and stable will not prohibit participation if deemed appropriate per the Investigator's judgment.

Additional Exclusion Criteria During or at the end of Screening or Run-in phase before randomization

E 28. Patient and/or parent(s)/caregiver(s)/legal guardian(s) who has/have withdrawn consent before enrollment/randomization (starting from signed ICF/IAF).

E 29. Despite screening of the patient, enrollment/randomization is stopped at the study level.

17.7.2.6.3 Criteria for temporarily delaying screening, enrollment, and administration of the study treatment

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 3 (see Section 17.7.2.16) should be considered for screening, enrollment, and administration of the study treatment.

17.7.2.7 Study treatment

17.7.2.7.1 Investigational medicinal product(s)

17.7.2.7.1.1 Dupilumab

Route of administration:

- Dupilumab for children ≥15 kg and ≤30 kg: 150 mg/mL in prefilled syringe to deliver a dose of 100 mg q2w in a 0.67 mL SC injection.

  OR

- Dupilumab for children ≥15 kg and ≤30 kg: 150 mg/mL in prefilled syringe to deliver a dose of 300 mg q4w in a 2 mL SC injection.
- Dupilumab for children >30 kg: 175 mg/mL in prefilled syringe to deliver a dose of 200 mg q2w in a 1.14 mL SC injection.

Dose regimen: Dupilumab 200 mg SC q2w for children with body weight >30 kg and 100 mg SC q2w or 300 mg q4w for children with body weight ≥15 kg and ≤30 kg.

Patients with body weight ≥15 kg and ≤30 kg will receive dupilumab 100 mg q2w or 300 mg q4w in 1:1 ratio at randomization. The same dose regimen determined at baseline will be maintained and will not be adjusted upon weight gain or loss during the treatment period. A minimum of 3 patients assigned to treatment with each of the 3 dose regimens is targeted.

17.7.2.7.1.2 Preparation of investigational product

See Section 8.1.2.

17.7.2.7.1.3 Dosing schedule

Dupilumab is administered every 14±3 days q2w or every 28 days ±3 days q4w. The doses of investigational product must be separated by ≥11 days for q2w and ≥25 days for q4w to avoid overdose.

For IMP administrations coinciding with scheduled study site visits (q2w up to Visit 3 [Week 4] for patients receiving q2w doses, q4w up to Visit 8 [Week 24], and approximately every 12-16 weeks up to the EOT visit), the IMP administrations can be performed by the Investigator or designee at site visits following clinic procedures and blood collection (see Section 17.7.2.2.2).

Patients should be monitored for a minimum of 30 minutes at the study site after IMP injections, to assess any ISR (for example for any signs or symptoms of a hypersensitivity reaction). If the parent(s)/caregiver(s)/legal guardian(s) or the Investigator decides not to administrate IMP at home, the other injections can be performed at the study site by way of unscheduled visits. Administrations are encouraged to occur at site wherever possible. If this is not possible, administration can be done by trained care givers or nurses at home.

The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home. It is possible to start home administration provided parent(s)/caregiver(s)/legal guardian(s) who have been trained to administer IMP by demonstration of at least 3 injections by the Investigator or designee followed by at least 3 successful IMP administration under close supervision of the Investigator or designee. For all visits scheduled only for IMP administration, parent(s)/caregiver(s)/legal guardian(s) may decide to do the injection of IMP at home (ie, home administration of IMP). These parent(s)/caregiver(s)/legal guardian(s) will be trained by the Investigator or designee to administer IMP, by demonstration eg, at Visit 1 (Week 0), Visit 2 (Week 2), and Visit 3 (Week 4) for q2w doses and Visit 1 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8) for q4w doses (injections performed by Investigator or designee). After parent(s)/caregiver(s)/legal guardian(s)

have successfully administered IMP under close supervision of the Investigator or designee eg, at Week 6, Visit 4 (Week 8), Week 10, and Visit 5 (Week 12) for q2w doses and Visit 5 (Week 12), Visit 6 (Week 16), and Visit 7 (Week 20) for q4w doses, the Investigator may approve them to perform home administration of IMP.

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 the injections can be performed at the study site by way of unscheduled visits or to administer IMP at these time points at the patient's home by qualified site personnel and/or healthcare professionals (for example visiting nurse service).

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 or IMP doses during the study. For any patient who misses a site visit or IMP dose, the parent(s)/caregiver(s)/legal guardian(s) should be reminded to be diligent to avoid missed visits and IMP doses 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 17.7.2.2.2) even if >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 (eCRF) 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.

Between the protocol-scheduled onsite visits, interim visits may be required for IMP dispensing. As an alternative to these visits, dupilumab may be supplied from the site to the patient/parent(s)/caregiver(s)/legal guardian(s) via a Sponsor-approved courier company where allowed by local regulations and approved by the patient.

17.7.2.7.2 Noninvestigational medicinal product(s)

17.7.2.7.2.1 Inhaled corticosteroids alone or in combination with a second controller

The recognized second controller medication for combined use with ICS (dose-levels in children 6 to <12 years old) as background therapy during this study will include the following classes: LABA, LTRA, LAMA, or methylxanthines. Please refer to Appendix A (see Section 17.1) for an

indicative (not exhaustive) list of recognized second controller medications approved for this study. Fluticasone propionate must be ≥200 mcg daily. These controller medications will not be dispensed or supplied by the Sponsor.

Route of administration:

- Oral inhalation via MDI or DPI (for example ICS, ICS combination, albuterol/salbutamol, etc.); for other background controllers according to label that is applicable to pediatric patients.

Dose regimen:

- Inhaled corticosteroids: ICS alone or in combination with a second controller as prescribed.

For patients experiencing a deterioration of asthma during the study, the ICS with/without second controller dose may temporarily be increased, up to 4-fold for a maximum of 10 days, as indicated and upon recommendation of the physician or Investigator. Treatment may then be changed to SCS (severe exacerbation event) or reverted back to the original ICS with/without second controller 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 Section 17.1 Appendix A and Section 17.7.2.14 Appendix 1) 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 the screening visit (Visit 0).

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 Section 17.7.2.14.

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 (Visit 0), any changes in ongoing asthma medications must occur more than 1 month in advance of the screening visit (Visit 0) Day 1, in order to maintain a stable dose for at least 1 month prior to Day 1 (Section 17.7.2.6). 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 17.7.2.6).

Open-label treatment period

During this period, patients will continue to take their controller medication(s) used during the screening period. The dose and baseline regimen of controller medications 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).

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 treatment period or following early discontinuation of IMP, patients will continue into the post-treatment period. During the post-treatment period, patients will receive their background controller regimen based on Investigator's judgement.

17.7.2.7.2.2 Reliever medication

See Section 8.2.2.

17.7.2.7.2.3 Systemic corticosteroids

See Section 8.2.3.

17.7.2.7.3 Blinding procedures

See Section 8.3.

17.7.2.7.4 Method of assigning patients to treatment group

The study medication will be administered only to patients included in this study following the procedures described in the clinical study protocol. The 7-digit serialized treatment kit number will be generated centrally by the Sanofi clinical supply team. The IMPs are packaged in accordance with this list.

Dose regimen will be 200 mg q2w for patients with body weight >30 kg, 100 mg q2w or 300 mg q4w in 1:1 ratio for patients with body weight ≥15 kg to ≤30 kg. The same dose regimen determined at baseline will be maintained and will not be adjusted upon weight gain or loss during the treatment period. A minimum of 3 patients assigned to treatment with each of the 3 dose regimens is targeted.

Patients will be identified with a 12-digit patient ID. The investigational site will enter the patient tracking information for patient identification number, into the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS) during each scheduled protocol visit. Treatment allocation will be performed centrally by IVRS/IWRS. The clinical site coordinator

will document the patient number and the treatment kit number in the eCRF and in the patient's source documents, and the patient number on the IMP label prior to dispensing to the patient.

Patients will be considered to be enrolled in the study once a treatment kit number has been assigned by the IVRS/IWRS. Therefore, it is important that all inclusion/exclusion criteria are confirmed and all required procedures are completed prior to the enrollment contact to the IVRS/IWRS. Detailed IVRS/IWRS procedure will be provided in the IVRS/IWRS site manual.

17.7.2.7.5 Investigational medicinal product packaging and labeling

See Section 8.5.

17.7.2.7.6 Storage conditions and shelf life

See Section 8.6.

17.7.2.7.7 Responsibilities

See Section 8.7.

17.7.2.7.8 Concomitant medication

See Section 8.8.

17.7.2.7.8.1 Prohibited concomitant medication

The following concomitant treatments are not permitted during the Screening Period or during the Treatment Period:

- SCS for treatment other than severe exacerbation of asthma and/or high-potency topical steroids within 30 days before the screening visit (Visit 0), during the screening period, and/or during the treatment phase of this study. Intra-articular steroids are not allowed to be used in the above mentioned period.
- IgE therapy (eg, omalizumab) within 130 days or interleukin-5 antagonist (e.g. mepolizumab) within 110 days prior to screening visit (Visit 0), or any other biologic therapy/immunosuppressant to treat inflammatory disease or autoimmune disease within 2 months prior to screening visit (Visit 0).
- Allergen immunotherapy (except if initiated more than 3 months prior to Visit 0 and dose stable 1 month prior to Visit 0).
- IVIG therapy.
- Live Attenuated Vaccines: refer to Appendix B. Live (attenuated) vaccines are allowed in the screening period, if taken at least 4 weeks prior to the administration of the first dose of investigational medicinal product (ie, at least 4 weeks prior to visit 1).

- Asthma relievers other than salbutamol/albuterol: their use is not recommended unless in exceptional circumstances during the study period (eg, prescribed by a physician not participating in the study).
- Exposure to another antibody within a time period prior to Visit 0 that is less than 5 half lives of the antibody. In case the half-life is not known, then the minimum interval since exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 0.
- Any investigational treatment and procedure.

17.7.2.7.9 Cautioned concomitant medication (Cytochrome P450 enzyme substrates)

See Section 8.8.2.

17.7.2.8 Assessment of investigational medicinal product

17.7.2.8.1 Primary endpoint

The primary endpoint in the Japan substudy is change from baseline in % predicted FEV1 at Week 12.

17.7.2.8.2 Secondary endpoints

The secondary efficacy endpoints of this study are:

- Annualized rate of severe asthma exacerbation events, during the treatment period.
- Change from baseline in pre-bronchodilator % predicted FEV1 at Weeks 2, 4, 8, 24, 52, and 64.
- Change from baseline in other lung function measurements (absolute FEV1, FVC, FEF 25-75%) at Weeks 2, 4, 8, 12, 24, 52, and 64.
- Change from baseline at Week 2, 4, 8, 12, 24, 36, 52, and 64 in ACQ-IA.

See Section 9.2.1.1 on assessment of severe asthma exacerbation.

17.7.2.8.2.1 Assessment of lung function by spirometry

Lung function parameters will be assessed by centralized spirometry at screening visit (Visit 0), Visit 1 (Week 0), Visit 2 (Week 2), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 8 (Week 24), EOT (Week 52), and EOS visits (Week 64).

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 prebronchodilator measured parameters, including FEV1, peak expiratory flow (PEF), FVC, and FEF 25% to 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours), and withholding the last dose of LAMA for at least 24 hours.

At all related visits, spirometry will be performed either in the AM or PM, but preferably in the AM, and 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 the sitting position; however, if necessary to undertake the testing with the patient standing or in another position, this should be noted on the spirometry report. For any patient, 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 patient 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% to 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 patient is seen and spirometry is carried out. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (that is 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.

17.7.2.8.2.2 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.

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 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 spirometry 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 Section 17.7.2.15).

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 (10).

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 and baseline for eligibility evaluation.

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.

17.7.2.8.3 Other secondary endpoints

17.7.2.8.3.1 Long-term safety and tolerability

Long-term safety and tolerability for this study is the number (n) and percentage (%) of patients experiencing any TEAE during total study periods (definition see Section 10.4.1.1).

Additional analyses will describe the number (n) and percentage (%) of patients experiencing any:

- Serious adverse events (SAE definition refers to Section 10.4.1.2).
- Adverse events of special interest (AESI definition refers to Section 10.4.1.3).
- Adverse events related to IMP.

- Adverse events leading to permanent IMP discontinuation.
- Adverse events other than ISR.

Adverse events, including SAEs and AESI, will be collected at any time during study starting from signed consent form. The Investigator will ask the patient and parents how he/she has felt since the last study visit.

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.

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.

Adverse events for each patient will be monitored and documented from the time the patient gives informed consent/assent at Visit 0 until the EOS visit, except for:

- Serious adverse events.
- Adverse events that are ongoing at database lock.

Adverse events, AESIs, SAEs, AEs leading to IMP discontinuation and deaths will be reported as described in Section 10.4.1 and analyzed as in Section 17.7.2.10.4.3.

Laboratory tests, vital signs, physical examination, or electrocardiogram (ECG) abnormalities are to be recorded as AEs only if they meet the criteria defined in Section 10.4.3, and are assessed as described in Section 17.7.2.8.3.5, Section 17.7.2.8.3.2, Section 9.1.2 and Section 17.7.2.8.3.4. In addition to assessment of primary endpoint, below parameters are used on an ongoing basis during the study to monitor safety of participants and will be presented in a descriptive manner.

17.7.2.8.3.2 Vital signs

Vital signs including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), and body temperature (degrees Celsius) will be measured at each onsite visit except for IMP administration only visits.

Vital signs will include height (cm) and body weight (kg). Height will be measured at each onsite visit except for the IMP administration only visit and Visit 9 (Week 36). Weight will be measured at each onsite visit except for the IMP administration only visit.

17.7.2.8.3.3 Physical examinations

See Section 9.1.2.

17.7.2.8.3.4 Electrocardiograms

Electrocardiogram (ECG) variables will be recorded by a standard 12-lead ECG. ECGs will be performed at screening, EOT, and EOS (see Section 17.7.2.2.2).

17.7.2.8.3.5 Clinical laboratory values

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.

Globally, guidelines for blood collection volume limits for pediatric studies range between 1% and 5% of total blood volume (TBV) for a single draw (or during a 24-hour period) and up to 10% of TBV over 8 weeks (9). Scheduled collections in the current protocol, for the smallest possible patient (15 kg), remain within this limit for every 3 months. For all scheduled blood collection visits, the total volume does not exceed 1.5 mL/kg for the smallest possible patient.

Refer to Section 17.7.2.2.2 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 are:

Hematology:

To include blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

Serum chemistry:

To include creatinine, blood urea nitrogen, glucose, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), ALT, AST, ALP, electrolytes (sodium, potassium, chloride), bicarbonate, and CPK. Patients' fasting or nonfasting 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.

Urinalysis:

Urinalysis will be conducted by dipstick during onsite visit. The parameters include pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen, and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, further urine test is under Investigator's judgement.

Refer to Section 17.7.2.2.2 (Study Flow Chart) for the schedule of urinalysis performed throughout this study.

Pregnancy test

A urine pregnancy test must be negative at Visit 0 and Visit 1 for enrolling girls who have commenced menstruating, and a urine dipstick pregnancy test will be performed at subsequent onsite visits prior to administration of IMP. In case of a positive urine test, a serum pregnancy test should be performed to confirm. Patients found to have a positive urine pregnancy test, confirmed by a positive serum pregnancy test will be excluded from the study. Patients with a false positive urine pregnancy test manifested as a positive urine pregnancy test but a negative serum pregnancy test will be allowed to be enrolled. Refer to Section 17.7.2.2.2 (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.

Clinical laboratory testing at screening visit (Visit 0) 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). For eligibility interpretation for hepatitis serology, refer to Table 6.

Table 6 - 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.

Abbreviations: 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 Section 17.4.

17.7.2.8.3.6 Dupilumab systemic exposure and immunogenicity

See Section 9.2.2.1.

17.7.2.8.3.6.1 Sampling time

Predose blood samples will be collected for determination of functional dupilumab concentration in serum and anti-dupilumab antibodies (including neutralizing antibodies) on days designated in the Study Flow Chart (see Section 17.7.2.2.2). The date of collection should be recorded in the patient eCRF. The date and time also will be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

In the event of any SAE or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe ISR lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes. An unscheduled systemic drug concentration page ("PK page") in the eCRF must be completed as well.

Further follow-up of individual patients will be considered based on the overall assessment of antibody titers and clinical presentation.

17.7.2.8.3.6.2 Handling procedure

See Section 9.2.2.1.2.

17.7.2.8.3.6.3 Bioanalytic method

See Section 9.2.2.1.3.

17.7.2.8.3.7 Pharmacodynamics

Pharmacodynamics are the evolution of:

- Serum: Total IgE.
- FeNO.

Refer to Section 17.7.2.2.2 Study Flow Chart for the schedule of sample collection throughout this study.

Biomarkers include total IgE which will be measured with a quantitative method (for example ImmunoCAP) approved for diagnostic testing and antigen-specific IgE, which will be detected using panels of antigens appropriate to the location of the clinical site (quantitative ImmunoCAP test; Phadia).

FeNO assessment 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.

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

17.7.2.8.4 Appropriateness of measurements

See Section 9.4.

17.7.2.9 Study procedures

The substudy consists of 3 periods:

- Screening period (Visit 0).
- Open-label treatment period (52 weeks; Visits 1-10).

  During the open-label treatment period, patients will continue their background therapy dose regimen used during screening period.
- Post-treatment period (12 weeks; Visit 11).

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 in the treatment period and ±1 week for the remaining study period.

Spirometry should be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). Spirometry should be performed at visits as detailed in Section 17.7.2.8.2.1.

Once every 2 weeks IMP administration must be separated by at least 11 days. Once every 4 weeks IMP administration must be separated by at least 25 days. The treatment period visits occur q2w up to Visit 3 (Week 4), q4w up to Visit 8 (Week 24), and approximately every 12-16 weeks up to the EOS visit as detailed in Section 17.7.2.7.1.3.

See Section 17.7.2.7.1.3 for Investigational medicinal product administration.

At the time of permanent treatment discontinuation, patients will perform the ETD visits including early EOT visit and early EOS visit. Early EOT will be performed 2 weeks (with a ±3 days window) after last IMP injection whenever possible. If the time of decision taken for permanent IMP discontinuation is >2 weeks after last IMP injection, this early EOT visit should be scheduled as early as possible from permanent discontinuation of IMP decision.

All the assessments defined for the EOT Visit 10 will be performed during this early EOT. Early EOS visit will be performed 12 weeks after early EOT visit with a ±1 week window. All the assessment defined for the EOS Visit 11 will be performed during this early EOS visit.

Patients should be reminded that sexually active 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. Procedures:
   a) ECG

b) FeNO levels
c) Spirometry

2. Safety and laboratory assessments.
3. Investigational medicinal product administration, if planned, IMP dispensation and return.
4. Controller therapy and medication withhold for next spirometry reminder.

17.7.2.9.1 Visit schedule

17.7.2.9.1.1 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 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.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol (see Section 17.7.2.2.2), 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 enrollment (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 21-35 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. 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 0 procedures must be repeated, for further instructions related to re-screening) unless a prior assessment is performed within the time frame permitted prior to study entry.

17.7.2.9.1.2 Screening visit (Visit 0; 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 history, atopic and food allergy medical history, surgical history, prior and concomitant medications and menstruation status for female patients of childbearing potential.
- Review entry criteria to assess eligibility, with special attention to assess the following:
  - Prescribed treatment dosage meets the definition of medium to high-dose ICS (see Section 17.7.2.14) 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 (Visit 0).

    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 0) 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.
- Interview to collect vaccination information and vaccination plan during the treatment period. Remind live vaccines are not authorized.
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height).
- Perform physical examination.
- Administer ACQ-5-IA for children (6 to <12 years old).
  - Verify if ACQ-5-IA score is ≥1.5.
- Perform 12 lead ECG.
- Measure FeNO.
  - FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.
  - Entry criteria at Visit 0 include blood eosinophil count ≥150 cells/µL or FeNO ≥20 ppb.
- Perform spirometry:
  - Entry criteria at Visit 0 include the requirement of a specific FEV1 and demonstration of reversibility as specified in Section 17.7.2.6.1. See below for additional directions,
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours,
  - 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 salbutamol 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 (Visit 0) and up to the day of the actual baseline visit (Visit 1).
    Note: Documented reversibility or positive airway hyperresponsiveness to methacholine within 12 months prior to Screening V0 is considered acceptable.
- Menstruation status for female patients of childbearing potential.
- Obtain blood samples for screening clinical laboratory determinations:
  - Hematology (see Section 17.7.2.8.3.5 for details),
  - Entry criteria at Visit 0 include blood eosinophil count ≥150 cells/µL or FeNO ≥20 ppb,
  - Serum chemistry (see Section 17.7.2.8.3.5 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.
- Dispense paper diary, provide instructions for daily use, and remind patient and their parent(s)/caregiver(s)/legal guardian(s) to bring it to the next visit.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication throughout the study.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller as used during the screening period and instruct them to record daily usage in the paper diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol 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.
- Schedule a site visit within a maximum of 35 days (Visit 1, Week 0) and request patient and their parent(s)/caregiver(s)/legal guardian(s) to come at approximately the same time of this visit.

17.7.2.9.1.3 Enrollment: Visit 1 (Week 0, Day 1)

- Reconfirm eligibility based on review of inclusion/exclusion criteria.
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height).

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Assess menstruation status and perform urine dipstick pregnancy test for female patients who commenced menstruating, ie, are of childbearing potential.
- Administer ACQ-IA (ACQ-7) and assess if ACQ-5 score is ≥1.5.
- Compliance with use of the mandatory background therapy, ICS in combination with one controller product as used just prior to screening, as defined as:
  - ≥80% of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient diary during the screening period.
- Measure FeNO:
  - FeNO 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 17.7.2.6.1. See below for additional directions.

- Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their duration of action, for example, withholding the last dose of salbutamol/albuterol 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 prior to administration of investigational product,
- Pre-bronchodilator FEV1 must be ≤95% of predicted normal or pre-bronchodilator FEV1/FVC ratio <0.85,
- Patients must meet the inclusion criteria for spirometry at Visit 1 prior to enrollment. If a patient's FEV1 does not qualify, then the patient will not be enrolled.

If the patient meets all inclusion and does not meet any exclusion criteria:

- Call IVRS/IWRS to register visit: Enroll the patient and receive the first assignment for 1 treatment kit number. Refer to Section 17.7.2.7.1.1.
  - Note: If entry criteria are not met: Call IVRS/IWRS to register visit and Screen-fail the patient.
- Perform blood sampling (prior to administration of IMP) for the following tests:
  - Clinical laboratory testing: hematology/biochemistry (refer to Section 17.7.2.8.3.5),
  - Systemic drug concentration and ADA (refer to Section 9.2.2.1),
  - Biomarker set, total IgE, and antigen-specific IgE (refer to Section 17.7.2.8.3.7).
- Dispense and administer IMP:
  - The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home. For those parent(s)/caregiver(s)/legal guardian(s) who wish to learn and train to home-administer the IMP injection (see Section 17.7.2.7.1.3 for details):

- They will be trained by the Investigator or designee to administer IMP, by demonstration eg, at V1, V2, and V3 for q2w doses and V1, V3, and V4 for q4w doses (injections performed by Investigator). The training of parent(s)/caregiver(s)/legal guardian(s) for IMP injection is to be documented in the patient's study file.
- Patients should be monitored for at least 30 minutes after study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.

- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication throughout the study.
- Remind patient and their 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.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol 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.
- Schedule a site visit 2 weeks later (Week 2 ± 3 days) at approximately the same time of this visit.

17.7.2.9.1.4 Open-label treatment period (Week 2 to Week 52 [Visits 2-10])

17.7.2.9.1.4.1 Visit 2 (Week 2 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight and height).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Administer ACQ-7.
- Measure FeNO:
  - FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry:
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Assess menstruation status.

- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP for children receiving q2w doses:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if IMP administrated on site.
  - The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home. If parent(s)/caregiver(s)/legal guardian(s) wish to learn and train to home administer the IMP injection (see Section 17.7.2.7.1.3 for details), they will continue to be trained by the Investigator or designee to administer IMP, by demonstration eg, at Visit 1, Visit 2, and Visit 3 for q2w doses and V1, V3, and V4 for q4w doses (injections performed by Investigator or designee). The training should be documented in the patient's medical records.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled according to their action duration, for example withholding the last dose of salbutamol/albuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Schedule a site visit 2 weeks later (Week 4 ±3 days) at approximately the same time of this visit.

17.7.2.9.1.4.2 Visit 3 (Week 4 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight and height).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Assess menstruation status.
- Administer ACQ-7.
- Measure FeNO:
  - FeNO 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours, or withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Obtain blood samples for:
  - Hematology (refer to Section 17.7.2.8.3.5),
  - Serum chemistry (refer to Section 17.7.2.8.3.5).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of at least 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
  - The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home. If parent(s)/caregiver(s)/legal guardian(s) wish to learn and train to home administer the IMP injection (see Section 17.7.2.7.1.3 for details), they will continue to be trained by the Investigator or designee to administer IMP, by demonstration eg, at Visit 1, Visit 2, and Visit 3 for q2w doses and V1, V3, and V4 for q4w doses (injections performed by Investigator or designee). The training should be documented in the patient's medical records. Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled according to their action duration, for example withholding the last dose of salbutamol/albuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Schedule a site visit 4 weeks later (Week 8 ±3 days) at approximately the same time of this visit.

17.7.2.9.1.4.3 Visit 4 (Week 8 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight and height).

- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Administer ACQ-7.
- Measure FeNO:
  - FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry:
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Assess menstruation status.
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site,
  - Record observation of at least 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
  - The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home(see Section 17.7.2.7.1.3 for details). If parent(s)/caregiver(s)/legal guardian(s) have been trained by the Investigator or designee to administer IMP by demonstration at not less than 3 visits, under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will perform the injection, including feedback on technique by the Investigator or delegate. The training should be documented in the patient's medical records.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled according to their action duration, for example withholding the last dose of salbutamol/albuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.

- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold the IMP dosing to secure an interval of 14 ±3 days prior to next onsite visit (Visit 5) for patients receiving IMP administration at home.
- Schedule a site visit 4 weeks later (Week 12 ±3 days) at approximately the same time of this visit.

17.7.2.9.1.4.4 Visit 5 (Week 12 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight and height).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Administer ACQ-7.
- Measure FeNO:
  - FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry:
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Perform physical examination.
- Assess menstruation status.
- Obtain blood samples for:
  - Hematology (refer to Section 17.7.2.8.3.5),
  - Serum chemistry (refer to Section 17.7.2.8.3.5).
- Systemic drug concentration and ADA (see Section 9.2.2.1.1 for details).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Urinalysis (dipstick).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site.

- The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home (see Section 17.7.2.7.1.3 for details). If parent(s)/caregiver(s)/legal guardian(s) have been trained by the Investigator or designee to administer IMP by demonstration at not less than 3 visits, under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will perform the injection, including feedback on technique by the Investigator or delegate. The training should be documented in the patient's medical records.
- Record observation of at least 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.

- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Schedule a site visit 4 weeks later (Week 16 ±3 days) at approximately the same time of this visit.

17.7.2.9.1.4.5 Visit 6 (Week 16 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight and height).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Assess menstruation status.
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site.
  - The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home (see Section 17.7.2.7.1.3 for details). If parent(s)/caregiver(s)/legal guardian(s) have been trained by the Investigator or designee to administer IMP by demonstration at not less than 3 visits, under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will perform the injection, including feedback on technique by the Investigator or delegate. The training should be documented in the patient's medical records.
  - Record observation of a minimum of 30 minutes after the injections monitored by IMP giver if patients receive IMP at home.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication as instructed by Investigator.

- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Schedule a site visit 4 weeks later (Week 20±3 days) at approximately the same time of this visit.

17.7.2.9.1.4.6 Visit 7 (Week 20 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight and height).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Assess menstruation status.
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site.
  - The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home (see Section 17.7.2.7.1.3 for details). If parent(s)/caregiver(s)/legal guardian(s) have been trained by the Investigator or designee to administer IMP by demonstration at not less than 3 visits, under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will perform the injection, including feedback on technique by the Investigator or delegate. The training should be documented in the patient's medical records.
  - Record observation of a minimum of 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators prior to next study visit when spirometry is scheduled according to their action duration, for example withholding the last dose of salbutamol/albuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold the IMP dosing to secure an interval of 14 ±3 days prior to next onsite visit (Visit 8) for patients receiving IMP administration at home.

- Schedule a site visit 4 weeks later (Week 24±3 days) at approximately the same time of this visit.

17.7.2.9.1.4.7 Visit 8 (Week 24 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight and height).
- Call IVRS/IWRS to register visit and obtain treatment kits number.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Perform physical examination.
- Administer ACQ-7.
- Measure FeNO:
  - FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry:
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Assess menstruation status.
- Obtain blood samples for:
  - Hematology (see Section 17.7.2.8.3.5 for details),
  - Serum chemistry (see Section 17.7.2.8.3.5 for details).
- Systemic drug concentration and ADA (see Section 9.2.2.1 for details).
- Total IgE and antigen-specific IgE (refer to Section 17.7.2.8.3.7).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Urinalysis (dipstick).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site.
  - The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home (see Section 17.7.2.7.1.3 for details). If parent(s)/caregiver(s)/legal guardian(s) have been trained by the Investigator or

designee to administer IMP by demonstration at not less than 3 visits, under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will perform the injection, including feedback on technique by the Investigator or delegate. The training should be documented in the patient's medical records.

- Record observation of a minimum of 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.

- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Schedule a site visit 12 weeks later (Week 36 ±3 days) at approximately the same time of this visit.

17.7.2.9.1.4.8 Telephone contact at Week 28 and 32 (±3 days)

See Section 10.1.2.8.

17.7.2.9.1.4.9 Visit 9 (Week 36 [±3 days])

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight).
- Call IVRS/IWRS to register visit and obtain treatment kits number.

  Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Administer ACQ-7.
- Assess menstruation status.
- Obtain blood samples for:
  - Hematology (see Section 17.7.2.8.3.5 for details),
  - Serum chemistry (see Section 17.7.2.8.3.5 for details).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Dispense and administer IMP:
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection if patients receive IMP on site.
  - The injection training is for parent(s)/caregiver(s)/legal guardian(s) who are willing to perform injection administration at home (see Section 17.7.2.7.1.3 for details). If parent(s)/caregiver(s)/legal guardian(s) have been trained by the Investigator or designee to administer IMP by demonstration at not less than 3 visits, under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will

perform the injection, including feedback on technique by the Investigator or delegate. The training should be documented in the patient's medical records.
- Record observation of a minimum of 30 minutes after the injection monitored by IMP giver if patients receive IMP at home.

- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Schedule a site visit 16 weeks later (Week 52 ±3 days) at approximately the same time of this visit.

17.7.2.9.1.4.10 Telephone contact at Weeks 40, 44, and 48 (±3 days)

See Section 10.1.2.10.

17.7.2.9.1.4.11 Visit 10 (Week 52 [±3 days]), End-of-treatment visit

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height).
- Call IVRS/IWRS to register EOT visit.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Administer ACQ-7.
- Measure FeNO:
  - FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry:

  Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Perform physical examination.
- Assess menstruation status.
- Perform 12-lead ECG.
- Obtain blood samples for:
  - Hematology (see Section 17.7.2.8.3.5 for details),
  - Serum chemistry (see Section 17.7.2.8.3.5 for details).
- Systemic drug concentration and ADA (see Section 9.2.2.1 for details).
- Total IgE and antigen-specific IgE (refer to Section 17.7.2.8.3.7).

- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Urinalysis (dipstick).
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol as reliever medication as instructed by Investigator.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller.
- Schedule a site visit 12 weeks later (Week 64 ±1 week) at approximately the same time of this visit.

17.7.2.9.1.5 Post-treatment period (12 weeks)

17.7.2.9.1.5.1 Telephone contact at Weeks 56 and 60 (±1 week)

See Section 10.1.3.1.

17.7.2.9.1.5.2 Visit 11: (Week 64 [±1 week]), end-of-study visit

- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight and height).
- Call IVRS/IWRS to register EOS visit.
- Record all concomitant medication use (including but not limited to asthma background controller, reliever, and vaccine); inquire about AEs/SAEs.
- Perform physical examination.
- Administer ACQ-7.
- Measure FeNO:
  - FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry:
  - Spirometry must be done at the study site approximately the same time of the day (preferably in the morning, but it could be done at a different time of the day). 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 for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours.
- Assess menstruation status.
- Perform 12-lead ECG.
- Obtain blood samples for:
  - Hematology (see Section 17.7.2.8.3.5 for details),

- Serum chemistry (see Section 17.7.2.8.3.5 for details).

- Systemic drug concentration and ADA (see Section 9.2.2.1 for details).
- Total IgE and antigen-specific IgE (refer to Section 17.7.2.8.3.7).
- Obtain urine pregnancy test (dipstick) if female patients are of childbearing potential (who have commenced menstruating).
- Obtain urinalysis test (dipstick).

17.7.2.9.2 Definition of source data

See Section 10.2.

17.7.2.9.3 Handling of patient temporary or permanent treatment discontinuation and of patient study discontinuation

See Section 10.3.

17.7.2.9.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgement that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 17.7.2.6.1 and Section 17.7.2.6.2), AE is sufficiently resolved and unlikely to recur after resuming therapy with IMP.

In addition, the following conditions will be causes for temporary treatment discontinuation:

- Infections or infestations that do not respond to medical treatment.
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Section 17.4 on Guidelines for management of specific laboratory abnormalities.
- Any administration of live attenuated vaccines (refer to Appendix B, Section 17.2) during the study period.

Temporary discontinuation may lead to permanent discontinuation after Sponsor's review on a case by case basis.

17.7.2.9.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

See Section 10.3.2.

17.7.2.9.3.3 List of criteria for permanent treatment discontinuation

See Section 10.3.3.

17.7.2.9.3.4 Handling of patients after permanent treatment discontinuation

See Section 10.3.4.

17.7.2.9.3.5 Procedure and consequence for patient withdrawal from study

See Section 10.3.5.

17.7.2.9.4 Obligation of the investigator regarding safety reporting

See Section 10.4.

17.7.2.9.5 Obligations of the sponsor

See Section 10.5.

17.7.2.9.6 Safety instructions

See Section 10.6.

17.7.2.9.7 Adverse events monitoring

See Section 10.7.

17.7.2.10 Statistical considerations

17.7.2.10.1 Determination of sample size

For the Japan substudy, the primary objective is to evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma. Assuming the change from baseline in % predicted FEV1 at Week 12 among the Japan substudy follows a normal distribution with mean of 10.74% and standard deviation of 14.12%, a sample size of 16 for the Japan sub-study will lead to a half-width of the 95% confidence interval being 7.5%. A minimum of 3 patients assigned to treatment in each of the 3 dose regimens is targeted.

The sample size calculations were performed using nQuery Advisor.

17.7.2.10.2 Disposition of patients

See Section 11.2.

17.7.2.10.3 Analysis population

See Section 11.3 for the definition of analysis populations.

The primary analysis population for the Japan substudy is the efficacy population.

17.7.2.10.4 Statistical methods

All analyses on analysis populations defined in Section 11.3 will be implemented for non-Japan study and Japan substudy separately.

For Japan substudy, the planned analyses will be performed on the observed data from the Japan substudy in each analysis population from the substudy. More details about the specific analysis for Japan substudy will be specified in the SAP.

17.7.2.10.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be summarized for the Japan substudy in the safety population using the same analysis approach as defined for the full analysis set of the non-Japan study in Section 11.4.1.1 and Section 11.4.1.2.

17.7.2.10.4.2 Analyses of efficacy endpoint

The efficacy analyses will be done descriptively on the observed data for the Japan substudy in the substudy efficacy population. The baseline value for the applicable efficacy parameters is the baseline from LTS14424 study, which is defined as the last available measurement prior to the first IMP dose in LTS14424 study.

For the continuous efficacy variables, descriptive statistics (mean, SD, median, minimum, and maximum) will be presented for the parameter and its change from baseline over visits, confidence interval will be presented as appropriate. In addition, figure of mean change from baseline (with corresponding standard error) will be presented for the continuous efficacy parameter over visits.

For the categorical efficacy variables, the number and percentage will be presented over time for the patients who have data available at that time point.

For severe exacerbation events, total number of severe exacerbation events, total patient-years, unadjusted annualized severe exacerbation event rate, and individual patient annualized severe exacerbation event rate (number, mean, SD, median, minimum, maximum) during the treatment period will be summarized.

17.7.2.10.4.3 Analyses of safety data

The safety analyses will be performed descriptively on the observed data in the safety population. The baseline value for the applicable safety parameters is the baseline from LTS14424 study, which is defined as the last available measurements prior to the first IMP dose in LTS14424 study.

The treatment-emergent period is from the date of first IMP injection to the date of the last IMP injection + 14 weeks for the patients who end the dupilumab treatment on either 100 mg q2w or 200 mg q2w regimen; and, the treatment emergent period is from the date of first IMP injection to the date of the last IMP injection +16 weeks for the patients who end the dupilumab treatment on 300 mg q4w regimen.

Same analysis approach as defined for the full analysis set of the non-Japan study in Section 11.4.3.1.1 to Section 11.4.3.1.4 will be used for the safety analysis for Japan substudy.

17.7.2.10.4.4 Analyses of systemic drug concentration, anti-drug antibodies, and pharmacodynamics variables

Pharmacokinetic analysis

The PK analyses will be performed by dose regimen for the Japan substudy in the PK population using the same descriptive analysis method as defined for the full analysis set of the non-Japan study in Section 11.4.4.1. The baseline value of each applicable PK variable is the baseline from LTS14424 study, which is defined as the last available measurements prior to the first IMP dose in LTS14424 study.

Anti-drug antibodies analysis

The ADA analyses will be performed for the Japan substudy in the ADA population using the same analysis approach as defined for the full analysis set of the non-Japan study in Section 11.4.4.2. The baseline value of each applicable ADA variable is the baseline from LTS14424 study, which is defined as the last available measurements prior to the first IMP dose in LTS14424 study.

17.7.2.10.4.5 Pharmacodynamics

The biomarker analyses will be applied descriptively on the observed data for the Japan substudy in safety population using the same descriptive analysis method as defined for the full analysis set of the non-Japan study in Section 11.4.4.3. The baseline value for the applicable pharmacodynamics (PD) variables is the baseline from LTS14424 study, which is defined as the last available measurements prior to the first IMP dose in LTS14424 study.

17.7.2.10.5 Interim analysis

There is no interim analysis planned for the Japan substudy.

17.7.2.10.6 Planned database lock

There will be a separate database lock for the Japan substudy to occur after the last patient has completed the last visit from Japan.

17.7.2.11 Ethical and regulatory considerations

See Section 12.

17.7.2.12 Study monitoring

See Section 13.

17.7.2.13 Additional requirements

See Section 14.

17.7.2.14 Appendix 1: Low, medium, and high-dose inhaled corticosteroids – children aged 6 to <12 years (Japan)

Inhaled Corticosteroid	Total Daily Dose (mcg)		
	Low	Medium	High
Fluticasone propionate	-100	-200	-400
Beclomethasone dipropionate	-100	-200	-400
Ciclesonide	-100	-200	-400
Budesonide	-200	-400	-800
Budesonide inhalation solution	-250	-500	-1000

Source: Adapted from Japanese Guidelines for Childhood Asthma 2020.

17.7.2.15 Appendix 2: Asthma control questionnaire–interviewer administered (ACQ-IA) for children 6 to <12 years

Asthma Control Questionnaire, 7-question version (ACQ-7)

Of note, ACQ-IA version in Japanese will be used for the Japan substudy. North American English version has been added in this Amended Protocol as an example only.

ASTHMA CONTROL QUESTIONNAIRE (ACQ-IA)

INTERVIEWER-ADMINISTERED
(for children 6-10 years)
NORTH AMERICAN ENGLISH VERSION

For further information:

[redacted] MCSP, MSc
Professor
[redacted]
[redacted] England
Telephone: [redacted]
Fax: [redacted]
E-mail: [redacted]
Web: [redacted]

JULY 2011

ACQ-IA – North American /English- revised July 2011
ID6133 / ACQ-IA_AU1.0_eng-US/CAori.doc

ASTHMA CONTROL QUESTIONNAIRE©
(NORTH AMERICAN ENGLISH VERSION)
INTERVIEWER-ADMINISTERED

PATIENT ID: _____

DATE: _____

ASTHMA CONTROL QUESTIONNAIRE (for children 6-10 years)

Please read these instructions carefully before administering the questionnaire

Parents may be present during the interview but you should encourage the child to respond and only ask the parent to help if the child is having difficulties.

Some younger children may have difficulty understanding the meaning of some questions. First, you should read each question to the child exactly as written in the text. If the child doesn't understand, read the question again using the secondary wording (marked with 'a'). Try not to place your own interpretation on the question.

The questionnaire will ask how the child's asthma has been during the last week (7 days). Check that the child understands this time frame. If in doubt, ask the parent to identify an event that occurred a week previously (e.g. a football match) and then ask the child to tell you how she/he has been since that event. Make sure that the child understands that we want to know how their asthma has been **on average** during the week, not about one specific asthma event.

Show the child the response card and explain the options. Explain the concept of the 7 responses. Explain that 0 means that they have not had any asthma symptoms and have not been limited at all in their daily activities and that 6 means that their symptoms and activity limitations have been really, really bad. Explain that the other numbers (1-5) represent levels in between. For children who can read, we suggest that you ask them to read aloud each of the responses. For younger children, start by reading to them just the 7 responses to question one (both number and words) and check that they understand the meaning of the words (then repeat at the beginning of each question).

Reassure the child that there are no right or wrong answers.

ASTHMA CONTROL QUESTIONNAIRE© (NORTH AMERICAN ENGLISH VERSION) INTERVIEWER-ADMINISTERED

PATIENT ID: _____

DATE: _____

First, read each question to the child using the primary wording. If the child does not fully understand the question, read it again using the secondary wording marked with 'a' (e.g. 2a, 3a etc.).

1. During the past week, how often were you **woken by your asthma** during the night?

2. During the past week, how **bad were your asthma symptoms when you woke up** in the morning?

2a During the past week, how **bad were your asthma symptoms (for instance, hard to breathe, wheeze, cough) when you woke up** in the morning?

3. During the past week, how **limited were you in your activities** because of your asthma?

3a During the past week, how **bothered were you in the things you do every day** because of your asthma?

4. During the past week, how much **shortness of breath** did you experience because of your asthma?

4a During the past week, how much **shortness of breath (hard or difficult to breathe, breathless)** did you have because of your asthma?

5. During the past week, how much time did you **wheeze?**

6. During the past week, how many **puffs/inhalations of short-acting bronchodilator** (e.g. Ventolin/Bricanyl) have you used each day?

6a During the past week, how many **puffs of your Reliever (quick relief, rescue)** have you used each day?

ASTHMA CONTROL QUESTIONNAIRE©
(NORTH AMERICAN ENGLISH VERSION)
INTERVIEWER-ADMINISTERED

PATIENT ID: _____

DATE: _____

RESPONSE SHEET

Question	Response (0-6)
1. Woken by asthma	.....
2. Asthma symptoms on waking	.....
3. Activity limitation	.....
4. Short of breath	.....
5. Wheeze	.....
6. Bronchodilator	.....

Please circle the response (0-6) for the child's FEV_1% predicted

7.	FEV_1pre-bronchodilator:	0	> 95% predicted
		1	95 - 90%
	FEV_1predicted:.....	2	89 - 80%
		3	79 - 70%
	FEV_1%predicted:.....	4	69 - 60%
	(Record actual values on the dotted	5	59 - 50%
	lines and score the FEV_1 % predicted	6	< 50% predicted
	in the next column)		

ACQ-IA – North American /English- revised July 2011
ID6133 / ACQ-IA_AU1.0_eng-US/CAori.doc

ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID: _____
(NORTH AMERICAN ENGLISH VERSION)
INTERVIEWER-ADMINISTERED DATE: _____

RESPONSE CARD

QUESTION 1
0 Never
1 Hardly ever
2 A few times
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

QUESTION 2
0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

QUESTION 3
0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

QUESTION 4
0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

QUESTION 5
0 Never
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time

QUESTION 6
0 None
1 1 - 2 puffs/inhalations most days
2 3 - 4 puffs/inhalations most days
3 5 - 8 puffs/inhalations most days
4 9 - 12 puffs/inhalations most days
5 13 - 16 puffs/inhalations most days
6 More than 16 puffs/inhalations most days

ACQ-IA – North American /English- revised July 2011
ID6133 / ACQ-IA_AU1.0_eng-US/CAori.doc

17.7.2.16 Appendix 3: Contingency Measures for Japan for a regional or national emergency that is declared by a governmental agency

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency; this agreement must be provided in writing by the sponsor and will be kept in the Investigator file.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in separate study documents.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, screening and enrollment may be temporarily delayed/halted.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

17.7.2.16.1 Study procedures

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

1. New screenings during a regional or national emergency declared by a governmental agency can be performed only if allowed by local competent authorities and after Sponsor’s agreement is obtained. Rescreening will be permitted when the situation normalizes and only if allowed by local competent authorities and after Sponsor’s agreement is obtained.
2. If onsite visits or alternative location (out of patient’s home) are not possible, all visits from Week 2 (including those planned to be done onsite) will be performed at home by a trained healthcare professional and if allowed by local competent authorities for:
   - Treatment administration
   - Monitoring of injection site reactions, AEs and SAEs
   - Collect study samples for safety, and pregnancy test (if applicable)
   - Perform study examinations (eg, Measuring vital signs)

3. IMP Injection Training: In case of emergency (eg, natural disaster, pandemic) different training ways (eg, training remotely with instruction provided by phone) can be performed (and will be documented in the participant's study file).
4. After Sponsor agreement is obtained, the IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the patients.

The use of a local laboratory may be allowed for safety follow up in case the central lab cannot be used.

If onsite or home visits are not possible, the Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment. All data collected remotely will be properly documented in the patient's medical record and the study CRF.

For all assessments which will not be performed remotely, the assessment windows will be extended until patients may access the site.

If onsite visit and home visit are not possible, a temporary treatment discontinuation may be considered. The Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment.

Contingencies implemented due to emergency will be documented in the participant's medical record.

17.8 APPENDIX H: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Clinical Trial Summary.

AMENDED PROTOCOL 05 (01 February 2021)

Overall Rationale for the Amendment

The purpose of this amendment is to add a substudy of pediatric asthma patients from Japan within Study LTS14424 in order to evaluate efficacy, PK, and safety in this population. Patients in Japan were not included in the parent Study EFC14153, and this amendment adds a substudy of Japanese patients aged 6 to <12 years with uncontrolled persistent asthma. The primary objective of the substudy of Japanese patients aged 6 to <12 years with asthma is to evaluate the efficacy of dupilumab.

The description of the substudy of Japanese patients is outlined in Section 17.7.2 (Country specific requirements for Japan).

Protocol amendment summary of changes table

Section # and Name	Description of change	Brief Rationale
Section 3 List of abbreviations	New abbreviations added.	Update
Section 4.2 Rationale	Japan specific wording added.	Clarifying text provided in order to highlight information that is specific to patients from Japan
Section 16 Bibliographic references	New references added and internal cross references updated throughout the document.	Update
Section 17.7.2 Country specific requirements for Japan & all 17.7.2 subsections	Sections added under appendix G. Numerical numbering newly inserted for all appendices under section 17 (appendix A changed to section 17.1 -appendix A, etc.).	Japan specific wording
Section 17.8 Appendix H: Protocol amendment history	Protocol amendment history updated.	Update
Throughout the document	New sections added. Table of contents updated. In-text references updated in relation to the update of sections.	Update

AMENDED PROTOCOL 04 (15 April 2020)

This amended protocol 04 is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This amendment is in response to the current COVID-19 pandemic, which has made it challenging for patients to reach onsite visits or may interrupt access to IMP. The current eligibility criteria for LTS14424 requires that patients complete study treatment in parent study EFC14153, and that they roll-over to LTS14424 at the EFC14153 end-of-treatment (EOT) visit. In order to ensure that otherwise eligible patients are able to enter Study LTS14424, Visit 1 will be allowed to occur at the EFC14153 EOT visit, the EFC14153 end-of-study (EOS) visit, or for up to 12 weeks after completion of EFC14153 EOS visit, and patients that do not complete all study treatments in EFC14153 due to the COVID-19 pandemic will still be eligible for LTS14424.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary 1.1 Graphical Study design 1.2 Study flow chart (footnotes) 6.2.1 Duration of study participation for each patient 7.1 Inclusion criteria 8.1 Investigational medicinal product 9 Assessment of Investigational medicinal Product 10.1.1 Enrollment: Visit 1 of present study (Start-of-treatment, Week 0)	To allow later entrance in LTS14424 for EFC14153 patients who are not able to perform the EFC14153 EOT visit onsite to rollover at V28/EOT, or to receive last IMP doses in parent study EFC14153 due to the COVID19 pandemic.	The LTS14424 Study is an Open Label Extension study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients who participated in Study EFC14153. The sponsor's intent was to allow all eligible patients to continue to the open label extension study. However, due to the current restrictions in place related to the COVID-19 pandemic, many patients may not be able to complete their treatment or go to sites for the combined Study EFC14153 EOT visit/Study LTS14424 Visit1. Therefore to allow these patients to remain eligible for LTS14424, the sponsor is providing more flexibility. Patients who did not receive last IMP doses or could not enroll at LTS14424 at V28/EOT of parent study EFC14153 due to COVID-19 pandemic will be allowed to enroll in Study LTS14424 at either EFC14153 EOS Visit or until 12 weeks afterEFC14153 EOS Visit.
11.4 Statistical methods 11.4.2 Analyses of efficacy endpoints 11.4.3.1.3. Death	To remove the monthly 300 mg dose specific analysis set	The current protocol requires that patients who are ≤30kg start or switch to 300 mg q4w dosing at an onsite visit. However, due to the current COVID-19 situation, many patients have not been able or will not be able to present to sites. As this will result in a smaller total number of patients exposed to 300 mg q4w, the sponsor will evaluate the safety and efficacy of patients exposed to 300 mg q4w regimen together with the other dose regimens in the full analysis set.
1.2 Study Flowchart footnote g 8.1.3 Dosing schedule 10.1.1 Enrollment: Visit 1 of present study (Start-of-treatment, Week 0)	To allow at home administration of 300 mg monthly doses from the second administration onwards (following first 300 mg administered onsite)	Due to COVID-19 pandemic, some patients may not be able to return monthly to sites for onsite administration of IMP 300 mg. This amendment will still require that patients switch/ initiate 300 mg dose onsite, but will allow patients to receive subsequent doses at home. Previous experience with this dose, including 122 children age 6 to <12 years old exposed to 300 mg q4w in the pivotal phase III Atopic dermatitis study (R668-AD-1652) supports the acceptability of at home administration for this dose.

AMENDED PROTOCOL 03 (12 December 2019)

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

Overall Rationale for the Amendment

The purpose of this amendment is to modify the dupilumab dose for children with body weight ≤30 kg from 100 mg every 2 weeks (q2w) to 300 mg every 4 weeks (q4w). This update provides data to support harmonization of dosing across indications and decreases overall burden by shifting from q2w to q4w dosing in children ≤30 kg. Pharmacokinetic (PK) modeling supports that this dose achieves a concentration that is within the therapeutic window for dupilumab in

asthma. This dose was recently demonstrated to have a favorable safety profile and to be effective for atopic dermatitis (AD) patients age 6-11 years with body weight <30kg, including patients with comorbid asthma. Therefore, given the similar PK that have been observed across healthy volunteers as well as patients with AD and asthma, the Sponsor anticipates a similar profile in children with asthma.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary 1.1 Graphical flow chart 1.2 Study flow chart 4.2 Rationale 8.1 Investigational medicinal product 8.4 Method of assigning patients to treatment group 10.1.1 Enrollment: Visit 1 of present study (Start of treatment, Week 0) 10.1.2 Open-label treatment period (Week 0 to Week 52 [Visits 2-10])	To change dupilumab dose for children with body weight ≤30 kg from 100 mg q2w to 300 mg q4w	The PK profile for dupilumab has been demonstrated to be similar across healthy patients as well as across indications including AD and asthma. Wherever possible, the sponsor would like to enable harmonization of dosing posology across patients of similar age and weight. The recent AD 6-11 years clinical trial (R668-AD-1652) demonstrated that the dose 300 mg q4w was efficacious and has an acceptable safety profile for patients age 6-11 with body weight 15 to <30 kg. Therefore, the Sponsor proposes to introduce this same dose regimen in to LTS14424 in order to collect safety and clinical data in asthma patients of a similar age and body weight. This harmonization of dosing posology is intended to reduce overall patient burden through less frequent dosing with an anticipated exposure range similar to that demonstrating an efficacious dose with an acceptable safety profile in the AD patients aged 6-11 years of age and 15 to <30 kg. Subsequent to the start of LTS14424, the AD study evaluating the efficacy and safety of dupilumab for the treatment of children age 6-11 years old with severe atopic dermatitis (R668-AD-1652) was completed. Two doses for children with baseline weight <30kg were evaluated: 100 mg q2w and 300 mg q4w. In that study, the 300 mg q4w dose was found to be effective and had an acceptable safety profile. Of note, 46.7% of the patients enrolled in R668-AD-1652 had comorbid asthma. In addition, modeling data supports that the 300 mg q4w dose approximates the therapeutic concentration in adults. PK modeling incorporating data from the clinical development program in asthma populations identifies that 300 mg q4w in children 15 to 30 kg is expected to match adult and adolescent efficacious exposure at 300 mg q2w, within a safe treatment profile within the desired therapeutic window. The predicted C_{trough} for 300 mg q4w in pediatric patients 15 to 30 kg is similar to the adult and adolescent 300 mg q2w C_{trough}. The predicted C_{max} of 300 mg q4w in pediatric patients 15 to 30 kg does not exceed the adult 300 mg every week (qw) C_{max} in asthma Phase 2/3 studies. Therefore, based on the observed data in AD as well as modeling data in asthma populations, the 300 mg q4w dose is anticipated to be efficacious with a favorable safety profile in the same age and weight class for asthma. All newly enrolled children with body weight ≤30 kg will take 300 mg q4w and children ≤30 kg receiving 100 mg q2w will be switched to 300 mg q4w if they have more than 8 weeks before the planned end of the treatment period. Safety, PK and clinical data will be monitored in this population.

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary 9.2.2.2 Pharmacodynamics and phenotyping	To remove Immunoglobulins (Igs) as Other secondary endpoints	Immunoglobulins other than IgE are not being collected in this LTS14424.
10.4.1.1 Adverse event	Clarification on when an asthma exacerbation is to be reported as adverse event	Protocol-defined severe asthma exacerbation events are collected as efficacy endpoints. Only asthma exacerbations which fulfill a seriousness criterion should be reported as an AE (SAE).
10.4.1.3 Adverse event of special interest	Addition of relatedness to IMP in the AESI Anaphylactic reaction and systemic allergic reaction	To match dupilumab program AESI definition (Anaphylactic reaction and systemic allergic reaction related to IMP that require treatment).
10.6.4 Elevated liver function tests	To clarify that hepatitis serologies are not repeated for determining patients' eligibility in LTS14424	Hepatitis serologies are performed as part of the parent study (EFC14153) eligibility and not repeated before rolling over to LTS14424.
Clinical trial summary 11.1 Determination of Sample Size	Change in study sample size	The sample size for the parent study EFC14153 was reduced with a shift in focus to patients with type 2 inflammation as well as updated power calculations for this population, and at the same time, there has been a higher than anticipated roll-over rate from this study to LTS14424. Therefore, the Sponsor will update the anticipated sample size for LTS14424.
11.4 Statistical methods	To update analysis populations according to the dose regimen.	There will be two analysis sets of each analysis population. The full analysis set will include all data collected during LTS14424 study regardless of the dose regimen (including 300 mg q4w dose). The modified analysis set will censor the data observed on or after the first injection date of 300 mg q4w for the patients ever exposed to the 300 mg q4w regimen.
14.2 Record retention in study sites	To update retention of study documents in study sites from 15 to 25 years	The record retention in study sites was updated according to dupilumab program and to be consistent with the information provided in Informed consent form (ICF)/written patient information (WSI).

AMENDED PROTOCOL 02 (09 July 2018)

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

Overall rationale for the amendment:

To increase study sample size due to increase in number of participants in EFC14153 (parent study of LTS14424).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary; 11.1 Determination of Sample Size	Change in study sample size	Due to the increase in the sample size of EFC14153 (parent study of LTS14424), the number of participants in LTS14424 will also increase
Clinical Trial Summary; 9.2.1 Secondary safety and tolerability endpoints	Removal of secondary safety endpoint	The secondary endpoint "Safety and tolerability" is described in the Primary endpoint under of the name of TEAEs. Vital signs, physical examination, ECG and laboratory tests are measurements of safety and will be presented in a descriptive manner
9.3 Future Use of Samples; 12.2 Informed Consent; 14.5 Data Protection	Removal of Optional pharmacogenetic informed consent/assent form mention	No pharmacogenetics analysis is planned in this study
10.3.3 List of criteria for permanent treatment discontinuation	Pregnancy outcome follow-up period	To correct the information on when the follow-up shall end in case of pregnancy
1.2 Study Flow Chart; 9.2.2.2 Assessment of lung function by spirometry; 10.1.1 Enrollment: Visit 1 of present study (Start of treatment, Week 0); 10.1.2 Open-label treatment period (Week 0 to Week 52 [Visits 2-10]) and 10.1.3 Post-treatment period (12 weeks)	LAMA and Ultra LABA (vilanterol) withdrawal period before spirometry	To harmonize LAMA and Ultra LABA (vilanterol) 24h withdrawal period before spirometry information along the protocol
9.3 Future Use of Samples	Total volume of blood collected in a single visit	To correct the information that maximum volume of blood collected at Visit 10 (24 mL) represents 1.5 mL/kg for the smallest patient (16 kg)
1.2 Study Flow Chart	LTS14424 Visit 1 data	To correct the information that data for LTS14424 Visit 1 coming from EOT Visit from parent study will not be reported in LTS14424 eCRF
1.2 Study Flow Chart 10 Study procedures (10.1.2.1; 10.1.2.3; 10.1.2.6; 10.1.2.8; 10.1.2.10; 10.1.3.1;	Fasting condition	To remove the need of fasting condition before blood samples collection

AMENDED CLINICAL TRIAL PROTOCOL 01 (BRAZIL) BASED ON PROTOCOL AMENDMENT 01 (BRAZIL) (14 March 2018)

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

Overall rationale for the amendment:

To allow Brazilian patients who were prematurely discontinued from IMP in EFC14153 due to the need of Yellow Fever vaccination during Yellow Fever outbreak, to be included in LTS14424.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary; 7.1 Inclusion Criteria	To allow Brazilian patients who were prematurely discontinued from IMP in EFC14153 due to the need of Yellow Fever vaccination during Yellow Fever outbreak, to be included in LTS14424.	The LTS14424 study includes pediatric patients with asthma who completed the treatment in a Dupilumab asthma trial (EFC14153). Any Brazilian patient who was prematurely discontinued from the IMP (in Study EFC14153) due to the need of Yellow Fever Vaccination during the Yellow Fever outbreak will be allowed to be enrolled in LTS14424 provided that the required follow-up procedures are completed in study EFC14153.

Signature Page for VV-CLIN-0490297 v5.0
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