NCT03560466

# STATISTICAL ANALYSIS PLAN

## 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

**SAR231893-LTS14424**

---

**STATISTICIAN:** [redacted]

**DATE OF ISSUE: 27-Aug-2020**

---

Total number of pages: 62

## TABLE OF CONTENTS

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADA: | anti-drug antibodies |
| AE: | adverse event |
| AESI: | adverse event of special interest |
| ALP: | alkaline phosphatase |
| ALT: | alanine aminotransferase |
| AST: | aspartate aminotransferase |
| ATC: | anatomic category |
| BMI: | body mass index |
| CPK: | creatine phosphokinase |
| CV: | coefficient of variation |
| ECG: | electrocardiogram/electrocardiography |
| eCRF: | electronic case report form |
| FEF: | forced expiratory flow |
| FEV1: | forced expiratory volume in one second |
| FVC: | forced vital capacity |
| HLGT: | high-level group term |
| HLT: | high level term |
| ICS: | inhaled corticosteroid |
| IgE: | immunoglobuline |
| IMP: | investigational medicinal product |
| ISRs: | injection site reactions |
| IVRS/IWRS: | Interactive Voice Response System/Interactive Web Response System |
| K-M: | Kaplan-Meier |
| LLOQ: | lower limit of quantitation |
| MDI: | metered dose inhaler |
| MedDRA: | Medical Dictionary for Regulatory Activities |
| NAb: | neutralizing antibody |
| NIMP: | non-investigational medicinal product |
| PCSA: | potentially clinically significant abnormalities |
| PK: | pharmacokinetics |
| PT: | preferred term |
| q2w: | once every 2 weeks |
| q4w: | once every 4 weeks |
| SAE: | serious adverse event |
| SC: | subcutaneously |
| SCS: | systemic corticosteroids |
| SD: | standard deviation |
| SEM: | standard error of the mean |
| SOC: | system organ class |
| TEAE: | treatment-emergent adverse events |
| ULN: | upper limit of normal |
| WHO-DD: | World Health Organization-Drug Dictionary |

# 1 OVERVIEW AND INVESTIGATIONAL PLAN

## 1.1 STUDY DESIGN AND RANDOMIZATION

LTS14424 is a multinational, multicenter, open-label, single arm, 1-year treatment study evaluating dupilumab given subcutaneously (SC) for a period of 52 weeks. The study is designed 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 was designed to collect PK, safety, and clinical response information on patients with asthma who weigh ≤30 kg and who are treated with dupilumab 300 mg q4w.

Patients receive their first dose of dupilumab in the LTS14424 study at Visit 1 which is Week 0 that corresponds to EOT visit (Week 52) of the parent EFC14153 study. For patients who are not able to perform the EFC14153 EOT visit onsite due to the COVID-19 pandemic, LTS14424 Visit 1 (Week 0) can occur at the EFC14153 EOS visit or for up to 12 weeks after the EFC14153 EOS visit. The initial planned treatment regimen is based on the patients' weight at enrollment in LTS14424: 200mg q2w for children >30 kg, and 100mg q2w for children ≤30 kg. Protocol amendment 3 updated the dose for children ≤30 kg to 300 mg q4w, and all children in this weight category with at least 8 weeks remaining before the planned end of treatment period were to be switched to this dose at the time of amendment approval. All newly enrolled children with body weight ≤30 kg will take 300 mg q4w. At subsequent visits, for all patients whose body weight increases from ≤30 kg to >30 kg, their dupilumab dose will be increased to 200 mg SC q2w and then maintained during the remaining treatment period.

Approximately 354 patients from parent study (EFC14153) will be enrolled into LTS14424 study.

## 1.2 OBJECTIVES

### 1.2.1 Primary objectives

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).

### 1.2.2 Secondary objectives

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.

## 1.3 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 a previous dupilumab asthma clinical trial (EFC14153). 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 the previous dupilumab asthma clinical study.

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

## 1.4 STUDY PLAN

The clinical trial consists of 3 periods:

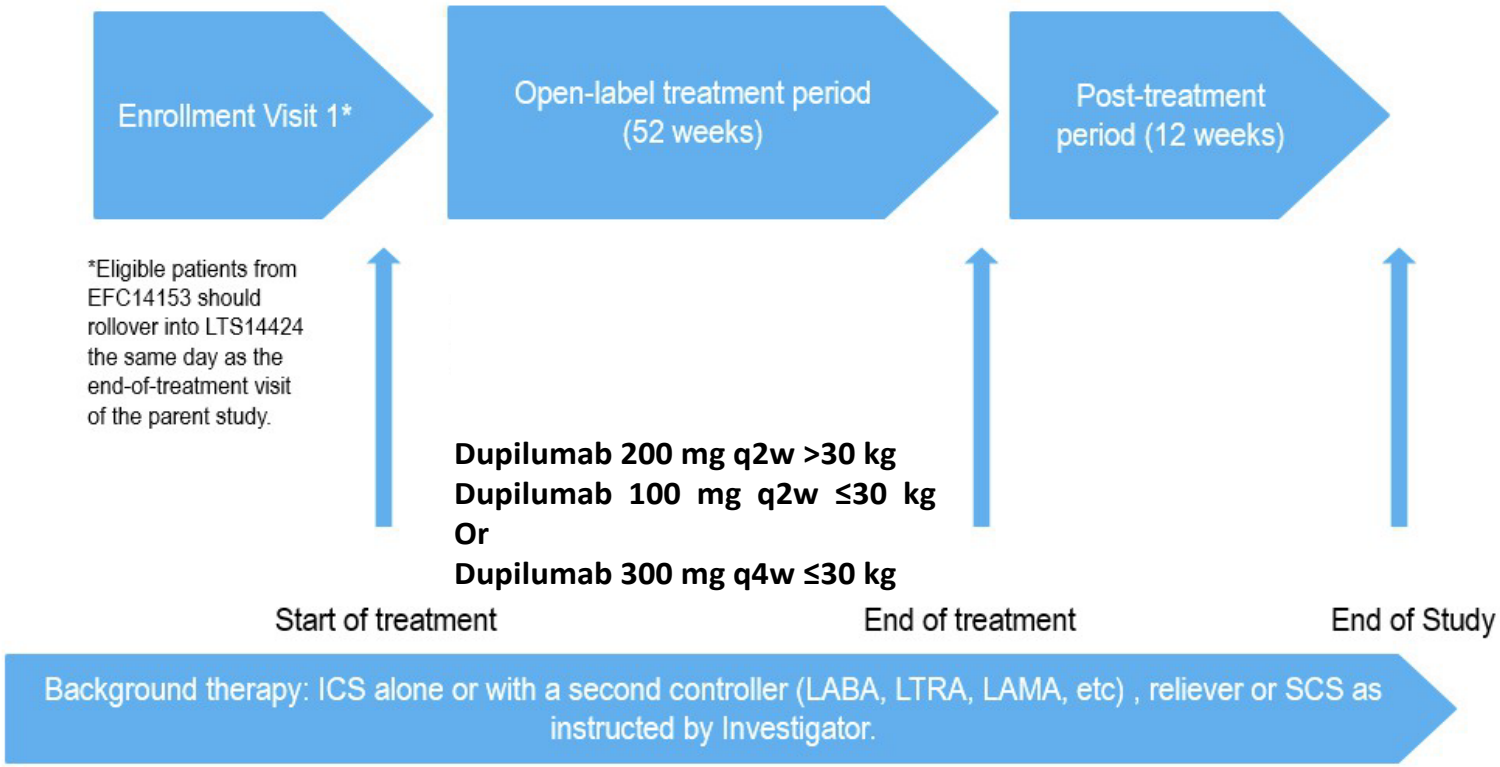
- Enrollment: Eligible patients from EFC14153 will rollover into LTS14424 the same day as the end-of-treatment (EOT) visit of the parent study. In the specific situation of COVID-19 pandemic, when patients cannot reach onsite EOT visit for study EFC14153, enrollment into LTS14424 may also be done on 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.
- Post-treatment period: 12 weeks.

At enrollment, patients must be on background therapy (ICS alone or with a second controller) as in the 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).

During the treatment period, the investigator, based on his/her medical judgement of the patients' asthma control status, may modify the dose of the patient's asthma controller medication(s) to achieve adequate control of patient's asthma. Patients may use albuterol/salbutamol or levalbuterol/levosalbutamol as reliever medication as needed during the study. Patients may be placed on systemic corticosteroids (SCS) at any time as clinically indicated based on the presence of symptoms consistent with a severe asthma exacerbation, as per the Investigator's judgement.

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.

### 1.4.1 Graphical Study Design




* 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.

## 1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled).

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section. "Principal features of the analysis" encompass the confirmatory aspects of the trial, including the primary and key secondary endpoints/analyses, and the analysis populations associated with these analyses.

**Table 1 - Protocol amendment statistical changes**

| Amendment Number | Date Approved | Rationale | Description of statistical changes |
|---|---|---|---|
| 2 | 09-Jul-2018 | Due to the increase in the sample size of EFC14153 (parent study of LTS14424) from 294 to 471. | Due to the increase in the sample size of EFC14153 (parent study of LTS14424) from 294 to 471, the number of participants in LTS14424 will also increase from 236 to 377. |
| 3 | 12-Dec-2019 | 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. | Due to decrease of sample size in the EFC14153 study from 471 to 408 and considering the roll-over rate, sample size expected is around 354 patients. |
| 3 | 12-Dec-2019 | Due to the addition of a new regimen of 300 mg q4w | 300 mg q4w is added as a new regimen for children of ≤ 30 kg. The analysis will be based on two analysis sets, one including all data regardless of the dose regimen, the other excluding data on or after exposure to the 300 mg q4w regimen. |

## 1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

**Table 2 - Statistical analysis plan statistical changes**

| SAP version number | Date approved | Rationale | Description of statistical changes |
|---|---|---|---|
| 2 | 27-Aug-2020 | 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 after EFC14153 EOS Visit. | The definition of pre-dose measurements at Week 0 of LTS14424 is changed to the last available measurements prior to the first IMP dose in LTS14424 study |
| 2 | 27-Aug-2020 | There are a very limited number of patients who are exposed to the new dosage Dupilumab 300 mg q4w. As a consequence, the full analysis set and modified analysis set is highly overlapped. Safety subgroup analyses will be performed on the full analysis set which represents the overall safety evaluation of the study population. | "The planned subgroup analyses for key safety endpoints will be performed for each of the full and modified analysis sets of safety population" will be changed to "The planned subgroup analyses for key safety endpoints will be performed for the full analysis set of safety population" |
| 2 | 27-Aug-2020 | Antigen-specific IgE will be assessed along with the total IgE | Add analyses for antigen-specific IgE |

# 2 STATISTICAL AND ANALYTICAL PROCEDURES

***Generalities***

Generally, for each analysis population (Safety, Efficacy, Pharmacokinetics, and Anti-drug antibody) that is defined in Section 2.3, the planned analyses will be conducted in the following two analysis sets:

- The full analysis set: all data observed in the study. The analyses performed on the full analysis set are to evaluate the long-term safety, efficacy, PK and etc. of all the dose regimens that are investigated in the LTS14424 study, that is, dupilumab 100 mg q2w, 300 mg q4w and 200 mg q2w.
- The modified analysis set: 1) For patients never exposed to 300 mg q4w: all observed data will be included 2) For patients that switch from 100 mg q2w to 300mg q4w in LTS14424: data will be included up to the date of first dose of 300 mg q4w with censoring data observed on or after this date 3) For patients that initiate the study on 300 mg q4w (i.e. receive 300 mg q4w at Day 0) no data will be included in this analysis set. The analyses performed on the modified analysis set are to focus on the long-term safety, efficacy, PK and etc. of the same regimens as the parent study, that is, dupilumab 100 mg q2w and 200 mg q2w.

***Observation period***

The observation period will be divided into 4 epochs which are defined in Table 3 according to the two analysis sets.

The treatment-emergent adverse event period will include both treatment and residual treatment epochs that are defined in Table 3. The post-treatment adverse event period will be the post-treatment epoch.

The pre-treatment adverse event period will be from the start of AE reporting in LTS14424 up to the first dose of IMP in LTS14424. For all the periods aforementioned, both date and time shall be used in the determination of the periods, as long as they will be available.

**Table 3 - Study epoch definition by analysis set**

| Analysis Set | Epoch | Applicable Patients | Epoch Start | Epoch End |
|---|---|---|---|---|
| Full analysis set | **Screening** | All | -- | The day before the date of first IMP |
| | **Treatment** | Patients with last IMP on 100mg/200mg q2w regimen | Date of the first IMP in LTS14424 | Date of last IMP +14 days |
| | | Patients with last IMP on 300 mg q4w regimen | Date of the first IMP in LTS14424 | Date of last IMP +28 days |
| | **Residual treatment** | Patients with last IMP on 100mg/200mg q2w regimen | Date of last IMP +15 days | Date of last IMP +14 days +12 weeks (84 days) |

| Analysis Set | Epoch | Applicable Patients | Epoch Start | Epoch End |
|---|---|---|---|---|
| | | Patients with last IMP on 300 mg q4w regimen | Date of last IMP +29 days | Date of last IMP +28 days +12 weeks (84 days) |
| | **Post-treatment** | All | Residual treatment Epoch End date +1 day | Open ended |
| Modified analysis set (not applicable to patients who initiate the treatment on 300 mg q4w regimen since Week 0 of LTS14424) | **Screening** | All | -- | The day before the date of first IMP |
| | **Treatment** | Patients on 100 mg/200 mg q2w regimen only | Date of the first IMP in LTS14424 | Date of last IMP +14 days |
| | | Patients who switched regimen from 100 mg q2w to 300 mg q4w | Date of the first IMP in LTS14424 | The date before the first dose of 300 mg q4w |
| | **Residual treatment** | Patients on 100 mg/200 mg q2w regimen only | Date of last IMP +15 days | Date of last IMP +14 days +12 weeks (84 days) |
| | | Patients who switched regimen from 100 mg q2w to 300 mg q4w | N/A | N/A |
| | **Post-treatment** | Patients on 100 mg/200 mg q2w regimen only | Residual treatment Epoch End date + 1 day | Open ended |
| | | Patients ever switch regimen from 100 mg q2w to 300 mg q4w | N/A | N/A |

## 2.1 ANALYSIS ENDPOINTS

The baseline values of endpoints in LTS14424 are defined as the original baseline of the parent study, unless otherwise specified. In addition to the baseline, the pre-dose measurements at Week 0 of LTS14424 are defined as the last available measurements prior to the first IMP dose in LTS14424 study.

### 2.1.1 Demographic and baseline characteristics

***Demographic characteristics***

Demographic characteristics are

- Baseline age in years (quantitative and qualitative variable: 6-8, 9–11 years).
- Age in years at Week 0 of LTS14424 (quantitative and qualitative variable: 7-9 years, 10 and above).
- Gender (Male, Female).
- Region (Latin America: Argentina, Brazil, Colombia, Chile and Mexico; Eastern Europe: Poland, Hungary, Romania, Lithuania, Russia, Ukraine and Turkey; Western Countries: Australia, Canada, Italy, South Africa, Spain, and USA).

- Race (Caucasian/White, Black/of African descent, Asian/Oriental, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Other).
- Ethnicity (Hispanic, Not Hispanic).
- Baseline height in cm.
- Height in cm at Week 0 of LTS14424.
- Baseline weight in kg (quantitative and qualitative variable: weight ≤30, weight >30 kg).
- Weight in kg at Week 0 of LTS14424 (quantitative and qualitative variable: weight ≤30, weight >30 kg).
- Baseline BMI in $kg/m^2$ (quantitative and qualitative variable: BMI<20, BMI≥20 $kg/m^2$).
- BMI in $kg/m^2$ at Week 0 of LTS14424 (quantitative and qualitative variable: BMI<20, BMI≥20 $kg/m^2$).

The data for demographic characteristics will be obtained from the original baseline of the parent study.

***Medical or surgical history***

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the patient.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database locks.

Comorbidity history will be summarized separately. The following comorbid diseases will be summarized.

- Atopic dermatitis history (Yes, Ongoing condition).
- Allergic conjunctivitis history (Yes, Ongoing condition).
- Allergic rhinitis history (Yes, Ongoing condition).
- Allergic conjunctivitis and/or rhinitis history (Yes, Ongoing condition).
- Chronic rhinitis history (Yes, Ongoing condition).
- Chronic sinusitis history (Yes, Ongoing condition).
- Eosinophilic esophagitis history (Yes, Ongoing condition).
- Food allergy history (Yes, Ongoing condition).
- Hives history (Yes, Ongoing condition).

A patient will be considered to have an atopic medical condition if the patient has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or allergic rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline (parent study) total IgE ≥100 IU/mL and at least 1 antigen-specific IgE is positive (≥0.35 IU/mL) at baseline of parent study.

The data of medical or surgical history will be obtained from the original baseline of the parent study.

***Disease characteristics at baseline***

The following baseline disease characteristics will be summarized:

- ICS dose level (medium, high as defined in Appendix C).
- ICS dose level at Week 0 of LTS14424 (medium, high as defined in Appendix C).
- Age at asthma onset (years).
- Time since first diagnosis of asthma (years).
- Time since last asthma exacerbation (months).
- Number of asthma exacerbations experienced 1 year before Visit 1 of the parent study.
- Number of asthma exacerbations required hospitalization or urgent medical care 1 year before Visit 1 of the parent study (quantitative and qualitative variable: 0, 1, 2, 3, ≥4).
- Baseline eosinophil count (Giga/L).
- Baseline eosinophil count category (<0.15, ≥0.15 and <0.3, ≥0.3 Giga/L).
- Eosinophil count (Giga/L) at Week 0 of LTS14424.
- Eosinophil count category (<0.15, ≥0.15 and <0.3, ≥0.3 Giga/L) at Week 0 of LTS14424.
- Baseline FeNO (ppb).
- Baseline FeNO category (<20, ≥20 and < 35, ≥35 ppb).
- FeNO (ppb) at Week 0 of LTS14424.
- FeNO category (<20, ≥20 and < 35, ≥35 ppb) at Week 0 of LTS14424.
- Baseline spirometry data and spirometry data at Week 0 of LTS14424, including pre-bronchodilator forced expiratory volume in 1 second (FEV1) (L), percentage (%) predicted FEV1, post-bronchodilator FEV1 (L) and FEV1 reversibility (%).
- Baseline serum total IgE (IU/mL).
- Serum total IgE (IU/mL) at Week 0 of LTS14424.
- Baseline TARC (pg/mL).

The data of baseline disease characteristics will be obtained from the original baseline of the parent study, unless otherwise specified. Any technical detail related to computation, dates, and imputation for missing dates is described in Section 2.5.

### 2.1.2 Prior or concomitant medications

All medications taken within 30 days before screening of parent study and until the end of LTS14424 study, including asthma controller medications, reliever medications and systemic corticosteroids are to be reported in the electronic case report form (eCRF) pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database locks.

- Prior medications are any treatments taken by patient prior to the first IMP administration in the parent study. Prior medications can be discontinued before the first IMP administration in parent study or can be maintained during treatment phase in parent study.
- Concomitant medications in parent study are any treatments received by patient concomitantly to the IMP in the parent study, from (on/after) the first administration of IMP up to the last available information in parent study before rolling over into the LTS14424 study.
- Concomitant medications are any treatments received by patient concomitantly to the IMP in the LTS14424 study, from (on/after) the first administration of IMP to the end of post-treatment follow-up period. A given medication can be classified both as a prior medication and as a concomitant medication.

#### *2.1.2.1 Salbutamol/albuterol or levosalbutamol/levalbuterol reliever medication*

Patients may use 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.

The reliever medication will be recorded as number of puffs in eCRF. The conversion factor is shown as below.

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

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

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

| Levosalbutamol/Levalbuterol nebulizer solution-total daily dose (mg) | Number of Puffs* |
|---|---|
| 0.63 | 2 |
| 1.25 | 4 |
| 2.5 | 8 |
| 3.75 | 12 |
| 5 | 16 |

* 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 = 3.75 mg → 12 puffs.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

### 2.1.3 Efficacy endpoints

Efficacy endpoints are secondary endpoints of this study. The following efficacy endpoints will be analyzed:

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

For spirometry parameters, the baseline values are the original baseline from the parent study.

#### *2.1.3.1 Severe Exacerbation Events*

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.

The severe exacerbation events are collected on eCRF page “Severe Asthma Exacerbation”.

Both number and annualized rate of severe exacerbation events will be analyzed. For each analysis set, the total number of events is defined as the number of events that have onset between the start date and the end date of the Treatment Epoch (Table 3).The standardized on-treatment duration (in years) will be calculated by (End date of the Treatment Epoch - Start date of the Treatment Epoch +1)/365.25.

#### *2.1.3.2 Percentage (%) predicted FEV1 and other spirometry assessments*

The percentage (%) predicted FEV1 is part of the spirometry assessment that will be performed at Visit 1 (Week 0), Visit 2 (Week 2), Visit 4 (Week 8), Visit 5 (Week 12), Visit 8 (Week 24), Visit 10 (Week 52/ EOT), and Visit 11 (Week 64/ EOS). The other parts of the spirometry assessment, including the absolute FEV1, Forced Vital Capacity (FVC, absolute and % predicted) and Forced Expiratory Flow (FEF) 25-75% (absolute and % predicted), will be performed at the same visits as above. For Visit 1, spirometry pre-bronchodilator parameters 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 EFC14153 EOS visit or at LTS14424 Visit 1.

For the analysis based on the full analysis set, all spirometry data collected in the study regardless of the dose regimen will be included. For the modified analysis set, the spirometry data collected on or after the day of the first IMP of 300 mg q4w will be censored for patients who will be exposed to 300 mg q4w regimen in LTS14424 study. Particularly, all spirometry data from patients with initial dosage as 300 mg q4w will be excluded from the modified analysis set.

### 2.1.4 Safety endpoints

The primary endpoint of this study is the number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAE). Adverse events (AEs), serious adverse events (SAE), adverse events of special interest (AESI), adverse events leading to treatment discontinuation are collected at each visit from the time of informed consent signature to the end of study. The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG and physical examination.

Generally, for scheduled on-site safety assessments, including laboratory, vital sign, ECG, physical examination, all data collected in the study regardless of the dose regimen will be included for the full analysis set. For the modified analysis set, data collected on or after the day of the first IMP of 300 mg q4w will be censored for patients who will be exposed to 300 mg q4w regimen in LTS14424 study. Particularly, all data from patients with initial dosage as 300 mg q4w will be excluded from the modified analysis set.

#### *2.1.4.1 Adverse events variables*

***Adverse event observation period***

- Pre-treatment adverse events are adverse events that developed or worsened or became serious during the pre-treatment adverse event period.
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period.
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment adverse event period.

Pre-treatment, treatment-emergent, and post-treatment emergent adverse event periods are defined in Section 2.

All adverse events (including serious adverse events and adverse events of special interest) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Adverse events of special interest (AESI) and other selected AE groupings will be searched based on the same criteria used in the parent study (Table 4).

**Table 4 - Criteria for adverse events of special interest and other selected AE groupings**

| AE Grouping | Criteria |
|---|---|
| **AESI** | |
| Anaphylactic reaction | Anaphylactic reaction algorithmic approach (*Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1*): includes anaphylactic reaction narrow SMQ (20000021) terms; for selection based on occurrence of multiple symptoms, the symptoms must have occurred within 24 hours of each other, which are related to IMP and requires treatments |
| Hypersensitivity (medically reviewed) | Hypersensitivity narrow SMQ (20000214) and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by medical review (documented process) for selection of relevant systemic hypersensitivity events |
| Severe injection site reactions that last longer than 24 hours or serious injection site reaction | HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time -AE start date/time) ≥24 hours or ongoing |
| Severe or serious infection | Primary SOC = 'infections and infestations' and with severe or serious status |
| Parasitic infection | The Infection Type 'Parasitic' was checked on the eCRF page "Infection Event Form" |
| Opportunistic infection | The question "Has the AE been assessed as opportunistic infection?" is answered "Yes" on the eCRF page "Infection Event Form" |
| Drug-related hepatic disorder | Drug-related hepatic disorders - Comprehensive search narrow SMQ (20000006) |
| Pregnancy | Primary SOC = 'Pregnancy, puerperium and perinatal conditions', or PT in (Aborted pregnancy, False negative pregnancy test, Pregnancy test positive, Pregnancy test urine positive, Ectopic pregnancy termination) |
| Symptomatic overdose with IMP | The question "Is the event a Symptomatic Overdose with IMP?" is answered "Yes" on the eCRF page "Adverse Event" |
| Symptomatic overdose with noninvestigational medicinal product (NIMP) | The question "Is the event a Symptomatic Overdose with non-IMP?" is answered "Yes" on the eCRF page "Adverse Event" |
| **Other selected AE grouping** | |
| Injection site reaction | HLT = 'Injection site reaction' |
| Malignancy | Sub-SMQ (20000091) - Malignant or unspecified tumors |
| Partner pregnancy | PT in (Pregnancy of partner, Miscarriage of partner) |

| AE Grouping | Criteria |
|---|---|
| Conjunctivitis (narrow) | PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis) |
| Conjunctivitis (broad) | PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia) |
| Eosinophilia | HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased' |

#### *2.1.4.2 Deaths*

The death observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the time from start of treatment in LTS14424 study to the end of the study.
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period.
- Death poststudy: deaths occurring after the end of the study.

#### *2.1.4.3 Laboratory safety variables*

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and standard international units will be used in all listings and tables. Baseline values for clinical laboratory variables will be the original baseline from the parent study.

Blood samples for clinical laboratories will be taken at Visit 1 (Week 0), Visit 3 (Week 4), Visit 5 (Week 12), Visit 8 (Week 24), Visit 9 (Week 36), Visit 10 (Week 52/EOT), Visit 11 (Week 64/EOS) and/or early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology:
  - **Red blood cells and platelets and coagulation:** erythrocytes, hemoglobin, hematocrit, platelet count,
  - **White blood cells:** leukocytes, with five-part differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils).
- Clinical chemistry
  - **Metabolism**: glucose, total cholesterol, total protein, creatine phosphokinase (CPK), albumin,
  - **Electrolytes**: sodium, potassium, chloride, bicarbonate,
  - **Renal function**: creatinine, blood urea nitrogen,
  - **Liver function**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin.
- Serum Immunoglobulins: Total IgE and antigen-specific IgE.

Urine samples will be collected as follows:

- **Urinalysis** - include pH, glucose, ketones, leukocyte esterase, blood, protein, nitrate, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, further urine test is under Investigator's judgement. Testing is performed at Visit 1 (Week 0), Visit 5 (Week 12), Visit 8 (Week 24), Visit 10 (Week 52/EOT), Visit 11 (Week 64/EOS) and/or early termination.
- **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.

Technical formulas are described in Section 2.5.1.

#### *2.1.4.4 Vital signs variables*

Vital signs include 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 every scheduled visit. Height (cm) will be measured at Visit 1 (Week 0) and Visit 10 (Week 52/EOT). Baseline values for vital signs will be the original baseline from the parent study.

#### *2.1.4.5 Electrocardiogram variables*

A standard 12-lead ECG will be performed at Visit 1 (Week 0), Visit 10 (Week 52/EOT), Visit 11 (Week 64/EOS) and/or early termination. ECGs were recorded automatically by the device at the Investigator site. Baseline values for ECG will be the original baseline from the parent study.

#### *2.1.4.6 Physical examination*

Physical examinations 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, will be measured at Visit 1 (Week 0), Visit 5 (Week 12), Visit 8 (Week 24), Visit 10 (Week 52/EOT), Visit 11 (Week 64/EOS) and/or early termination. The overall assessment, 'Normal' or 'Abnormal', will be provided by investigator. In case of clinically significant findings, corresponding AE should be reported in adverse event eCRF form.

### 2.1.5 Pharmacokinetic variables

The pre-dose serum PK sampling will be collected at Visit 1 (Week 0), Visit 5 (Week 12), Visit 8 (Week 24), Visit 10 (Week 52/EOT), Visit 11 (Week 64/EOS) and/or early termination. The baseline values for PK variables are the original baseline from the parent study.

### 2.1.6 Immunogenicity variables

Samples for anti-drug antibodies (ADAs) are collected at Visit 1 (Week 0), Visit 5 (Week 12), Visit 8 (Week 24), Visit 10 (Week 52/EOT), Visit 11 (Week 64/EOS) and/or early termination. 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. The baseline used to define ADA variables refers to the baseline value in the parent study.

The immunogenicity variables include ADA status (positive or negative) and titer as follows:

- Number of patients with ADA negative

  ADA negative is defined as ADA assay is negative at all times or exhibit a pre-existing immunoreactivity.

- Number of patients with ADA positive

  ADA positive is defined as either treatment-boosted or treatment-emergent response in the ADA assay.

- Number of patients with pre-existing immunoreactivity.

  Pre-existing immunoreactivity is defined as either an ADA positive response in the assay at baseline of the parent study with all post first dose ADA results negative in the current study, or an ADA positive response at baseline of the parent study with all post first dose ADA results in the current study less than 4-fold of the baseline titer levels of the parent study.

- Number of patients with treatment-emergent response in the ADA assay.

  Treatment-emergent response is defined as a positive response in the ADA assay post first dose in the current study, when baseline status in the parent study is negative or missing. The treatment-emergent response is further characterized as:

  - Persistent response - defined as a treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative sample in between,
  - Indeterminate response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay,
  - Transient response - defined as a treatment-emergent ADA positive response that is not considered persistent or indeterminate.

- Number of patients with treatment-boosted response in the ADA assay.

  Treatment-boosted response is defined as a positive response in the ADA assay post first dose in the current study that is greater than or equal to 4-fold of the baseline titer levels of the parent study, when baseline status of the parent study is positive.

- Titer values (titer value category):
  - Low (titer <1,000),
  - Moderate (1,000 ≤ titer ≤10,000),
  - High (titer >10,000).
- ADA positive samples will be further characterized for the presence of neutralizing antibody (NAb) response.

### 2.1.7 Pharmacodynamic endpoints

#### *2.1.7.1 Whole blood biomarkers*

Blood eosinophil counts will be measured as part of laboratory hematology at Visit 1 (Week 0), Visit 3 (Week 4), Visit 5 (Week 12), Visit 8 (Week 24), Visit 9 (Week 36), Visit 10 (Week 52/EOT), Visit 11 (Week 64/EOS) and/or early termination.

#### *2.1.7.2 Serum biomarkers*

Serum total IgE and antigen-specific IgE will be measured at Visit 1 (Week 0), Visit 8 (Week 24), Visit 10 (Week 52/EOT), Visit 11 (Week 64/EOS) and/or early termination.

## 2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations for LTS14424 only, unless otherwise specified.

- Screened patients are defined as the patients who signed the informed consent/assent.
- Enrolled patients consist of all the patients who signed the informed consent/assent and had a treatment kit number allocated and recorded in the 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 1 dose or part of a dose of the IMP in the LTS14424 study.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or a summary table:

- Screened patients.
- Screen failure patients and reasons for screen failure.
- Non-enrolled but treated patients.
- Enrolled patients.
- Enrolled but not treated patients.
- Enrolled and treated.
- Patients who did not complete the study treatment period as per protocol.
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation.
- Patients who discontinued from the study.
- Patients who discontinued from the study by main reason for permanent study discontinuation.

Reasons for treatment discontinuation and study discontinuation will be supplied in tables giving numbers and percentages by treatment category as defined in Section 2.4. This summary will be provided by treatment category of each analysis set as defined in Section 2 and may also be further subgrouped by region/pooled countries.

A patient will be considered as lost to follow-up at the end of study if he/she is not assessed at the last protocol planned visit.

All critical or major deviations potentially impacting safety evaluation, drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment category of each analysis set.

Additionally, the analysis populations for safety, PK and Anti-drug antibody will be summarized in a table by number of patients on the enrolled population.

- Safety population (for both safety and efficacy analyses).
- Pharmacokinetics population.
- Anti-drug antibody population.

### 2.2.1 Randomization and drug dispensing irregularities

There is no randomization procedure in LTS14424. Drug-dispensing irregularities occur whenever:

- A patient is dispensed an IMP not corresponding to the patient's actual weight, such as
    a) A patient is dispensed an IMP of 200 mg while patient's actual weight is ≤30 kg,
    b) A patient is dispensed an IMP of 100 mg or 300 mg while patent's actual weight is >30 kg.
- A patient is dispensed an IMP kit not allocated by the IVRS, such as,
    a) A patient at any time in the study is dispensed a different treatment kit than as assigned,
    b) A non-enrolled patient is treated with IMP reserved for enrolled patients.

Drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among enrolled patients (number and percentages). Non-enrolled and treated patients will be described separately.

Drug-dispensing irregularities to be prospectively identified include but are not limited to:

| Drug allocation irregularities |
|---|
| Kit dispensation without IVRS transaction |
| Erroneous kit dispensation |
| Kit not available |
| Patient enrolled twice |
| Patient switched to another site |

## 2.3 ANALYSIS POPULATIONS

The primary analysis population is the safety population. All safety and efficacy analyses will be performed based on the safety population. For each analysis population defined in this section below, the planned analyses will be conducted in two analysis sets: 1) the full analysis set, which will include all data observed in the study 2) the modified analysis set, which will censor the data observed on or after the date of first dose of 300 mg q4w (if applicable) from the full analysis set. Details about the two analysis sets and their corresponding observation periods can be found at the beginning of Section 2.

### 2.3.1 Safety population

The safety population is defined as all patients exposed to at least 1 dose or part of a dose of the IMP during LTS14424 study regardless of the amount of treatment administered, ie, the exposed population.

Enrolled patients for whom it is unclear whether they took the IMP or not will be included in the safety population as enrolled.

### 2.3.2 Efficacy population

The efficacy population is the same as the safety population.

### 2.3.3 Pharmacokinetics (PK) population

The PK population will consist of all the patients in the safety population who had at least 1 non-missing and evaluable predose serum concentration value after the first dose of dupilumab in the LTS14424 study.

### 2.3.4 Anti-drug antibody (ADA) population

The ADA Population will consist of all the patients in the safety population with at least 1 non-missing ADA result following the first dose of dupilumab in the LTS14424 study.

## 2.4 STATISTICAL METHODS

***Generalities***

For each analysis set defined in Section 2, the planned analyses will be presented by below treatment categories according to the actual treatment groups in the parent study EFC14153:

- Placebo-Dupilumab, defined as the patients who have been in the actual placebo arm of the parent study and exposed to dupilumab in LTS14424.
- Dupilumab-Dupilumab, defined as the patients who have been in the actual dupilumab arm of the parent study and exposed to dupilumab in LTS14424.
- All, defined as all patients from Placebo-Dupilumab and Dupilumab-Dupilumab categories.

### 2.4.1 Demographics and baseline characteristics

The demographics and baseline characteristics will be summarized for each analysis set (Section 2) of safety population according to the treatment category. The data for demographics and baseline characteristics will be obtained from the original baseline of the parent study. Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients.

Parameters described in Section 2.1.1 will be summarized for each analysis set of safety population by the treatment category using descriptive statistics.

Medical and surgical history will be summarized for each analysis set of safety population by the treatment category, by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC based on the overall group. Comorbidity history and atopic medical history will be summarized separately.

### 2.4.2 Prior or concomitant medications

The prior medications, concomitant medications in parent study, and concomitant medications described in Section 2.1.2 will be presented for each analysis set (Section 2) of safety population by the treatment category.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications, concomitant medications in parent study, and concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment categories. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, the ICS in combination with controller medication(s) and reliever medications will be summarized separately.

#### *2.4.2.1 ICS in combination with controller medication(s)*

ICS in combination with controller medications within 30 days prior to screening of parent study will be summarized for each analysis set (Section 2) of safety population by the treatment category, and will be sorted by decreasing frequency of standard medication name in the overall category.

The prescription of ICS in combination with controller medication(s) at enrollment of LTS14424 will be summarized by treatment category and overall. Number (%) of patients will be presented by medication names and ICS dose level (medium/high as defined in Appendix C) according to the classification specified in (1).

### 2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized for each analysis set (Section 2) of safety population by the treatment category.

#### *2.4.3.1 Extent of investigational medicinal product exposure*

The extent of IMP exposure will be assessed by the duration of IMP exposure in LTS14424 study.

For each analysis set, duration of IMP exposure is defined as End date of the Treatment Epoch – Start date of the Treatment Epoch +1 as defined in Table 3, regardless of unplanned intermittent discontinuations (see Section 2.5.2 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

>0 and ≤2 weeks

> 2 and ≤4 weeks

> 4 and ≤8 weeks

> 8 and ≤12 weeks

> 12 and ≤16 weeks

…

…

> 48 and ≤52 weeks

> 52 weeks

Additionally, the cumulative duration of treatment exposure, will be provided in patient years by treatment category and overall.

Number and percentage of patients will be summarized by total number of injections they received during the LTS14424 study.

#### *2.4.3.2 Compliance*

A given administration 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. An administration is considered compliant if an injection is performed, regardless the actual amount of solution injected.

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations that the patient was planned to take during the treatment epoch as defined in Table 3.

Treatment compliance percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized.

Cases of overdose of IMP (defined as at least twice the intended dose during an interval of less than 11 days for 100/200 mg q2w regimen or less than 25 days for 300 mg q4w regimen) will be summarized by numbers and percentages of patients with at least 1 overdose by treatment category. Different overdose intense by dose interval, ie, 1 day, 2 days, etc., will also be summarized. More generally, dosing irregularities will be listed in Section 2.2.1.

### 2.4.4 Analyses of efficacy endpoints

All analyses will be done descriptively for each analysis set (Section 2) of safety population by the treatment category. The baseline value for efficacy parameters will be the original baseline from the parent study.

The efficacy analyses will be performed for each analysis set of safety population, and the following populations:

- Exposed patients with type 2 inflammation phenotype at baseline of parent study: either blood eosinophil ≥0.15 Giga/L or FeNO ≥20 ppb.
- Exposed patients with blood eosinophil ≥0.3 Giga/L at baseline of parent study.
- Exposed patients with blood eosinophil ≥0.15 Giga/L at baseline of parent study.
- Exposed patients with blood FeNO ≥20 ppb at baseline of parent study.

The number of patients with one or more severe exacerbation events (number and qualitative variable: Yes/No), number of severe exacerbation events (qualitative variable: 0, 1, 2, 3, ≥4), total number of severe exacerbation events, total patient-years, unadjusted annualized severe exacerbation event rate, and duration (days) of a single severe exacerbation (number, mean, SD,

median, minimum, maximum) during the treatment period will be presented by treatment categories for each analysis set of safety population. Annualized rate will also be analyzed for severe exacerbation with use of SCS for ≥3 days only, and those with hospitalization or with emergency room visit only.

For the spirometry efficacy variables listed in Section 2.1.3, descriptive statistics (mean, SD, median, minimum and maximum) will be presented for the parameter and its change from baseline over visits for each analysis set of safety population by the treatment category. In addition, figure of mean change from baseline (with corresponding standard error) will be presented for the continuous efficacy parameter over visits for each analysis set of safety population by the treatment category.

If there were patients who had a long gap between the parent EOT visit and the first dose in LTS14424 study, additional analyses excluding such patients may be conducted for the annualized rate of severe asthma exacerbation and change in % predicted FEV1 on the full analysis set of safety population by the treatment category.

#### *2.4.4.1 Subgroup analyses*

Subgroup analyses will be performed for key efficacy variables (severe exacerbation and Percentage (%) predicted FEV1) for each analysis set of safety population:

- ICS dose group: patients on the medium or high ICS dose at the original baseline in the parent study.
- Blood eosinophil (Giga/L) groups at baseline of parent study: ≥0.3, <0.3 Giga/L; ≥0.15, <0.15 Giga/L; <0.15, ≥0.15 - <0.3, ≥0.3 - <0.5, and ≥0.5 Giga/L.
- Blood FeNO (ppb) groups at baseline of parent study: <20, ≥20 - <35, and ≥35 ppb.
- Baseline age group (6-8, 9-11 years).

#### *2.4.4.2 Multiplicity issues*

Not applicable.

### 2.4.5 Analyses of safety data

The summary of safety results will be presented for each analysis set (Section 2) of safety population by the treatment category, unless otherwise specified.

***General common rules***

All safety analyses will be performed on the safety population as defined in Section 2.3.1, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not enrolled) will be listed separately (if applicable).
- The baseline value for safety parameters is defined as the original baseline from the parent study.

- In addition to the baseline values, the pre-dose measurements at Week 0 in LTS14424 will be presented in the by-visit summary/figure for laboratory, vital signs or ECG parameters. The pre-dose measurements at Week 0 are the last available measurements prior to the first IMP dose in LTS14424 study.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests, vital signs, and ECG (Appendix A).
- PCSA criteria will determine which patients had at least 1 PCSA during the analysis set specific treatment-emergent adverse event period as defined in Section 2, taking into account all evaluations performed during the treatment-emergent adverse event period, including non-scheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period for each analysis set of safety population by the treatment category.
- For quantitative safety parameters, descriptive statistics will be used to summarize results and change from baseline values for each analysis set of safety population by the treatment category. Summaries will include the endpoint value and/or the worst on-treatment value. The endpoint value is commonly defined as the value collected at the date of last IMP dose +1 dose interval (14 days for last IMP as 100/200 mg q2w and 28 days for last IMP as 300 mg q4w) or the end of treatment visit. If this value is missing, this endpoint value will be the closest value prior to the last administration of IMP + 1 dose interval. The worst value is defined as the nadir and/or the peak post-baseline (up to last administration of IMP + 1 dose interval) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.
- All of the values including unscheduled measurements will be assigned to the appropriate safety analysis visit window. The safety analysis visit window is defined in Section 2.5.3.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

#### *2.4.5.1 Analyses of adverse events*

***Generalities***

The primary endpoint of this study is the number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAE). Pre-treatment and post-treatment adverse events will be described separately if applicable.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment-emergent, unless there is definitive information to

determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.2.

Adverse event incidence tables will be presented by system organ class (SOC), high level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order, to summarize the number (n) and percentage (%) of patients experiencing at least one AE in each analysis set of safety population by the treatment category. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment category. The denominator for computation of percentages is number of patients in each analysis set of safety population by the treatment category. In all AE incidence tables, the total patient years (in the unit of 100 patient-years) of each analysis set of safety population by the treatment category will be presented in the corresponding column headers.

The number of events per 100 patient-years (adjusted for the total duration of exposure) of each analysis set of safety population by the treatment category will be presented for each AESI during the corresponding treatment-emergent period.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on the results for the overall patients across treatment categories, unless otherwise specified.

The following treatment-emergent adverse event summaries for each analysis set of safety population by the treatment category will be generated.

***Analysis of all treatment-emergent adverse events***

- Overview of treatment-emergent adverse events, summarizing number (%) of patients (including total patient years in column headers) with any:
  - Treatment-emergent adverse event,
  - Treatment-emergent serious adverse event,
  - Treatment-emergent adverse event leading to death,
  - Treatment-emergent adverse event leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients (including total patient years in column headers) with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be sorted in alphabetical order.
- All TEAEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least 1 treatment-emergent adverse event, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

- All TEAEs by primary SOC, showing the number (%) of patients (including total patient years in column headers) with at least 1 treatment-emergent adverse event, will be presented by the internationally agreed SOC order.
- All possibly drug-related TEAEs by primary SOC and PT, showing number (%) of patients (including total patient years in column headers) with at least 1 TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least 1 TEAE by severity (ie, mild, moderate, or severe), sorted by the order defined above.
- Number (%) of patients (including total patient years in column headers) experiencing TEAE(s) presented by primary and secondary SOC, HLGT, HLT, and PT sorted by SOC internationally agreed order. The other level (HLGT, HLT, PT) will be presented in an alphabetic order.
- A listing will be provided for all TEAEs.

***Analysis of all treatment-emergent serious adverse event(s)***

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients (including total patient years in column headers) with at least 1 treatment-emergent serious adverse event, will be presented by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent serious adverse events by primary SOC and PT, showing number (%) of patients (including total patient years in column headers) with at least 1 TEAE, will be presented by SOC internationally agreed order and decreasing incidence of PTs within SOC.
- A listing of all serious adverse events will be presented.

***Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation***

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients (including total patient years in column headers) will be presented by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs leading to treatment discontinuation, by primary SOC and PT, showing number (%) of patients (including total patient years in column headers) with at least 1 TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC.
- A listing will be provided for all treatment-emergent adverse events leading to treatment discontinuation.

***Analysis of adverse events of special interest (AESI) and other selected AE groupings***

Summaries of AESI defined by the search criteria:

- All treatment-emergent AESIs and other selected AE groupings identifiable by MedDRA terms, by AESI category and PT, showing the number (%) of patients (including total patient years in column headers), will be presented by decreasing incidence of PT within each AESI category.
- An overview summary within each treatment-emergent AESI and other selected AE groupings will include:
  - Number (%) of patients with any TEAE,
  - Number (%) of patients with any SAE (regardless of treatment-emergent status),
  - Number (%) of patients with any treatment-emergent SAE,
  - Number (%) of patients with any AE leading to death,
  - Number (%) of patients with any TEAE leading to permanent treatment discontinuation,
  - Number (%) of patients with any TEAE by maximum intensity, corrective treatment, and final outcome,
  - Cumulative incidence (K-M estimates) up to specified time points (Week 4, Week 12, Week 24, Week 36, Week 52, Week 64).

  Notes for the last bullet: when TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.
- Number of treatment-emergent AESIs and other selected AE groupings per 100 patient-years (total number of events adjusted for the total duration of exposure) will be presented by decreasing incidence of PT within each AESI and other selected AE groupings category.
- The time-to-first AESI 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.
- A listing will be provided for AESIs.

***Analysis of pre-treatment and post-treatment adverse events***

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least 1 pre-treatment AE, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All pre-treatment SAEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least 1 pre-treatment SAE, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

- All post-treatment AEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least 1 post-treatment AE, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All post-treatment SAEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least 1 post-treatment SAE, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

***Analysis of adverse events***

- All pre-treatment, treatment-emergent, or post-treatment AEs by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers) with at least 1 AE, will be presented by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

If there were patients who had a long gap between the parent EOT visit and the first dose in LTS14424 study, additional analyses excluding such patients may be conducted for the key safety variables listed below on the full analysis set of safety population by the treatment category.

- Overview of TEAEs.
- All TEAEs by primary SOC and PT.
- All treatment-emergent serious adverse events by primary SOC and PT.
- All TEAEs leading to treatment discontinuation by primary SOC and PT.
- All treatment-emergent AESIs and other selected AE groupings identifiable by MedDRA terms by AESI category.

#### *2.4.5.2 Deaths*

The following summaries of deaths will be generated for the safety population, unless otherwise specified.

- Number (%) of patients who died by study period (on-study, on-treatment, poststudy)
- Deaths in non-enrolled patients or enrolled but not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients (including total patient years in column headers) sorted by internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC and PT showing number (%) of patients (including total patient years in column headers) sorted by internationally agreed SOC order, and by alphabetical order of PT within each SOC.
- All pre-treatment and post-treatment AE leading to death by primary SOC and PT, showing the number (%) of patients (including total patient years in column headers), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

- A listing of deaths will be provided.

#### *2.4.5.3 Analyses of laboratory variables*

The baseline value of all laboratory variables is the original baseline from the parent study. The pre-dose measurement at Week 0 of LTS14424 will be separately presented in the summaries or plots over time.

The summary statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, and endpoint) for each analysis set (Section 2) of safety population by the treatment category. For each continuous parameters listed in Section 2.1.4.3, mean change from baseline with corresponding standard error at each visit will be plotted for each analysis set of safety population by the treatment category . This section will be organized by biological function as in Section 2.1.4.3.

For all laboratory variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should use the centralized data only, and should include the measurements obtained at either scheduled or unscheduled visits.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period as defined in Section 2 will be summarized by biological function, and by the treatment category for each analysis set of safety population, regardless of the baseline level and/or according to the following status at baseline of parent study and at Week 0 of LTS14424 study, respectively:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For parameters for which no PCSA criterion is defined, similar table(s) using the normal range will be provided.

For PCSA analyses, the laboratory measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local test results should be used, as long as their available dates/time is different from each other's. Centralized data will be used preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time for a given laboratory test.

A listing of patients with at least 1 PCSA during the treatment-emergent adverse event period will be provided and will display the whole profile over time of all parameters of the corresponding biological function. In this listing, baseline, endpoint value and individual values will be flagged when lower or higher than the lower or upper laboratory limits and/or when reaching the absolute limit of abnormality criteria.

***Drug-induced liver injury***

Additional analysis of liver-related adverse events will be performed if necessary.

#### *2.4.5.4 Analyses of vital sign variables*

The baseline value of all vital sign variables is the original baseline from the parent study. The pre-dose measurement at Week 0 of LTS14424 will be separately presented in the summaries or plots over time.

The summary statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum) of all vital signs variables (measurements and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, and endpoint) for each analysis set (Section 2) of safety population by the treatment category. For all vital sign variables, the mean change from baseline with corresponding standard error at each visit will be plotted for each analysis set of safety population by the treatment category.

For all vital sign variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should include the measurements obtained at either scheduled or unscheduled visits.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period as defined in Section 2 will be summarized for each analysis set of safety population by the treatment category irrespective of the baseline level and/or according to the following status at baseline of parent study and at Week 0 of LTS14424 study, respectively:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For PCSA analyses, the vital sign measurements obtained at either scheduled or unscheduled visits should be used.

#### *2.4.5.5 Analyses of electrocardiogram variables*

The baseline value of all ECG variables is the original baseline from the parent study. The pre-dose measurement at Week 0 of LTS14424 will be separately presented in the summaries or plots over time.

The summary statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum) of all ECG variables (measurements and changes from baseline) will be calculated for each visit or study assessment (baseline and each post-baseline time point, and endpoint) for each analysis set (Section 2) of safety population by the treatment category. For all ECG parameters, the mean change from baseline with corresponding standard error at each visit will be plotted by the treatment category for each analysis set of safety population.

For all ECG variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should include the measurements obtained at either scheduled or unscheduled visits.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period as defined in Section 2 will be summarized by treatment category for each analysis set of safety population irrespective of the baseline level and/or according to the following status at baseline of parent study and at Week 0 of LTS14424 study, respectively:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For PCSA analyses, the ECG measurements obtained at either scheduled or unscheduled visits should be used.

#### *2.4.5.6 Subgroup analyses*

Subgroup analyses will be performed for several key safety variables (treatment-emergent AE/SAE/AESI/AE leading to permanent treatment discontinuation) for full analysis set of safety population by:

- Race (Caucasian/White, Black/of African descent, Asian/Oriental, all the other).
- Sex (Female, Male).
- Ethnicity (Hispanic, Not Hispanic).
- Baseline weight group (≤30, >30 kg).

### 2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

The baseline value of PK and PD variables is the original baseline from the parent study.

#### *2.4.6.1 Pharmacokinetic analysis*

The PK analyses will be performed for each analysis set (Section 2) of PK population (Section 2.3.3).

For the full analysis set, PK analysis will be presented in the PK population by visit according to the dose regimen (100 mg q2w or 200 mg q2w or 300 mg q4w) to which the PK sampling is exposed. That is if a patient is switched from 100 mg q2w to 200 mg q2w, the results from PK sampling before or on date of the switch will summarized in 100 mg q2w group and results from PK sampling after the switch will be summarized in 200 mg q2w group. Similarly, if a patient is switched from 100 mg q2w to 300 mg q4w, the results from PK sampling before or on date of the switch will be summarized in 100 mg q2w group and results from PK sampling after the switch will be summarized in 300 mg q4w group.

Similarly for modified analysis set, PK analysis will be presented in PK population by visit according to the dose regimen (100 mg q2w, 200 mg q2w) to which the PK sampling is exposed at each visit.

Serum concentrations of dupilumab will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and

maximum by visit. If date and/or time of the drug intake and/or sampling are missing, then the concentration will not be taken into account. For the patients from the Dupilumab arm of parent study, one-half of LLOQ will be used if the pre-dose concentration values at Week 0 of LTS14424 are below the lower limit of quantitation (LLOQ = 78 ng/ml); For the patients from the Placebo arms of parent study, the pre-dose concentration value at Week 0 of LTS14424 should use 0 if the pre-dose concentration values at Week 0 of LTS14424 are below the lower limit of quantitation. Values will be expressed in the tables with no more than three significant figures.

#### *2.4.6.2 Pharmacodynamics*

For all biomarkers noted in the Section 2.1.7, the biomarker will be analyzed for each analysis set (Section 22) of the safety population by the treatment category.

For eosinophil count and serum total IgE, descriptive statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum), change from baseline and percentage change from baseline over visits will be presented. In addition, the mean, mean change from baseline, mean percentage change from baseline with corresponding standard error will be plotted across visits. For biomarkers showing substantial skewness, the geometric means will also be presented.

For antigen-specific IgEs with a positive (≥0.35 IU/mL) incidence of greater than 25% at baseline, values at each visit, absolute change from baseline and percent changes from baseline will be summarized in descriptive statistics. Values reported as below the LLOQ will be imputed as a value one half of the LLOQ.

Number and percentage of patients with no positive (≥0.35 IU/mL) antigen-specific IgE result, with positive (≥0.35 IU/mL) result for only one antigen, and with positive (≥0.35 IU/mL) results for at least two antigens will be summarized by treatment group and time point. Same analysis will also be performed using LLOQ as the threshold.

For eosinophil count, with subgrouping the patients into original baseline EOS ≤0.5 Giga/L and >0.5 Giga/L, the mean change from baseline will be plotted over visits for each of the two subgroups and overall. And table showing number (%) of patients who have peak post-baseline EOS count ≥1 Giga/L, ≥3 Giga/L and ≥5 Giga/L will be presented for each of the two subgroups and overall.

### 2.4.7 Analyses of Immunogenicity

The baseline value used to define ADA variables is the original baseline from the parent study. The ADA analyses will be performed for each analysis set (Section 2) of ADA population (Section 2.3.4) by treatment category.

The ADA variables described in Section 2.1.6 will be summarized using descriptive statistics. Frequency tables of the proportion of patients developing ADA positivity in the ADA assay, neutralizing antibody status in the NAb assay, pre-existing immunoreactivity, treatment-emergent, treatment-boosted, persistent, indeterminate, transient ADA responses and titers will be presented.

Listing of all ADA maximum titer levels and neutralizing antibody status will be provided for ADA positive patients.

ADA variable will be summarized by baseline weight group (≤30, >30 kg).

If there were patients who had a long gap between the parent EOT visit and the first dose in LTS14424 study, additional analyses excluding such patients may be conducted for the status in the ADA assay in the current study on the full analysis set of ADA population.

#### 2.4.7.1 Status in the ADA assay at baseline of the parent study

The following summary will be provided for each analysis set of ADA population by the treatment category:

- Number (%) of patients negative in the ADA assay at baseline of parent study.
- Number (%) of patients positive in the ADA assay at baseline of parent study:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the titer for the patients positive in the ADA assay at baseline of the parent study,
  - Number (%) of patients with neutralizing antibody status (negative or positive in the NAb assay).

#### 2.4.7.2 Status in the ADA assay in the current study

The following summary will be provided based on each analysis set of ADA population by the treatment category:

- Number (%) of patients with ADA status (negative or positive in the ADA assay) at time points analyzed:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the maximum post-baseline titer for ADA positive patients,
  - ADA titers using descriptive statistics (median, Q1, Q3, minimum and maximum) at ADA time points analyzed,
  - Number (%) of patients with neutralizing antibody status (negative or positive in the NAb assay) for the ADA positive patients.
- Number (%) of patients with pre-existing immunoreactivity.
- Number (%) of patients with treatment-boosted anti-drug antibodies:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the maximum post-baseline titer for treatment-boosted ADA patients.
- Number (%) of patients with treatment-emergent ADA:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the maximum post-baseline titer for treatment-emergent positive patients,
  - Number (%) of patients in the low, moderate or high titer category with treatment-emergent positive response,

- Number (%) of patients with transient, indeterminate, or persistent treatment-emergent ADA response.

- Number (%) of patients with neutralizing antibody results (negative or positive in the NAb assay).

#### 2.4.7.3 Impact of ADA on clinical safety

The safety assessment will focus on the following events:

- Serious or severe injection site reactions (ISRs) that last longer than 24 hours.
- Hypersensitivity reactions (SMQ hypersensitivity narrow search and confirmed by medical review).
- Anaphylactic reactions (SMQ anaphylactic reaction narrow search).

Correlations between ADA variables (eg, ADA maximum titers, neutralizing antibody status, treatment-emergent, treatment-boosted, transient, indeterminate and persistent ADA responses) and safety may be explored.

#### 2.4.7.4 Impact of ADA on clinical efficacy

Correlations between ADA variables (eg, ADA maximum titers, neutralizing antibody status, treatment-emergent, treatment-boosted, transient, indeterminate and persistent ADA responses) and efficacy endpoints may be explored for each analysis set of ADA population by the treatment category:

- Annualized rate of severe exacerbation events.
- Change from baseline in % predicted FEV1.

#### 2.4.7.5 Impact of ADA on PK

Associations between ADA variables (eg, ADA maximum titers, neutralizing antibody status) and descriptive summaries of concentration of dupilumab in serum may be explored for each analysis set of safety population by the treatment category. Plot of individual concentration-time profiles of functional dupilumab in serum over visits may also be provided by ADA classifications (negative at all time, pre-existing immunoreactivity, treatment-boosted anti-drug antibodies, and treatment-emergent anti-drug antibodies [further separated by NAb status and maximum titer category]) for each analysis set of safety population by the treatment category.

## 2.5 DATA HANDLING CONVENTIONS

### 2.5.1 General conventions

The following formulas will be used for computation of parameters.

***Demographic formulas***

Baseline age is calculated as following:

Baseline age = integer part of (informed consent date of parent study–birth date)/365.25

Age of onset of asthma is calculated as following:

Age of onset of asthma = integer part of (asthma onset date prior to parent study – birth date)/365.25

BMI is calculated as following:

BMI = Weight in kg / (height$^2$ in meters)

***Renal function formulas***

Creatinine clearance (CLcr) value will be derived using the equation of glomerular filtration rate (GFR) Bedside Schwartz

GFR (mL/min/1.73 m2) = k $\times$ height (cm) / sCr (standardized serum creatinine, mg/dL),

where the coefficient k=0.55 for patients ≥6 and <12 years old, 0.65 for adolescent (≥12 years old) male patients, or k=0.55 for adolescent (≥12 years old) female patients.

### 2.5.2 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

As per the study design, the statistical method of the data analyses for LTS14424 study is based on the descriptive summary statistics using observed data only; and, no model-based imputation for missing data will be performed. The missing scheduled assessment(s) or visit(s) due to the COVID-19 pandemic will be documented in the protocol deviations.

***Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing***

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on eCRF page “Treatment Status”. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the eCRF and should not be approximated by the last returned package date.

***Handling of medication missing/partial dates***

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior and concomitant medication.

***Handling of adverse events with missing or partial date/time of onset***

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

***Handling of adverse events when date and time of first investigational medicinal product administration is missing***

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of enrollment of LTS14424 should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

***Handling of missing assessment of relationship of adverse events to investigational medicinal product***

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

***Handling of missing severity/grades of adverse events***

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

***Handling of potentially clinically significant abnormalities***

If a patient has a missing baseline he will be grouped in the category “normal/missing at baseline.”

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 Giga/L or >ULN if ULN ≥0.5 Giga/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

### 2.5.3 Windows for time points

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP dose injection in LTS14424 study. Selected safety variables will be summarized by the analysis window as defined in Table 5 for the by-visit descriptive analysis. For all laboratory/vital sign/ECG variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should use the centralized data only (if applicable), and should include the measurements obtained at either scheduled or unscheduled visits. For PCSA analyses, the measurements of laboratory/vital sign/ECG variables obtained at either scheduled visits or unscheduled visits should be used; and, both the centralized and local test results should be used (if applicable), as long as their available dates/time are different from each other's. All available safety measurements (from either scheduled or unscheduled visit) will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used.

The pre-dose measurements at Week 0 of LTS14424 are defined as the last available measurements prior to the first IMP dose in LTS14424 study.

**Table 5 - Time window for safety variables**

| Visit | Week | Target day | Vital Signs Urine Pregnancy Test | | ECG | | Physical Examination, Urine Analysis | | Hematology, Serum Chemistry | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Minimum days | Maximum days | Minimum days | Maximum days | Minimum days | Maximum days | Minimum days | Maximum days |
| 1 | 0 | Derived | | Up to 1st IMP dose date/time | | Up to 1st IMP dose date/time | | Up to 1st IMP dose date/time | | Up to 1st IMP dose date/time |
| 2 | 2 | 15 | After 1st IMP dose date/time | 21 | | | | | | |
| 3 | 4 | 29 | 22 | 42 | | | | | After 1st IMP dose date/time | 56 |
| 4 | 8 | 57 | 43 | 70 | | | | | | |
| 5 | 12 | 85 | 71 | 98 | | | After 1st IMP dose date/time | 126 | 57 | 126 |
| 6 | 16 | 113 | 99 | 126 | | | | | | |
| 7 | 20 | 141 | 127 | 154 | | | | | | |
| 8 | 24 | 169 | 155 | 210 | | | 127 | 266 | 127 | 210 |
| 9 | 36 | 253 | 211 | 308 | | | | | 211 | 308 |
| 10 (EOT) | 52 | 365 | 309 | d# | After 1st IMP dose date/time | d# | 267 | d# | 309 | d# |
| 11 (EOS) | 64 | 449 | d# +1 | | d# +1 | | d# +1 | | d# +1 | |

Note:
# d= max [last IMP dose +1 dose interval (14 days for last IMP as 100/200 mg q2w and 28 days for last IMP as 300 mg q4w), EOT date].

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the day of the first IMP injection in LTS14424 study. And for the endpoints not measured daily, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 6. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. The pre-dose measurements at Week 0 of LTS14424 are defined in the same way as in the paragraph prior to Table 5.

**Table 6 - Time window for efficacy variables**

| Visit | Week | Target day | Spirometry | |
|---|---|---|---|---|
| | | | Minimum days | Maximum days |
| 1 | 0 | Derived | | Up to 1st IMP dose date/time |
| 2 | 2 | 15 | After 1st IMP dose date/time | 35 |
| 3 | 4 | 29 | | |
| 4 | 8 | 57 | 36 | 70 |
| 5 | 12 | 85 | 71 | 126 |
| 6 | 16 | 113 | | |
| 7 | 20 | 141 | | |
| 8 | 24 | 169 | 127 | 266 |
| 9 | 36 | 253 | | |
| 10 (EOT) | 52 | 365 | 267 | d# |
| 11 (EOS) | 64 | 449 | d# +1 | |

Note:

# = max [last IMP dose +1 dose interval (14 days for last IMP as 100/200 mg q2w and 28 days for last IMP as 300 mg q4w), EOT date].

For the pharmacokinetics/pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP dose injection in LTS14424 study. Pharmacodynamics variables will be summarized by the analysis window as defined in Table 7 for the by visit descriptive analyses. All available values of scheduled measurements will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. The pre-dose measurements at Week 0 of LTS14424 are defined in the same way as in the paragraph prior to Table 5.

**Table 7 - Time window for pharmacokinetics and pharmacodynamics variables**

| Visit | Week | Target day | PK, ADA | | Serum total IgE and Ag-specific IgE | |
|---|---|---|---|---|---|---|
| | | | Minimum days | Maximum days | Minimum days | Maximum days |
| 1 | 0 | Derived | | Up to 1st IMP dose date/time | | Up to 1st IMP dose date/time |
| 2 | 2 | 15 | | | | |
| 3 | 4 | 29 | | | | |
| 4 | 8 | 57 | | | | |
| 5 | 12 | 85 | After 1st IMP dose date/time | 126 | | |
| 6 | 16 | 113 | | | | |
| 7 | 20 | 141 | | | | |
| 8 | 24 | 169 | 127 | 266 | After 1st IMP dose date/time | 266 |
| 9 | 36 | 253 | | | | |
| 10 (EOT) | 52 | 365 | 267 | d# | 267 | d# |
| 11 (EOS) | 64 | 449 | d# +1 | | d# +1 | |

Note:
# = max [last IMP dose +1 dose interval (14 days for last IMP as 100/200 mg q2w and 28 days for last IMP as 300 mg q4w), EOT date].

### 2.5.4 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the by-visit summaries and figures, as well as the computation of baseline, worst values, and PCSAs.

### 2.5.5 Pooling of centers for statistical analyses

Not applicable.

### 2.5.6 Statistical technical issues

None.

# 3 INTERIM ANALYSIS

This is 1-year treatment safety study. At the time of the initial dupilumab marketing authorization application for the treatment of Asthma in pediatric of 6 to <12 years old, an interim database lock will be performed. In addition, interim analyses/reports may be prepared to support regulatory submissions or other purposes. No alpha adjustment is needed for the final CSR.

# 4 DATABASE LOCK

At the time of the initial dupilumab marketing authorization application for the treatment of Asthma in pediatric of 6 to <12 years old, an interim database lock will be performed. Additional database snapshots may be performed to support regulatory submission of an indication in dupilumab project. The final database lock is planned to occur after last patient completes the last visit.

# 5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

# 6 REFERENCES

1. Global Initiative for Asthma (GINA) [Internet]. Global strategy for asthma management and prevention. 2018. [Cited 2020 Apr 08]. Available from www.ginasthma.org.

# 7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Summary of statistical analyses

Appendix C: Low, Medium, and High daily doses of Inhaled Corticosteroids (Children 6-11 years) - Estimated clinical comparability

Appendix D: Definition of Anaphylaxis

Appendix E: List of opportunistic infections

# Appendix A Potentially clinically significant abnormalities (PCSA) criteria (BTD-009536 Version 3.0 21-MAY-2014)

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES For Studies in Children**

| Parameter | Age range | PCSA | Comments |
|---|---|---|---|
| **ECG parameters** | | | Ref. : Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009 |
| HR | Birth/0 to 27 days old (Neonates) | ≤90 bpm and decrease from baseline ≥20 bpm<br>≥190 bpm and increase from baseline ≥20 bpm | |
| | 28 days/1 month to 23 months old (Infants) | ≤80 bpm and decrease from baseline ≥20 bpm<br>≥175 bpm and increase from baseline ≥20 bpm | |
| | 24 months/2 years to <6 years old (Children) | ≤75 bpm and decrease from baseline ≥20 bpm<br>≥140 bpm and increase from baseline ≥20 bpm | |
| | 6 to <12 years old (Children) | ≤50 bpm and decrease from baseline ≥20 bpm<br>≥120 bpm and increase from baseline ≥20 bpm | |
| | 12 to 16/18 years old (Adolescents) | ≤50 bpm and decrease from baseline ≥20 bpm<br>≥120 bpm and increase from baseline ≥20 bpm | |
| PR | Birth/0 to 27 days old (Neonates) | ≥120 ms | |
| | 28 days/1 month to 23 months old (Infants) | ≥140 ms | |
| | 24 months/2 years to <6 years old (Children) | ≥160 ms | |
| | 6 to <12 years old (Children) | ≥170 ms | |
| | 12 to 16/18 years old (Adolescents) | ≥180 ms | |
| QRS | Birth/0 to 27 days old (Neonates) | ≥85 ms | |
| | 28 days/1 month to 23 months old (Infants) | ≥85 ms | |
| | 2 to <6 years old (Children) | ≥95 ms | |
| | 6 to <12 years old (Children) | ≥100 ms | |
| | 12 to 16/18 years old (Adolescents) | ≥110 ms | |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**
**For Studies in Children**

| Parameter | Age range | PCSA | Comments |
|---|---|---|---|
| QTc | Birth/0 to <12 years old (Neonates, Infants, Children) | Absolute values (ms)<br>Borderline: 431-450 ms<br>Prolonged*: >450 ms<br>Additional: ≥500 ms<br>AND<br>Increase from baseline<br>Borderline: Increase from baseline 30-60 ms<br>Prolonged*: Increase from baseline >60 ms | **To be applied to QTcF**<br>*QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. |
| | 12 to 16/18 years old (Adolescents) | Borderline: 431-450 ms (Boys); 451-470 ms (Girls)<br>Prolonged*: >450 ms (Boys); >470 ms (Girls)<br>Additional: ≥500 ms<br>AND<br>Increase from baseline<br>Borderline: Increase from baseline 30-60 ms<br>Prolonged*: Increase from baseline >60 ms | |
| **Vital Signs** | | | Ref. : Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/ |
| SBP | Birth/0 to 27 days old (Neonates) | ≤60 mmHg and decrease from baseline ≥20 mmHg<br>≥85mHg and increase from baseline ≥20 mmHg | Based on definition of Hypertension as average SBP or DBP ≥95th percentile for gender, age, and height on ≥3 occasions |
| | 28 days/1 month to 23 months old (Infants) | ≤70 mmHg and decrease from baseline ≥20 mmHg<br>≥98 mmHg and increase from baseline ≥20 mmHg | |
| | 24 months/2 years to <6 years old (Children) | ≤70 mmHg and decrease from baseline ≥20mmHg<br>≥101mHg and increase from baseline ≥20 mmHg | |
| | 6 to <12 years old (Children) | ≤80 mmHg and decrease from baseline ≥20 mmHg | |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**
**For Studies in Children**

| Parameter | Age range | PCSA | Comments |
|---|---|---|---|
| | | ≥108 mmHg and increase from baseline ≥20 mmHg | |
| | 12 to 16/18 years old (Adolescents) | ≤90 mmHg and decrease from baseline ≥20 mmHg<br>≥119mmHg and increase from baseline ≥20 mmHg | |
| DBP | Birth/0 to 27 days old (Neonates) | ≤34 mmHg and decrease from baseline ≥10 mmHg<br>≥50mHg and increase from baseline ≥10 mmHg | |
| | 28 days/1 month to 23 months old (Infants) | ≤34 mmHg and decrease from baseline ≥10 mmHg<br>≥54mHg and increase from baseline ≥10 mmHg | |
| | 24 months/2 years to <6 years old (Children) | ≤34 mmHg and decrease from baseline ≥10 mmHg<br>≥59mHg and increase from baseline ≥10 mmHg | |
| | 6 to <12 years old (Children) | ≤48 mmHg and decrease from baseline ≥10 mmHg<br>≥72mHg and increase from baseline ≥10 mmHg | |
| | 12 to 16/18 years old (Adolescents) | ≤54 mmHg and decrease from baseline ≥10 mmHg<br>≥78mHg and increase from baseline ≥10 mmHg | |
| Orthostatic hypotension | All age ranges | SBP : St — Su ≤ - 20 mmHg<br>DBP : St — Su ≤ - 10 mmHg | |
| Temperature | All age ranges | Rectal, ear or temporal artery: ≥100.4 °F/38.0 °C<br>Oral or pacifier: ≥99.5 °F/37.5 °C<br>Axillary or skin infrared: ≥99 °F/37.2 °C | Ear temperature not accurate below 6 months of age |
| Respiratory rate | Birth/0 to 27 days old (Neonates) | < 30 per minutes<br>> 60 per minutes | Based on normal range |
| | 28 days/1 month to 23 months old (Infants) | < 24 per minutes<br>> 40 per minutes | |
| | 24 months/2 years to <6 years old (Children) | < 22 per minutes<br>> 34 per minutes | |
| | 6 to <12 years old (Children) | < 18 per minutes<br>> 30 per minutes | |
| | 12 to 16/18 years old (Adolescents) | < 12 per minutes<br>> 20 per minutes | |
| Sa02 | All age ranges | ≤95 % | |
| Weight | All ranges | ≥5 % weight loss from baseline | Based on identification of trends in the child's growth with a series of visits<br>WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007 |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**
**For Studies in Children**

| Parameter | Age range | PCSA | Comments |
|---|---|---|---|
| **Clinical Chemistry** | | | Ref Molleston JP et al. JPGN 2011; Moritz et al., Pediatrics 1999; Moritz et al., Pediatr Nephrol 2005 ; Sedlacek et al., Seminars in Dialysis 2006) Gong G et al. Clinical Biochemistry 2009; Masilamani et al. Arch Dis Children 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009 |
| ALT/SGPT | All age ranges | >3 ULN<br>By distribution analysis:<br>≥3 ULN<br>≥5 ULN<br>≥10 ULN<br>≥20 ULN | Based on normal ranges: 6 to 50 U/L (0-5 days), 5 to 45 U/L (1-19 years) |
| AST/SGOT | All age ranges | ≥3 ULN<br>By distribution analysis:<br>≥3 ULN<br>≥5 ULN<br>≥10 ULN<br>≥20 ULN | Based on normal ranges: 35 to 140 U/L (0-5 days), 15 to 55 U/L (1-9 years), 5 to 45 U/L (10-19 years) |
| Alkaline Phosphatase | All age ranges | ≥1.5 ULN | Based on normal ranges: 145 to 420 U/L (1-9 years), 130 to 560 U/L (10-11 years), 200 to 495 U/L (Boys 12-13 years), 105 to 420 U/L (Girls 12-13 years), 130 to 525 U/L (Boys 14-15 years), 70 to 130 U/L (Girls 14-15 years), 65 to 260 U/L (Boys 16-19 years), 50 to 130 U/L (Girls 16-19 years) |
| Total Bilirubin | All age ranges | ≥1.3 ULN | CF = mg x 1.7 = µmol<br>Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days) |
| Conjugated Bilirubin | All age ranges | >35% Total Bilirubin and TBILI≥1.3 ULN | CF = mg x 1.7 = µmol<br>Based on normal range: 0 to 0.4 mg/dL |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**
**For Studies in Children**

| Parameter | Age range | PCSA | Comments |
|---|---|---|---|
| ALT and Total Bilirubin | All age ranges | ALT ≥ 3 ULN and Total Bilirubin ≥ 2 ULN | |
| CPK | All age ranges | ≥3 ULN | |
| Creatinine | Birth/0 to <6 years old (Neonates, Infants, Children) | >53 µmol/L or 0.6 mg/dL | CF = mg x 8.8 = µmol<br>Based on normal ranges: ≤0.6 mg/dL (0-1 year), 0.5 to 1.5 mg/dL (1 to 16/18 years) |
| | 6 years to <12 years old (Children) | ≥90 µmol/L or 1.1mg/dL | |
| | 12 years to 16/18 years old (Adolsecents) | ≥132µmol/L or 1.5mg/dL | |
| Creatinine Clearance | All age ranges | 50 % of normal<br><60 ml/min/1.73m2 (After 1 year old) | Based on GFR Bedside Schwartz Formula<br>Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years) |
| Uric Acid | All age ranges | ≤2.0 mg/dL or 119 µmol/L<br>≥8.0 mg/dL or 476 µmol/L | CF = mg x 5.95 = µmol<br>Based on normal ranges: 2.4 to 6.4 mg/dL |
| Blood Urea Nitrogen (BUN) | Birth/0 to 27 days old (Neonates) | ≥4.3 mmol/L or 12 mg/dl | CF = g x 16.66 = mmol<br>Based on normal ranges: 3 to 12 mg/dL (NN; 5 to 18 mg/dL (other classes of age) |
| | 28 days/1 month to 16/18 years old (Infants, Children, Adolescents) | ≥6.4 mmol/L or 18 mg/dl | |
| Chloride | All age ranges | ≤80 mmol/L or 80 mEq/L<br>≥115 mmol/L or 115 mEq/L | CF = 1<br>Based on normal range: 98 to 106 |
| Sodium | All age ranges | ≤129 mmol/L or 129 mEq/L<br>≥150 mmol/L or 150 mEq/L | CF = 1<br>Based on normal range : 134 to 146 |
| Potassium | Birth/0 to 27 days old (Neonates) | ≤3.0 mmol/L or 3.0 mEq/L<br>≥7.0 mmol/L or 7.0 mEq/L | CF = 1<br>Based on normal ranges: 3.0 to 7.0 (NN); 3.5 to 6.0 (Infants); 3.5 to 5.0 (>Infants) |
| | 28 days/1 month to 23 months old (Infants) | ≤3.5 mmol/L or 3.5 mEq/L<br>≥6.0 mmol/L or 6.0 mEq/L | |
| | 24 months/2 years to 16/18 years old (Children, Adolescents) | ≤3.5 mmol/L or 3.5 mEq/L<br>≥5.5 mmol/L or 5.5 mEq/L | |
| Bicarbonate | All age ranges | ≤16 mmol/L or 16 mEq/L<br>≥30 mmol/L or 30 mEq/L | CF = 1<br>Based on normal range: 18 to 26 |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**
**For Studies in Children**

| Parameter | Age range | PCSA | Comments |
|---|---|---|---|
| Calcium total | All age ranges | ≤2.0 mmol/L or 8.0 mg/dL<br>≥2.9 mmol/L or 11.6 mg/dL | CF = mg x 0.025 = mmol<br>Based on normal range: 8.4 to 10.9 mg/dL |
| Calcium ionized | All age ranges | ≤1.0 mmol/L or 4.0 mg/dL<br>≥1.4 mmol/L or 5.6 mg/dL | CF = mg x 0.025 = mmol<br>Based on normal range: 4.0 to 5.1 mg/dL |
| Total Cholesterol | All age ranges | ≥6.20 mmol/L or 240 mg/dL | CF = g x 2.58 = mmol<br>Based on normal ranges: 45 to 182 mg/dL (1-3 years), 109 to 189 mg/dL (4-6 years), 126 to 191 mg/dL (Boys 6-9 years), 122 to 209 mg/dL (Girls 6-9 years), 130 to 204 mg/dL (Boys 10-14 years), 124-217 mg/dL (Girls 10-14 years), 114 to 198 mg/dL (Boys 15-19 years), 125 to 212 mg/dL (Girls 14-19 years) |
| Triglycerides | All age ranges | ≥4.0 mmol/L or 350 mg/dL | After >12 hours of fast)<br>CF = g x 1.14 = mmol<br>Based on normal ranges: 30 to 86 mg/dL (Boys 0-5 years), 32 to 99 mg/dL (Girls 0-5 years), 31-108 mg/dL (Boys 6-11 years), 35 to 114 mg/dL (Girls 6-11 years), 36 to 138 mg/dL (Boys 12-15 years), 43 to 138 mg/dL (Girls 12-15 years), 40 to 163 mg/dL (Boys 16-19 years), 40-128 mg/dL (Girls 16-19 years) |
| Lipasemia | All age ranges | ≥2 ULN | Based on normal ranges: 3 to 32 U/L (1-18 years) |
| Amylasemia | All age ranges | ≥2 ULN | Based on normal ranges: 10 to 30 U/L (NN), 10 to 45 U/L (1-18 years) |
| Glucose | All age ranges | Hypoglycaemia <2.7 mmol/L or 50 mg/dL<br>Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); ≥10.0 mmol/L or 180 mg/dL (unfasted) | CF = g x 5.55 = mmol<br>Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child) |
| CRP | All age ranges | >2 ULN or<br>>10 mg/L (if ULN not provided) | Based on normal ranges: <6 mg/L |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**
**For Studies in Children**

| Parameter | Age range | PCSA | Comments |
|---|---|---|---|
| **Hematology** | | | Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006 ; Division of Microbiology and Infections Diseases Pediatric Toxicity Tables, 2007 ; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995 |
| WBC | Birth/0 to 27 days old (Neonates) | <4.0 GIGA/L or 4,000 /mm3<br>>25.0 GIGA/L or 25,000 /mm3 | To be used if no differential count available<br>Based on normal ranges: 9,000 to 30,000 /mm3 (birth), 9,400 to 38,000 /mm3 (0-1 day), 5,000 to 21,000 /mm3 (1 day-1 month), 6,000 to 17,500 /mm3 (1 month-2 years), 5,000 to 17,000 /mm3 (2-6 years), 4,500 to 15,500 /mm3 (6-11 years), 4,500 to 13,500 /mm3 (11-18 years) |
| | 28 days/1 month to 23 months old (Infants) | <4.0 GIGA/L or 4,000 /mm3<br>>20.0 GIGA/L or 20,000 /mm3 | |
| | 24 months/2 years to <6 years old (Children) | <3.0 GIGA/L or 3,000 /mm3<br>>16.0 GIGA/L or 16,000 /mm3 | |
| | 6 to <12 years old (Children) | <5.0 GIGA/L or 5,000 /mm3<br>>17.0 GIGA/L or 17,000 /mm3 | |
| | 12 to 16/18 years old (Adolescents) | <4,5 GIGA/L or 5,000 /mm3<br>>13.5 GIGA/L or 17,000 /mm3 | |
| Lymphocytes (ALC) | Birth/0 to 27 days old (Neonates) | <1.2 GIGA/L or 1,200 /mm3<br>>17.0 GIGA/L or 17,000 /mm3 | Based on normal ranges: 2,000 to 11,500 /mm3 (0-1 days), 2,000 to 17,000 /mm3 (2 days-1 month), 3,000 to 13,500 /mm3 (1 month-2 years), 1,500 to 9,500 /mm3 (2-6 years), 1,500 to 8,000 /mm3 (6-10 years), 1,200 to 5,200 /mm3 (10-18 years) |
| | 28 days/1 month to 23 months old (Infants) | <2.0 GIGA/L or 2,000 /mm3<br>>13.5 GIGA/L or 13,500 /mm3 | |
| | 24 months/2 years to <6 years old (Children) | <1.0 GIGA/L or 1,000 /mm3<br>>9.5 GIGA/L or 9,500 /mm3 | |
| | 6 to <12 years old (Children) | <1.0 GIGA/L or 1,000 /mm3<br>>8.0 GIGA/L or 8,000 /mm3 | |
| | 12 to 16/18 years old (Adolescents) | <0.6 GIGA/L or 600 /mm3<br>>6.0 GIGA/L or 6,000 /mm3 | |
| Absolute Neutrophil Count (ANC) | Birth/0 to 27 days old (Neonates) | <4.0 GIGA/L or 4,000 /mm3 (1 day old)<br><1.5 GIGA/L or 1,500 /mm3 (2-7 days old)<br><1.25 GIGA/L or 1,250 /mm3 (>7 day-1 month old)<br>> 1 ULN | Based on normal ranges: 5,000 to 28,000 /mm3 (0-1 day), 1,000 to 10,000 (1 day-1 month), 1,000 to 8,500 (1-12 months), 1,500 to 8,500 (1 to 6 years), 1,500 to 8,000 (6 to 10 years), 1;800 to 8,000 (10 to 18 years) |
| | 28 days/1 month to 23 months old (Infants) | <1.0 GIGA/L or 1,000/mm3 (1-3 months)<br><1.2 GIGA/L or 1,200 /mm3 (3-24 months)<br>> 1 ULN | |
| | 24 months/2 years to <6 | <1.2 GIGA/L or 1,200 /mm3 | |

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**
**For Studies in Children**

| Parameter | Age range | PCSA | Comments |
|---|---|---|---|
| | years old (Children) | > 1 ULN | |
| | 6 to <12 years old (Children) | <1.2 GIGA/L or 1,200 /mm3<br>>1 ULN | |
| | 12 to 16/18 years old (Adolescents) | <1.2 GIGA/L or 1,200 /mm3<br>>1 ULN | |
| Eosinophils | All age ranges | >0.5 GIGA/L or 500 /mm3<br>Or >ULN if ULN >0.5 GIGA/L or 500 /mm3 | Based on normal ranges: 0 to 500 /mm3 (0-1 month), 0 to 300 /mm3 (1 month-18 years) |
| Hemoglobin | Birth/0 to 27 days old (Neonates) | <86 mmol/L or 12.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL | CF = g x 1.55 = mmol<br>Based on normal ranges: 15 to 20 g/dL (0-3 days), 12.5 to 18.5 g/dL (1-2 weeks), 10.0 to 13.0 g/dL (1-6 months), 10.5 to 13.0 g/dL (7 months-2 years), 11.5 to 13.0 g/dL (2-5 years), 11.5 to 14.5 (5-8 years), 12.0 to 15.2 g/dL (13-18 years) |
| | 28 days/1 month to 23 months old (Infants) | <1.40 mmol/L or 9.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL | |
| | 24 months/2 years to <16/18 years old (Children, Adolescents) | <1.55 mmol/L or10.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL | |
| Hematocrit | Birth/0 to 27 days old (Neonates) | < 0.39 l/l or 40 %<br>> 0.61 l/l or 47 % | CF = % x 0.01 = l/l<br>Based on normal ranges: 45 to 61% (0-3 days), 39 to 57% (1-2 weeks), 29 to 42% (1-6 months), 33 to 38% (7 months-2 years), 34 to 39% (2-5 years), 35 to 42% (5-8 years); 36 to 47% (13-18 years) |
| | 28 days/1 month to 23 months old (Infants) | < 0.29 l/l or 29 %<br>> 0.42 l/l or 42 % | |
| | 24 months/2 years to <16/18 years old (Adolescents) | < 0.32 l/l or 32 %<br>> 0.47 l/l or 47 % | |
| Platelets | All age ranges | <100 GIGA/L or 100,000 /mm3<br>> 700 GIGA/L or 700,000 /mm3 | Based on normal ranges: 250,000 to 450,000 /mm3 (NN); 300,000 to 700,000 /mm3 (1-6 months), 250,000 to 600,00 /mm3 (7 months-2 years), 250,000 to 550,000 /mm3 (2-12 years), 150,000 to 450,000 /mm3 (13-18 years) |
| **Urinalysis** | | | Patel HP, Pediatr Clin N Am, 2006 |
| Ketonuria | All age ranges | Presence | Semi-quantitative methods |
| Glycosuria | All age ranges | Presence | Semi-quantitative methods |
| Hematuria | All age ranges | ≥1+ | Semi-quantitative methods |
| Proteinuria | All age ranges | ≥1+ | Semi-quantitative methods |

# Appendix B Summary of statistical analyses

## *EFFICACY ANALYSIS*

| Endpoint | Analysis population | Primary analysis | Statistical Method | Supportive analysis | Subgroup analysis | Other analyses |
|---|---|---|---|---|---|---|
| *FEV1, % Predicted FEV1, FVC and FEF 25-75%* | *Safety* | *Measurement and change from baseline at all visits* | *Descriptive statistics based on two sets of safety population* | *No* | *Yes (Baseline ICS dose, EOS count, FeNO, type 2 inflammation phenotype and age subgroups)* | *No* |
| *Severe exacerbation: number of events/annualized event rate during the treatment period* | *Safety* | *Summary of number/annualized rate of severe exacerbation events during the treatment period* | *Descriptive statistics based on two sets of safety population* | *No* | *Yes (Baseline ICS dose, EOS count, FeNO, type 2 inflammation phenotype and age subgroups)* | *No* |

## *SAFETY ANALYSES*

| Endpoint | Analysis population | Primary analysis | Statistical Method | Supportive analysis | Subgroup analysis | Other analyses |
|---|---|---|---|---|---|---|
| *Adverse events* | *Safety* | *Follow safety guidelines* | *Descriptive statistics based on two sets of safety population* | *No* | *Yes (Race, Sex, Ethnicity, and Weight subgroups)* | *No* |
| *Lab/vital signs/physical examination/ECGs* | *Safety* | *Follow safety guidelines; PCSA analysis; Descriptive* | *Descriptive statistics based on two sets of safety population* | *No* | *No* | *No* |

## Appendix C Low, Medium, and High daily doses of Inhaled Corticosteroids (Children 6-11 years) - Estimated clinical comparability

| Inhaled Corticosteroid | Total Daily Dose (mcg) | | |
|---|---|---|---|
| | Low | Medium | High |
| Beclometasone dipropionate (CFC) | 100-200 | >200-400 | >400 |
| Beclometasone dipropionate (HFA) | 50-100 | >100-200 | >200 |
| Budesonide (DPI) | 100-200 | >200-400 | >400 |
| Budesonide (HFA) | 100-200 | >200-400 | >400 |
| Budesonide (nebules) | 250-500 | >500-1000 | >1000 |
| Ciclesonide (HFA) | 80 | >80-160 | >160 |
| Flunisolide (HFA) | 160 | >160-<320 | 320 |
| Fluticasone propionate (DPI) | 100-200 | >200-400 | >400 |
| Fluticasone propionate (HFA) | 100-200 | >200-500 | >500 |
| Mometasone furoate | 110-<220 | ≥220-<440 | ≥440 |
| Triamcinolone acetonide | 400-800 | >800-1200 | >1200 |

CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofuoroalkane propellant; nebules = nebulized solution

Source: Adapted from Global Initiative for Asthma (GINA) 2018 guidelines with the addition of Budesonide HFA and Flunisolide HFA information; modify low level of Mometasone furoate to 110-<220.

## Appendix D 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: 391-397)

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.

## Appendix E List of opportunistic infections

- Aspergillosis.
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers).
- Candidiasis - only systemic or extensive mucosal or cutaneous candidiasis.
- Coccidioides immitis (endemic south-western US and Central and South America).
- Cryptococcus.
- Cytomegalovirus.
- Herpes Simplex (disseminated).
- Herpes Zoster (disseminated; ophthalmic; involvement of 2 or more dermatomes).
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins).
- Listeriosis.
- Mycobacterium avium.
- Nontuberculosis mycobacteria.
- Pneumocystis pneumonia (PCP).

This list is indicative and not exhaustive.

Signature Page for VV-CLIN-0580224 v3.0
lts14424-16-1-9-sap

| | |
|---|---|
| Approve & eSign | [redacted] |
| Approve & eSign | [redacted] |

# STATISTICAL ANALYSIS PLAN (JAPAN SUBSTUDY)

| | |
|---|---|
| **Protocol 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 (country specific requirement for Japan)** |
| **Protocol number:** | **LTS14424** |
| **Compound number (INN/Trademark):** | **SAR231893 dupilumab/Dupixent®** |
| **Study phase:** | **Phase 3** |
| **Short Title:** | **Dupilumab in asthma Acronym: Liberty ASTHMA EXCURSION** |
| **Statistician:** | [redacted] |
| **Statistical project leader:** | [redacted] |
| **Date of issue:** | **25-Jun-2024** |

**Regulatory agency identifier number(s):**

| | |
|---|---|
| **IND:** | 105379 |
| **EudraCT/EU-trial number:** | 2017-003317-25 |
| **NCT:** | NCT03560466 |
| **WHO:** | U1111-1200-1757 |
| **EUDAMED:** | Not applicable |
| **Other:** | Not applicable |

Date: 25-Jun-2024 Total number of pages: 30

# TABLE OF CONTENTS

## LIST OF TABLES

# VERSION HISTORY

This Statistical Analysis Plan (SAP) for the LTS14424 Japan substudy is based on the protocol dated 21-Dec-2021 (amended protocol 06). The SAP for LTS14424 main study was separately created and finalized on 27-Aug-2020.

The first participant of the Japan substudy was randomized on 25-Jul-2022.

# 1 INTRODUCTION

## 1.1 STUDY DESIGN

The LTS14424 Japan substudy is a multicenter, open-label, single-arm, 1-year treatment study to evaluate the efficacy, safety, and tolerability of dupilumab in Japanese pediatric participants aged 6 to <12 years with uncontrolled, persistent asthma.

For participants with body weight >30 kg, the dose regimen is 200 mg q2w. For participants with body weight ≥15 kg to ≤30 kg, they were randomized in a 1:1 allocation ratio to dose regimen of either 100 mg q2w or 300 mg q4w. The dose regimen determined at baseline has been maintained and will not be adjusted upon weight gain or loss during the treatment period.

After a screening phase of 4[±1] weeks, participants were enrolled or randomized in the three dose regimens, and treated open-label for 52 weeks. Upon completion of the treatment period or following early discontinuation of investigational medicinal product (IMP), participants continue into a post-treatment period of 12 weeks. Thirteen participants were enrolled and a minimum of 3 participants were assigned to treatment with each of the 3 dose regimens.

## 1.2 OBJECTIVES AND ENDPOINTS

### Objectives

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

The secondary objectives of this substudy 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,
  - anti-drug antibodies (ADAs),
  - Biomarkers.

### Endpoints

The primary endpoint of this substudy is change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.

The secondary endpoints of this substudy include:

- 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.
- The number (n) and percentage (%) of patients experiencing any treatment-emergent adverse event.
- Serum dupilumab concentrations.
- ADAs.
- Serum: Total immunoglobulin (IgE).
- Fractional exhaled nitric oxide (FeNO).

### 1.2.1 Estimands

Primary estimand defined for main endpoints are summarized in Table 1. More details are provided in Section 3.2 and Section 3.3.

**Table 1 - Summary of primary estimand for the main endpoints**

| Endpoint Category | Estimand | | | |
|---|---|---|---|---|
| | **Endpoint** | **Population** | **Intercurrent event(s) handling strategy and missing data handling** | **Population-level summary** |
| **Primary objective:** To evaluate the efficacy of dupilumab in children from Japan who are 6 to <12 years of age with uncontrolled, persistent asthma. | | | | |
| Primary endpoint - continuous | Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12 | ITT | The intercurrent events (IEs) will be handled as follows:<br>• Discontinuing the study intervention before Week 12: all data collected after discontinuation will be used in the analysis (treatment policy strategy).<br>Missing data will not be imputed. | Descriptive statistics and 95% confidence interval (CI) of the mean change from baseline (based on t-distribution) will be provided. |
| Secondary endpoint – count data | Annualized rate of severe asthma exacerbation events, during the treatment period. | ITT | The following IE will be handled with treatment policy strategy. All assessments after starting such IE will be included.<br>• Discontinuing the study intervention<br>Missing data will not be imputed. | The unadjusted annualized severe exacerbation event rate will be presented. |

Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type.

# 2 ANALYSIS POPULATIONS

The following populations for analyses are defined. The primary population of the efficacy endpoints is the ITT population.

**Table 2 - Populations for analyses**

| Population | Description |
|---|---|
| Screened | All participants who signed the informed consent/assent. |
| Enrolled | All participants who signed the informed consent/assent and had a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was received or not. |
| Intent-to-treat (ITT) | All participants in the enrolled population.<br>Participants will be analyzed according to the dose regimen as enrolled. |
| Safety | All enrolled participants who have taken at least 1 dose of study intervention, regardless of the amount of treatment administered.<br>Participants will be analyzed according to the dose regimen they actually received. |
| Pharmacokinetic (PK) | The PK population includes all participants in the safety population who had at least 1 non-missing and evaluable predose serum concentration value after the first dose of dupilumab in the study.<br>Participants will be analyzed according to the dose regimen they actually received. |
| Anti-drug antibody (ADA) | ADA population includes all participants in the safety population with at least 1 non-missing ADA result following the first dose of dupilumab in the study.<br>Participants will be analyzed according to the dose regimen they actually received. |

# 3 STATISTICAL ANALYSES

## 3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number, mean, standard deviation (SD), median, minimum, and maximum for observed data and the change from baseline. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline values for efficacy, safety, PK, ADA and other endpoints are defined as the last available measurements prior to the first IMP dose if the participant is treated, or the last available value up to enrollment if the participant is not exposed to IMP.

Unless otherwise specified, all analyses will be performed on each dose regimen group and overall.

***Observation period***

The observation period will be divided into 4 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + 98 days for participants with IMP on 100 mg/200 mg q2w regimen, or to the last IMP administration + 112 days for participants on 300 mg q4w regimen. The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP + 14 days for participants with IMP on 100 mg/200 mg q2w regimen, or to the last administration of IMP + 28 days for participants on 300 mg q4w regimen.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

The on-study observation period is defined as the time from start of intervention until the end of the study defined as the status date collected on e-CRF page “Completion of End of Study”.

## 3.2 PRIMARY ENDPOINT ANALYSIS

The primary endpoint is the change from baseline in pre-bronchodilator percentage (%) predicted FEV1 at Week 12. The primary endpoint will be analyzed on the ITT population. Intercurrent events (IE) handling strategies are described below:

- The IE of discontinuing the study intervention before Week 12 will be handled with the treatment policy strategy. Data collected after such IEs will be included.

No missing data will be imputed. Descriptive statistics (number of participants, mean, SD, median, minimum and maximum) and 95% CI of the mean (based on t-distribution) will be provided.

## 3.3 SECONDARY ENDPOINTS ANALYSIS

Efficacy secondary endpoints are described in this section. Non-efficacy secondary endpoints analyses are defined in Section 3.5.2 (AE, SAE), Section 3.5.3.1 (laboratory abnormalities and vital signs), Section 3.6.1.1 (PK), Section 3.6.1.2 (immunogenicity), and Section 3.6.1.3 (biomarkers).

Statistical analyses for efficacy secondary endpoints will be conducted on the ITT population.

***Annualized rate of severe asthma exacerbation events***

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.

The annualized rate of severe exacerbation events is defined as the total number of severe exacerbation events with onset period from enrolled up to the Week 52 visit or last contact date (whichever comes earlier) per participant-year. The IE of discontinuing the study intervention will be handled with the treatment policy strategy. Data after such IEs will be included. For discontinuation of the study follow-up before Week 52, all observed events up to the time of study discontinuation will be included, and the observation duration is defined as from enrollment to the time of study discontinuation. No imputation will be performed for the unobserved events that may happen after the study discontinuation.

The number of participants with one or more severe exacerbation events (number and qualitative variable: Yes/No), number of severe exacerbation events (qualitative variable: 0, 1, 2, 3, ≥4), total number of severe exacerbation events, total participant-years, unadjusted annualized severe exacerbation event rate, and duration (days) of a single severe exacerbation (number, mean, SD, median, minimum, maximum) during the treatment period will be presented. Unadjusted annualized rate will also be analyzed for severe exacerbation with use of SCS for ≥3 days only, and those with hospitalization or with emergency room visit only.

***Change from baseline in lung function measurements***

For change from baseline in pre-bronchodilator % predicted FEV1, absolute FEV1, FVC, and FEF 25%-75%, IE handling strategies are similar to the primary endpoint. Descriptive statistics (number of participants, mean, SD, median, minimum and maximum) and the 95% CI (based on t-distribution) of the mean will be presented over visits (Weeks 2, 4, 8, 24, 52, 64 for % predicted FEV1, and Weeks 2, 4, 8, 12, 24, 52, 64 for the others). In addition, figure of mean change from baseline (with corresponding standard error) will be presented for the parameter over visits.

***Change from baseline in ACQ-IA***

The global ACQ-7-IA score is the mean of the 7 questions of the Asthma Control Questionnaire–Interviewer Administered, 7-question version (ACQ-IA-7), and global ACQ-5-IA is the mean of the first 5 items.

For change from baseline in global ACQ-5-IA and ACQ-7-IA scores, IE handling strategies are similar to the primary endpoint. The methods for handling missing values of the questions are described in Section 5.4. No missing data imputation will be performed for the global scores. Descriptive statistics (number of participants, mean, SD, median, minimum and maximum) and the 95% CI (based on t-distribution) of the mean will be presented over visits. Figure of mean change from baseline (with corresponding standard error) will be presented over visits.

## 3.4 MULTIPLICITY ISSUES

Not applicable.

## 3.5 SAFETY ANALYSES

All safety analyses will be performed on the safety population, unless otherwise specified, using the following common rule:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.

### 3.5.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population by dose regimen group and overall.

**Duration of IMP exposure**

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 15 days for the q2w regimens or + 29 days for the q4w regimen, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories: >0 and ≤2 weeks, >2 and ≤4 weeks, >4 and ≤8 weeks, >8 and ≤12 weeks, >12 and ≤16 weeks, …>48 and ≤52 weeks, >52 weeks.

Additionally, the cumulative duration of treatment exposure will be provided in participant-years overall.

**Treatment compliance**

A given administration will be considered noncompliant if the participant did not receive the number of administration as required by the protocol.

Percentage of treatment compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of participants whose compliance is <80% will be summarized.

Cases of overdose of IMP (defined as at least twice the intended dose during an interval of less than 11 days for 100/200 mg q2w regimen or less than 25 days for 300 mg q4w regimen) will be summarized by numbers and percentages of participants with at least 1 overdose.

### 3.5.2 Adverse events

**General common rules for adverse events**

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately if applicable.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. Missing severity will be left as missing.

The AE incidence tables will summarize the number (n) and percentage (%) of participants experiencing at least one AE in safety population. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages is number of participants in safety population.

The AE tables will be sorted as indicated in Table 3.

**Table 3 - Sorting of AE tables**

| AE presentation | Sorting rules |
|---|---|
| SOC, HLGT, HLT and PT | By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs |
| SOC and PT | By the internationally agreed SOC order and decreasing frequency of PTs |
| SMQ/CMQ and PT | By decreasing frequency of SMQs/CMQs and PTs |

## Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any severe TEAE
- Any treatment-emergent SAE
- Any TEAE leading to death
- Any TEAE leading to permanent study intervention discontinuation
- Any treatment-emergent AESI
- Any treatment-emergent other selected AE grouping
- Any treatment-emergent AE related to IMP

The AE summaries of Table 4 will be generated to summarize the number (%) of participants experiencing at least one event.

**Table 4 - Analyses of adverse events**

| Type of AE | MedDRA levels |
|---|---|
| All TEAE | Primary SOC, HLGT, HLT and PT |
| All TEAE | Primary SOC and PT |
| TEAE related to IMP | Primary SOC and PT |
| Treatment-emergent SAE | Primary SOC and PT |
| TEAE leading to intervention discontinuation | Primary SOC and PT |
| TEAE leading to death[a] | Primary SOC and PT |
| TEAE related to COVID-19 | Primary SOC and PT |

*a* Death as an outcome of the AE as reported by the Investigator in the AE page

## Analysis of adverse events of special interest (AESIs) and other selected AE groupings

Adverse events of special interest (AESIs) and other selected AE grouping defined in Table 5 will be selected for analyses. Tables will be sorted as indicated in Table 3.

**Table 5 - Criteria for AESIs and other selected AE groupings**

| AE Grouping | Criteria |
|---|---|
| **AESI** | |
| Anaphylactic reaction | Anaphylactic reaction algorithmic approach (*Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1*): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not. |
| Hypersensitivity (medically reviewed) | Hypersensitivity narrow SMQ (20000214) and [AE corrective treatment/therapy='Yes' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by medical review (documented process) for selection of relevant systemic hypersensitivity events |
| Severe injection site reactions that last longer than 24 hours or serious injection site reaction | HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time –AE start date/time) ≥24 hours or ongoing |
| Severe or serious infection | Primary SOC = 'Infections and infestations' and with severe or serious status |
| Parasitic infection | The Infection Type 'Parasitic' was checked on the eCRF page "Infection Event Form" |
| Opportunistic infection | The question "Has the AE been assessed as opportunistic infection?" is answered "Yes" on the eCRF page "Infection Event Form" |
| Drug-related hepatic disorder | Drug-related hepatic disorders - Comprehensive search narrow SMQ (20000006) |
| Pregnancy | "Pregnancy" checked on the Pregnancy eCRF page as reported by the investigator |
| Symptomatic overdose with IMP | The answers for both "Symptomatic Overdose" and "Overdose of SAR231893" are "Yes" on the eCRF page "Adverse Event". |
| Symptomatic overdose with noninvestigational medicinal product (NIMP) | The answers for both "Symptomatic Overdose" and "Overdose of NIMP" are both "Yes" on the eCRF page "Adverse Event". |
| **Other selected AE grouping** | |
| Injection site reaction | HLT = 'Injection site reaction' |
| Malignancy | Sub-SMQ (20000091) – Malignant or unspecified tumors |
| Partner pregnancy | "Partner Pregnancy" checked on the Pregnancy eCRF page as reported by the investigator |
| Conjunctivitis (narrow) | PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis) |
| Conjunctivitis (broad) | PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia) |
| Eosinophilia | HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased' |
| Keratitis | PT in (Keratitis, Allergic keratitis, Ulcerative keratitis, Atopic keratoconjunctivitis, Herpes ophthalmic, Ophthalmic herpes simplex, Corneal infection) |

The following summary will be provided:

- All treatment-emergent AESIs and other selected AE groupings identifiable by MedDRA terms, by AESI category and PT, showing the number (%) of participants will be presented by decreasing incidence of PT within each AESI category.

### 3.5.3 Additional safety assessments

#### *3.5.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)*

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: erythrocytes, hemoglobin, hematocrit, platelet count
  - White blood cells: leukocytes, with five-part differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Clinical chemistry:
  - Metabolism: glucose, total cholesterol, total protein, creatine phosphokinase (CPK), albumin
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Renal function: creatinine, blood urea nitrogen
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin
- Vital signs: systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, body weight, height.
- ECG variables: heart rate, PR, QRS, QRS axis, QT, QTc, RR.

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

**Quantitative analyses**

When relevant, for laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each analysis window, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only for laboratory variables.

For each continuous parameter for laboratory variables and vital signs, mean change from baseline with corresponding standard error will be plotted over time.

**Analyses according to PCSA**

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria.

For laboratory variables, a listing of participants with at least 1 PCSA during the treatment-emergent period will be provided and will display the whole profile over time of all parameters of the corresponding biological function. In this listing, baseline, endpoint value and individual values will be flagged when lower or higher than the lower or upper laboratory limits and/or when reaching the absolute limit of abnormality criteria.

## 3.6 OTHER ANALYSES

### 3.6.1 Other variables and/or parameters

#### *3.6.1.1 PK analyses*

The PK analyses will be performed on the PK population.

Serum concentrations of dupilumab will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per visits by each dose regimen group and overall. If date and/or time of the drug intake and/or sampling are missing, then the concentration will not be taken into account. When concentration values are below the lower limit of quantification (LLOQ), one-half of the LLOQ will be used except that the pre-dose concentration value at Week 0 will be used as 0 if the pre-dose concentration values at Week 0 are below the lower limit of quantitation. Values will be expressed in the tables with no more than three significant figures.

#### *3.6.1.2 Immunogenicity analyses*

The ADA analyses will be performed on the ADA population.

Samples for ADAs are collected at Week 0, Week 12, Week 24, Week 52/EOT, Week 64/EOS and/or early termination.

ADA incidence will be classified as the following:

- Pre-existing immunoreactivity is defined as: an ADA positive response in the assay at baseline with all post treatment ADA results negative, OR an ADA positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.
- Treatment-emergent response is defined as: a positive response in the ADA assay post first dose, when baseline results are negative or missing. Treatment-emergent ADA responses are further classified as Persistent, Indeterminate or Transient.
  - Persistent Response - defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days), with no ADA negative samples in between.
  - Indeterminate Response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
  - Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate
- Treatment-boosted response is defined as: a positive response in the ADA assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Titer value categories are as following:

- Low (Titer <1,000)
- Moderate (1,000 ≤ Titer ≤10,000)
- High (Titer >10,000)

Samples that are positive in the ADA assay will be further characterized for the presence of anti-dupilumab neutralizing antibodies (NAb).

ADA negative is defined as ADA assay is negative at all times or exhibit a pre-existing immunoreactivity.

ADA positive is defined as either treatment-boosted or treatment-emergent response in the ADA assay.

The following summary will be provided based on ADA population during treatment-emergent period by each dose regimen group and overall:

- Number (%) of participants negative in the ADA assay at baseline of the study.

- Number (%) of participants positive in the ADA assay at baseline of the study:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the titer for the participants positive in the ADA assay at baseline,
  - Number (%) of participants with neutralizing antibody status (negative or positive in the NAb assay).
- Number (%) of participants with ADA status (negative or positive in the ADA assay) at time points analyzed:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for ADA positive participants,
  - ADA titers using descriptive statistics (including number, median, Q1, Q3, minimum and maximum) at ADA time points analyzed,
  - Number (%) of participants with neutralizing antibody status (negative or positive in the NAb assay) for the ADA positive participants.
- Number (%) of participants with pre-existing immunoreactivity.
- Number (%) of participants with treatment-boosted anti-drug antibodies:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for treatment-boosted ADA participants.
- Number (%) of participants with treatment-emergent ADA:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for treatment-emergent positive participants,
  - Number (%) of participants in the low, moderate or high titer category with treatment-emergent positive response,
  - Number (%) of participants with transient, indeterminate, or persistent treatment-emergent ADA response.
- Number (%) of participants with neutralizing antibody results (negative or positive in the NAb assay).

#### *3.6.1.3 Biomarker analyses*

Biomarkers will be analyzed on the safety population.

For blood eosinophil count, FeNO, and serum total IgE, descriptive statistics (including number, mean, median, standard deviation, Q1, Q3, minimum and maximum), change from baseline and percentage change from baseline over visits will be presented. In addition, the mean, mean change from baseline, median percentage change from baseline will be plotted across visits.

For antigen-specific IgEs with a positive (≥0.35 IU/mL) incidence of greater than 25% at baseline, values at each visit, absolute change from baseline and percent changes from baseline will be summarized in descriptive statistics. Values reported as below the LLOQ (lower limit of quantitation) will be imputed as a value one half of the LLOQ.

Number and percentage of participants with no positive (≥0.35 IU/mL) antigen-specific IgE result, with positive (≥0.35 IU/mL) result for only one antigen, and with positive (≥0.35 IU/mL) results for at least two antigens will be summarized by time point. Same analysis will also be performed using LLOQ as the threshold.

For blood eosinophil count, with subgrouping the participants into baseline EOS ≤0.5 Giga/L and >0.5 Giga/L, the mean change from baseline will be plotted over visits for each of the two subgroups and overall. And table showing number (%) of participants who have peak post-baseline EOS count ≥1 Giga/L, ≥3 Giga/L and ≥5 Giga/L will be presented for each of the two subgroups and overall.

### 3.6.2 Subgroup analysis

Subgroup analyses will be performed for efficacy variables pre-bronchodilator percentage (%) predicted FEV1 and severe exacerbation for ITT population:

- ICS dose group: participants on the medium or high ICS dose at baseline.
- Blood eosinophil (Giga/L) groups at baseline: ≥0.3, <0.3 Giga/L.
- FeNO (ppb) groups at baseline: <20, ≥20 ppb; and <35, ≥35 ppb.
- Baseline age group (6-8, 9-11 years).
- Number of severe asthma exacerbations experienced in previous year before Visit 1: ≤1, =2, >2.
- Number of severe asthma exacerbations that required hospitalization or urgent medical care in previous year before Visit 1: 0, ≥1.

## 3.7 TIMING OF STATISTICAL ANALYSIS

A database lock for early analysis will be performed when all enrolled participants complete their Week 24 visit with no impact on the conduct of the study. All analyses described in this SAP up to the data cut-off date will be included. Early analysis of the substudy will support the Japan submission and will be included in the CSR.

A core database lock will be conducted when all participants have completed their 52-week treatment period. Analysis will be based on all data collected up to the data cut-off date and will be considered as the final analyses in the CSR.

The database will be updated at the end of the study for all participants to include the post-treatment follow-up information and updates for the events previously ongoing at the time of the core lock. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

## 3.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

There are no statistical changes for this Japan substudy in the protocol amendments.

# 4 SAMPLE SIZE DETERMINATION

The primary objective of this substudy 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 pre-bronchodilator % predicted FEV1 at Week 12 among the study participants follows a normal distribution with mean of 10.74% and standard deviation of 14.12%, a sample size of 16 will lead to a half-width of the 95% confidence interval being 7.5%. A minimum of 3 participants assigned to treatment in each of the 3 dose regimens is targeted.

The sample size calculations were performed using nQuery Advisor.

# 5 SUPPORTING DOCUMENTATION

## 5.1 APPENDIX 1 LIST OF ABBREVIATIONS

| | |
|---|---|
| ACQ-IA: | Asthma Control Questionnaire-Interviewer Administered |
| ADA: | anti-drug antibodies |
| AE: | adverse event |
| AESIs: | adverse events of special interest |
| ALP: | alkaline phosphatase |
| ALT: | alanine aminotransferase |
| AST: | aspartate aminotransferase |
| ATC: | anatomic category |
| BMI: | body mass index |
| CPK: | creatine phosphokinase |
| CV: | coefficient of variation |
| ECG: | electrocardiogram |
| eCRF: | electronic case report form |
| FEF: | forced expiratory flow |
| FeNO: | fractional exhaled nitric oxide |
| FEV1: | forced expiratory volume in one second |
| FVC: | forced vital capacity |
| HLGT: | high-level group term |
| HLT: | high level term |
| ICS: | inhaled corticosteroid |
| IEs: | intercurrent events |
| IgE: | immunoglobuline |
| ITT: | intent-to-treat |
| IVRS/IWRS: | Interactive Voice Response System/Interactive Web Response System |
| LLOQ: | lower limit of quantification |
| LLT: | lower-level term |
| MDI: | metered dose inhaler |
| MedDRA: | Medical Dictionary for Regulatory Activities |
| NIMP: | non-investigational medicinal product |
| PCSA: | potentially clinically significant abnormality |
| PK: | pharmacokinetics |
| PT: | preferred term |
| q2w: | once every 2 weeks |
| SAE: | serious adverse event |
| SCS: | systemic corticosteroids |
| SD: | standard deviation, standard deviation |
| SEM: | standard error of the mean |
| SOC: | system organ class |
| TE: | treatment-emergent |
| TEAE: | treatment-emergent adverse event |
| WHO-DD: | World Health Organization-Drug Dictionary |

## 5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

For participant study status, the total number of participants in each of the following categories will be presented by dose regimen group and overall:

- Screened participants.
- Screen failure participants and reasons for screen failure.
- Non-enrolled but treated participants.
- Enrolled participants.
- Enrolled but not treated participants.
- Enrolled and treated.
- Participants who discontinued study treatment period as per protocol.
- Participants who discontinued study treatment by main reason for permanent treatment discontinuation.
- Participants who discontinued from the study.
- Participants who discontinued from the study by main reason for permanent study discontinuation.

Reasons for treatment discontinuation and study discontinuation will be supplied in tables giving numbers and percentages.

A participant will be considered as lost to follow-up at the end of study if he/she is not assessed at the last protocol planned visit.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the enrolled population by dose regimen group and overall as well as displayed separately as related versus not related to COVID-19 if applicable.

## 5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

***Demographics, baseline characteristics, medical surgical history***

The following demographics and baseline characteristics will be summarized on enrolled population by dose regimen group and the overall group. Continuous data will be summarized using the number, mean, standard deviation (SD), median, minimum, and maximum of available data. Categorical and ordinal data will be summarized using the number and percentage of participants.

Medical and surgical history will be summarized on enrolled population by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC based on the overall group. Comorbidity history and atopic medical history will be summarized separately.

Demographic variables are

- Baseline age in years (quantitative and qualitative variable: 6-8, 9-11 years).
- Gender (Male, Female).
- Baseline height in cm.
- Baseline weight in kg (quantitative and qualitative variable: ≥15 to ≤30, >30 kg).
- Baseline BMI in $kg/m^2$ (quantitative and qualitative variable: <20, ≥20 $kg/m^2$).

The following baseline disease characteristics will be summarized:

- ICS dose level at baseline (medium, high).
- Age at asthma onset (years).
- Time since first diagnosis of asthma (years).
- Time since last asthma exacerbation (months).
- Number of asthma exacerbations experienced in previous year before Visit 1 (quantitative and qualitative variable: 1, 2, 3, ≥4).
- Number of asthma exacerbations required hospitalization or urgent medical care in previous year before Visit 1 (quantitative and qualitative variable: 0, 1, 2, 3, ≥4).
- Baseline eosinophil count (Giga/L).
- Baseline eosinophil count category (<0.15, ≥0.15 and <0.3, ≥0.3 Giga/L).
- Baseline FeNO (ppb).
- Baseline FeNO category (<20, ≥20 and < 35, ≥35 ppb).
- Baseline spirometry data, including pre-bronchodilator forced expiratory volume in 1 second (FEV1) (L) and percentage (%) predicted FEV1.
- Baseline serum total IgE (IU/mL).

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the participant. This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database locks.

The following comorbid diseases will be summarized:

- Atopic dermatitis history (Yes, Ongoing condition).
- Allergic conjunctivitis history (Yes, Ongoing condition).
- Allergic rhinitis history (Yes, Ongoing condition).

- Allergic conjunctivitis and/or rhinitis history (Yes, Ongoing condition).
- Chronic rhinitis history (Yes, Ongoing condition).
- Chronic sinusitis history (Yes, Ongoing condition).
- Eosinophilic esophagitis history (Yes, Ongoing condition).
- Food allergy history (Yes, Ongoing condition).
- Hives history (Yes, Ongoing condition).

A participant will be considered to have an atopic medical condition if the participant has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or allergic rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE ≥100 IU/mL and at least one positive antigen-specific IgE (≥0.35 IU/mL) at baseline.

***Prior or concomitant medications***

All medications taken within 30 days before screening and until the end of the study, including asthma controller medications, reliever medications and systemic corticosteroids are to be reported in the electronic case report form (eCRF) pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database locks.

- Prior medications are any treatments taken by participant prior to the first IMP administration in the study.
- Concomitant medications are any treatments received by participant concomitantly to the IMP in the study, from (on/after) the first administration of IMP to the last administration + 98 days. A given medication can be classified both as a prior medication and as a concomitant medication.

The prior and concomitant medications will be summarized for the enrolled population by dose regimen group and overall.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore participants may be counted several times for the same medication.

The table for prior medications and concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The ICS in combination with controller medication(s) and reliever medications will be summarized separately.

*ICS in combination with controller medications*

Participants may use 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.

ICS in combination with controller medications within 30 days prior to screening of the study will be summarized on the enrolled population by dose regimen group and overall, and will be sorted by decreasing frequency of standard medication name in the overall category.

The prescription of ICS in combination with controller medication(s) at enrollment will be summarized. Number (%) of participants will be presented by medication names and ICS dose level (medium/high) according to the classification specified in (1).

## 5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

### Demographic formulas

Age of onset of asthma is calculated as following:

Age of onset of asthma = year of asthma onset – year of birth

BMI is calculated as following:

BMI = Weight in kg / (height$^2$ in meters)

### Renal function formulas

Creatinine clearance (CLcr) value will be derived using the equation of glomerular filtration rate (GFR) Bedside Schwartz

GFR (mL/min/1.73 m2) = k × height (cm) / sCr (standardized serum creatinine, mg/dL),

where the coefficient k=0.55 for participants ≥6 and <12 years old, 0.65 for adolescent (≥12 years old) male participants, or k=0.55 for adolescent (≥12 years old) female participants.

### Calculation of ACQ-IA scores

The global ACQ-7-IA score is the mean of the 7 questions of the Asthma Control Questionnaire–Interviewer Administered, 7-question version (ACQ-7-IA), and global ACQ-5-IA is the mean of the first 5 items.

For ACQ-7-IA, if more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing score, it will be imputed (pro-rated) using the completed questionnaires from the previous visit. For instance, answer to question 5 is missing at Visit 2, and all questions are completed at Visit 1. Then the question 5 score at Visit 2 is imputed as: (sum of score at Visit 2/sum of scores excluding question 5 at Visit 1) × score of question 5 at Visit 1. If the questionnaire from the previous visit is not

complete either, the missing value will be imputed as the average of the completed questions within the current visit. Missing values of questions for ACQ-5-IA will be handled in the same way as for ACQ-7-IA score.

**Analysis windows for time points**

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP dose injection. Selected safety variables will be summarized by the analysis window as defined in Table 6 for the by-visit descriptive analysis. For all laboratory/vital sign/ECG variables, the summary statistics over visits for either measurements or mean change from baseline, and the plot of mean change from baseline over visits should use the centralized data only (if applicable), and should include the measurements obtained at either scheduled or unscheduled visits. All available safety measurements (from either scheduled or unscheduled visit) will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used.

**Table 6 - Time window for safety variables**

| | | Time windows for | | | |
|---|---|---|---|---|---|
| **Visit** | **Target day** | **Vital Signs, Urine Pregnancy Test** | **ECG** | **Urine Analysis** | **Hematology, Serum Chemistry** |
| Visit 0 (Week -4±1) | -28±7 | < -14 | $1^-$ | $1^-$ | < -14 |
| Visit 1 (Week 0) | 1 | -14 - $1^-$ | | | -14 - $1^-$ |
| Visit 2 (Week 2) | 15 | $1^+$ - 21 | | | |
| Visit 3 (Week 4) | 29 | 22 - 42 | | | $1^+$ - 56 |
| Visit 4 (Week 8) | 57 | 43 - 70 | | | |
| Visit 5 (Week 12) | 85 | 71 - 98 | | $1^+$ - 126 | 57 – 126 |
| Visit 6 (Week 16) | 113 | 99 – 126 | | | |

| Visit | Target day | Time windows for | | | |
|---|---|---|---|---|---|
| | | Vital Signs, Urine Pregnancy Test | ECG | Urine Analysis | Hematology, Serum Chemistry |
| Visit 7 (Week 20) | 141 | 127 – 154 | | | |
| Visit 8 (Week 24) | 169 | 155 – 210 | | 127 – 266 | 127 – 210 |
| Visit 9 (Week 36) | 253 | 211 – 308 | | | 211 – 308 |
| Visit10 (Week 52, EOT) | 365 | 309 – 406 | 1+ - 406 | 267 – 406 | 309 – 406 |
| Visit 11 (Week 64, EOS) | 449 | > 406 | > 406 | > 406 | > 406 |

Note: 1-: Up to 1st IMP dose date/time; 1+: after 1st IMP dose date/time.

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the day of the first IMP injection. And for the endpoints not measured daily, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 7. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used.

**Table 7 - Time window for efficacy variables**

| Visit | Target day | Time windows for | |
|---|---|---|---|
| | | Spirometry | ACQ-IA |
| Visit 0 (Week -4±1) | -28±7 | < -14 | < -14 |
| Visit 1 (Week 0) | 1 | -14 - 1- | -14 - 1- |
| Visit 2 (Week 2) | 15 | 1+ - 21 | 1+ - 21 |
| Visit 3 (Week 4) | 29 | 22 - 42 | 22 - 42 |
| Visit 4 (Week 8) | 57 | 43 - 70 | 43 - 70 |

| | | Time windows for | |
|---|---|---|---|
| **Visit** | **Target day** | **Spirometry** | **ACQ-IA** |
| Visit 5 (Week 12) | 85 | 71 - 126 | 71 - 126 |
| Visit 6 (Week 6) | 113 | | |
| Visit 7 (Week 20) | 141 | | |
| Visit 8 (Week 24) | 169 | 127 - 266 | 127 - 210 |
| Visit 9 (Week 36) | 253 | | 210 - 308 |
| Visit 10 (Week 52, EOT) | 365 | 267 - 406 | 309 - 406 |
| Visit 11 (Week 64, EOS) | 449 | > 406 | > 406 |

Note: $1^-$: Up to 1st IMP dose date/time; $1^+$: after 1st IMP dose date/time.

For the pharmacokinetics/pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP dose injection. Pharmacodynamics variables will be summarized by the analysis window as defined in Table 8 by visit descriptive analyses. All available values of scheduled measurements will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used.

**Table 8 - Time window for pharmacokinetics and pharmacodynamics variables**

| | | Time windows for | | |
|---|---|---|---|---|
| **Visit** | **Target day** | **PK, ADA** | **Serum total IgE and Ag-specific IgE** | **FeNO** |
| Visit 0 (Week -4±1) | -28±7 | | | < -14 |
| Visit 1 (Week 0) | 1 | 1- | $1^-$ | -14 - $1^-$ |
| Visit 2 (Week 2) | 15 | | | $1^+$ - 21 |
| Visit 3 (Week 4) | 29 | | | 22 - 42 |

| Visit | Target day | Time windows for | | |
|---|---|---|---|---|
| | | PK, ADA | Serum total IgE and Ag-specific IgE | FeNO |
| Visit 4 (Week 8) | 57 | | | 43 - 70 |
| Visit 5 (Week 12) | 85 | 1+ - 126 | | 71 - 126 |
| Visit 6 (Week 6) | 113 | | | |
| Visit 7 (Week 20) | 141 | | | |
| Visit 8 (Week 24) | 169 | 127 - 266 | 1+ - 266 | 127 - 266 |
| Visit 9 (Week 36) | 253 | | | |
| Visit 10 (Week 52, EOT) | 365 | 267 - 406 | 267 - 406 | 267 - 406 |
| Visit 11 (Week 64, EOS) | 449 | > 406 | > 406 | > 406 |

Note: 1-: Up to 1st IMP dose date/time; 1+: after 1st IMP dose date/time.

### Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the by-visit summaries and figures, as well as the computation of baseline, worst values, and PCSAs.

## 5.5 APPENDIX 5 LOW, MEDIUM, AND HIGH DAILY DOSES OF INHALED CORTICOSTEROIDS (CHILDREN 6-11 YEARS) - ESTIMATED CLINICAL COMPARABILITY

| 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.

# 6 REFERENCES

1. Global Initiative for Asthma (GINA) [Internet]. Global strategy for asthma management and prevention. Available from: www.ginasthma.org. 2018.

Signature Page for VV-CLIN-0674664 v1.0
lts14424-16-1-9-sap-jp-substudy

| | |
|---|---|
| Approve & eSign | [redacted]<br>Clinical<br>[redacted] |

| | |
|---|---|
| Approve & eSign | [redacted]<br>Clinical<br>[redacted] |