STATISTICAL ANALYSIS PLAN

A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma

SAR231893 – EFC14153

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ-7 IA:	Asthma Control Questionnaire–Interviewer Administered, 7-question version
ATS:	American Thoracic Society
ECG:	electrocardiogram
ERS:	European Respiratory Society
FEF:	Forced expiratorf flow
HCRU:	healthcare resource utilization
MCID:	minimal clinically important difference
MID:	minimally important difference
NRS:	Numerical Rating Scale
PEF:	peak expiratory flow

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

EFC14153 is a multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in children 6 to <12 years of age with uncontrolled persistent asthma. Patients with baseline body weight of <=30 kg will be assigned dupilumab 100mg Q2W/matching placebo, and patients with weight >30kg at baseline will be assigned dupilumab 200 mg Q2W/matching placebo. Both investigator and patients are unblinded to the dose level of dupilumab 200 mg/matching placebo or dupilumab 100 mg/matching placebo due to different volume (1.14 mL vs. 0.67 mL).

After a screening phase of 4±1 weeks, patients will be centrally randomized using permuted block randomization schedule via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 2:1 randomization ratio for dupilumab and placebo. Randomization will be stratified by ICS dose level (medium, high) at screening, eosinophil count (<0.3 Giga/L versus ≥0.3 Giga/L) at screening and regions (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).

Approximately 402 patients will be randomized in this study with approximately 345 patients having either baseline eosinophil ≥0.15 Giga/L or baseline FeNO ≥20 ppb, and approximately 255 patients having baseline eosinophil ≥0.3 Giga/L. [redacted]

1.2 OBJECTIVES

1.2.1 Primary objectives

- To evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma.

1.2.2 Secondary objectives

- To assess the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab in improving patient reported outcomes (PROs) including health related quality of life (HRQoL).
- To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies
- To evaluate the association between dupilumab treatment and pediatric immune responses to vaccines: any vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza vaccine

1.2.3 Exploratory objectives

- To explore baseline and on-treatment levels of biomarkers for their potential to predict and to associate with a treatment response
- [redacted]
- To evaluate the proportion of patients requiring increased dose of inhaled corticosteroids (ICS) or step up in the second controller medication regimen
- To evaluate the effect of dupilumab on additional PROs

1.3 DETERMINATION OF SAMPLE SIZE

The sample size of this study was based on a comparison between dupilumab versus placebo with regard to the primary endpoint of annualized rate of severe exacerbations over 52 weeks of treatment for the 3 populations of interest: patients with baseline blood eosinophils ≥0.3 Giga/L, patients with baseline blood eosinophils ≥0.15 Giga/L, and Type 2 inflammatory asthma phenotype populations (as defined in Section 2.3.1), with assuming the number of severe exacerbations follows a negative binomial distribution and a randomization ratio of 2:1.

[redacted]

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

To achieve target sample size for each of the populations stated above, at least a total of 402 patients in the overall population (268 for dupilumab and 134 for placebo) need to be randomized assuming approximately 86% of the randomized patients have the Type 2

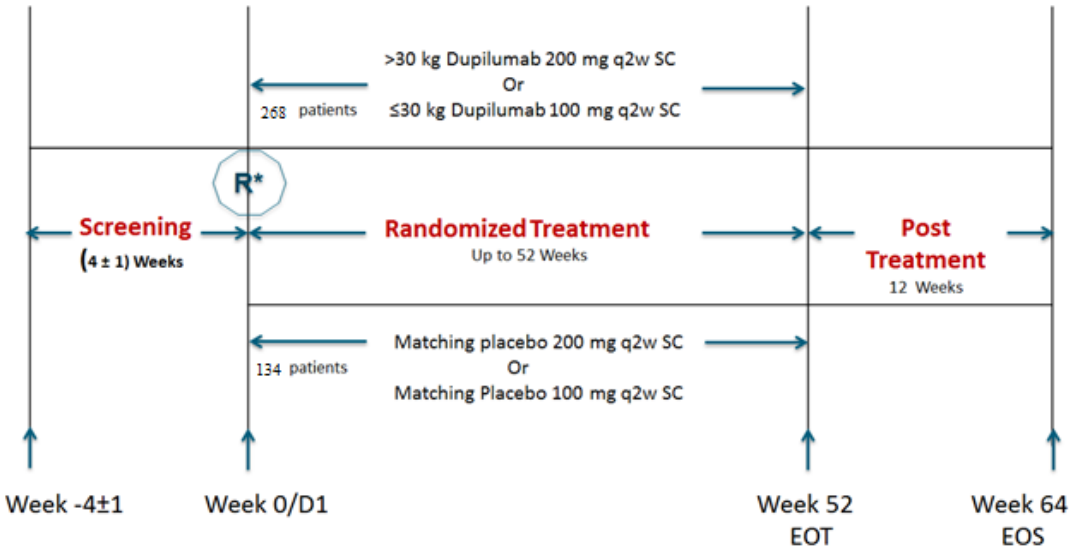
[redacted]

1.4 STUDY PLAN

The clinical trial consists of three periods:

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

1.4.1 Graphical Overview of Study Design



Background medication: medium dose ICS + second controller or high dose ICS alone or + second controller
D: day; EOT: end of treatment; EOS: end of study; ICS: inhaled corticosteroids; q2w: every 2 week; R: randomization; SC: subcutaneous

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) but before the study is unblinded.

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	31-May-2018	[redacted]	The following text: The sample size of this study was based on a comparison between dupilumab versus placebo with regard to the primary endpoints of annualized rate of severe exacerbations at Week 52. Assuming the number of severe exacerbations follows a negative binomial distribution with a dispersion parameter of 1.5, a placebo annualized rate of exacerbations being 1.0, a randomization ratio of 2:1, with 294 randomized patients (196 for dupilumab and 98 for matching placebo group), the study will have approximately 90% power to detect a 50% relative risk reduction (ie, annualized rate of 0.5 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05. This calculation assumes a linear discontinuation rate (20% at 1 year), thus the average exposure duration for patients is 0.9 year. Was replaced with: The sample size of this study was based on a comparison between dupilumab versus placebo with regard to the primary endpoints of annualized rate of severe exacerbations at Week 52. [redacted] This calculation also assumes a linear discontinuation rate (20% at 1 year), thus the average exposure duration for patients is 0.9 year.
3	18-October-2019	[redacted]	The following text was added: The sample size of this study was based on a comparison between dupilumab versus placebo with regard to the primary endpoints of annualized rate of severe exacerbations at Week 52. [redacted]

Amendment Number	Date Approved	Rationale	Description of statistical changes
			[redacted] This calculation also assumes a linear discontinuation rate (20% at 1 year), thus the average exposure duration for patients is 0.9 year. Was replaced by: The sample size of this study was based on a comparison between dupilumab versus placebo with regard to the primary endpoint of annualized rate of severe exacerbations over 52 weeks of treatment for the 3 populations of interest: patients with baseline blood eosinophils ≥0.3 Giga/L, patients with baseline blood eosinophils ≥0.15 Giga/L, and patients with Type 2 inflammatory asthma phenotype (baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb), with assuming the number of severe exacerbations follows a negative binomial distribution and a randomization ratio of 2:1. [redacted]

Amendment Number	Date Approved	Rationale	Description of statistical changes
			[redacted] The sample size calculation assumes a linear discontinuation rate (20% at 1 year), thus the average exposure duration for patients is 0.9 year. The assumed relative risk reductions are based on the results in the QUEST study. To achieve target sample size for each of the population stated above, at least 402 patients in total (268 for dupilumab and 134 for placebo) need to be randomized assuming approximately 86% of the randomized patients have baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb, assuming approximately 81% of the randomized patients have baseline blood eosinophils ≥0.15 Giga/L, and approximately 64% of the randomized patients have baseline blood eosinophils ≥0.3 Giga/L.
3	18-October-2019	[redacted]	The hypothesis testing on the primary endpoint of annualized severe exacerbation rate will be controlled with a two-sided Type I error of 0.05. Only nominal p-values are provided for secondary endpoints. Was replaced by: The hypothesis testing on the primary endpoint of annualized severe exacerbation rate will be controlled with a two-sided Type I error of 0.05 by incorporating a sequential testing procedure as below: For US and US reference countries: 1st: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period in patients with baseline blood eosinophils ≥0.3 Giga/L. 2nd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period in patients with baseline blood eosinophils ≥0.15 Giga/L. 3rd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on patients withtype 2 inflammatory asthma phenotype (baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb). For EU and EU reference countries: 1st: Annualized rate of severe exacerbation events during the 52-week placebo-controlled

Amendment Number	Date Approved	Rationale	Description of statistical changes
		[redacted]	treatment period based on patients with Type 2 inflammatory asthma phenotype (baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb). 2nd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period in patients with baseline blood eosinophils ≥0.15 Giga/L population. 3rd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period in patients with baseline blood eosinophils ≥0.3 Giga/L population. Multiplicity control for any secondary endpoints if considered will be specified in the SAP. Otherwise, nominal p-values will be provided.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This Statistical Analysis Plan (SAP) for study EFC14153 is based on the protocol dated 18 October 2019. This section summarizes major changes to the statistical analysis features in the SAP.

Table 2 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	23-OCT-2019	Not Applicable	Original version
2.0	Current version	Elaboration of Estimand	Clarification per FDA's recommendation.
		Analysis of systemic corticosteroid exposure	To evaluate efficacy of Dupilumab in reducing exposure to systemic corticosteroids
		Addition of the analysis of the annualized rate of loss of asthma control (LOAC)	To evaluate efficacy of Dupilumab in reducing Loss of Asthma Control (LOAC) events
		COVID19 pandemic relevant analysis:	To evaluate the impact of COVID19 pandemic on study conduct.
		Subgroup analysis, treatment exposure adjusted analysis for key adverse event endpoints	To further evaluate the safety of Dupilumab in subgroups of interest; To evaluate the safety of Dupilumab taking the duration of exposure into consideration.
		For analysis of Pre-bronchodilator % predicted FEV1, covariates of age, sex, and baseline height are removed from the model	The effect of age, sex, and height on the predicted FEV1 have already been accounted for in the predicted FEV1 calculation equation.

SAP Version	Approval Date	Changes	Rationale
		Add treatment-by-biomarker analysis for annualized severe exacerbation rate during the 52 week treatment period to explore FeNO's independent predictability of Dupilumab's treatment effect	Per FDA recommendation.
		Add treatment-by-biomarker analysis for Pre-bronchodilator % predicted FEV1 change from baseline at Week to explore FeNO's independent predictability of Dupilumab's treatment effect	Per FDA recommendation.
		Add quadrant analysis using different FeNO cutoff values	Per FDA recommendation.
		Remove subgroup analysis by baseline age group (6-8, 9-11 years)	Not a meaningful subgroup analysis.
		Remove subgroup analysis by Elevated IgE (Yes/No)	This is already a subgroup to evaluate the baseline IgE level, ie, Total IgE ((<100 IU/mL, ≥100 IU/mL)

Table 3 - Changes to the planned analysis approach in the protocol

SAP Version	Approval Date	Planned analysis in the protocol	Analysis in the statistical analysis plan	Rationale
2.0	Current version	When performing the key secondary endpoint analysis in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.15 Giga/L, and full ITT populations, the model will include change from baseline in % predicted FEV1 values up to Week 12 as response variables, and treatment, age, baseline weight, region, sex, ethnicity, baseline height, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates.	The model covariates are updated by removing age, sex, and baseline height: When performing the key secondary endpoint analysis in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.15 Giga/L, and full ITT populations, the model will include change from baseline in % predicted FEV1 values up to Week 12 as response variables, and treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates.	The effect of age, sex, and height on the predicted FEV1 have already been accounted in the predicted FEV1 calculation equation.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value of efficacy parameters is defined as the last available value up to randomization but prior to the first dose of study medication unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of investigational medicinal product (IMP). The baseline value of the other parameters is defined as the last available value prior to the first dose of IMP if the patient is treated, or the last available value up to randomization if the patient is not exposed to IMP.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the post-baseline summary statistics in the safety and efficacy sections (Section 2.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are

- Gender (Male, Female)
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Other)
- Age in years
- Ethnicity (Hispanic, non-Hispanic)
- 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)
- Weight in kg (quantitative and qualitative variable: $\leq$30, >30 kg)
- BMI in kg/m^2 (quantitative and qualitative variable: <20, $\geq$20 kg/m^2)

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 lock.

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)
- Nasal polyposis history (Yes, Ongoing condition)
- Chronic rhinitis and sinusitis with nasal polyposis
- Chronic rhinitis and sinusitis without nasal polyposis
- Eosinophilic esophagitis history (Yes, Ongoing condition)
- Food allergy history (Yes, Ongoing condition)
- Hives history (Yes, Ongoing condition)

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

A patient is considered to have elevated IgE if he/she has baseline total IgE ≥100 IU/mL and at least one aeroantigen specific IgE is positive (≥0.35 IU/mL).

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by treatment group separately:

- ICS dose level (medium, high as defined in Appendix C)
- Age at asthma onset
- Time since first diagnosis of asthma (years)
- Time since last severe asthma exacerbation (months)
- Number of severe asthma exacerbation experienced within 1 year before Visit 1 (quantitative variable 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 ppb and ≤35 ppb, >35)
- Baseline serum total IgE (IU/mL)
- Baseline serum TARC (pg/mL)
- Baseline spirometry data including pre-bronchodilator FEV1 (L), percent predicted FEV1, post-bronchodilator FEV1 (L) and FEV1 reversibility (%).
- AM and PM PEF (L/min)
- AM and PM symptom scores
- Number of nocturnal awakenings/day
- ACQ-5 score (ACQ-IA)
- ACQ-7 score (ACQ-IA)
- PAQLQ-IA global score
- Number of inhalations of salbutamol/albuterol and levosalbutamol/levabuterol per day
- Hypersensitivity to aspirin/NSAID (Yes, Ongoing condition)

Severe asthma exacerbation prior to the study is defined as any of the following events:

a) Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once.
b) Hospitalization or an emergency/urgent medical care visit for worsening asthma.

The aforementioned baseline values for the daily efficacy assessments are defined in Section 2.1.3.4. Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

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

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

- Prior medications are those the patient used prior to first IMP injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the first administration of IMP to the last administration of IMP + 98 days or till rollover to the LTS14424 study. A given medication can be classified as a prior medication, concomitant medication, and posttreatment medication at the same time.
- Posttreatment medications are those the patient took in the period from the last administration of IMP + 99 days to the end of the study

2.1.2.1 Inhaled corticosteroid in combination with one or two other controllers

On a daily basis throughout the study, the patient(s)/parent(s)/caregiver(s)/legal guardian(s) uses an electronic diary to record daily use of ICS in combination or concurrently with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor, but the sponsor will reimburse investigators for patients' use of controller drugs in the study to ensure all patients have access to their controllers.

Prior to screening, patients must be on a stable background therapy of a medium dose of ICS (total daily dose >200 mcg to 400 mcg of fluticasone propionate (DPI) or equipotent ICS daily dosage) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, etc.) to high dose of ICS (total daily dose >400 mcg of fluticasone propionate (DPI) or equipotent ICS daily dosage) alone or in combination with a second controller medication for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are **not** allowed to participate in this study. If patients take two different ICS, the total daily dose of ICS should be calculated to evaluate the eligibility criteria on daily dose of ICS which will be still considered as one controller. Please refer to medium and high dose of ICS in Appendix C. A list of recognized controller medications is provided in Appendix B and the conversion Table 5. Number of controllers taken by each patient will be counted by therapeutic drug class. All drugs in a therapeutic class will be only counted once.

During the randomized treatment period, patients will continue to take their controller medication(s) used during the screening period. The dose and regimen should not be changed unless being stepped up as instructed by the protocol after at least two severe asthma exacerbation events. Other change such as a transient increase in dose of ICS in addition to other rescue medication will be allowed to treat acute symptoms of asthma as per investigator's guidance.

Upon completing the randomized treatment period, patients not continuing with the long-term, open-label extension study will proceed to be treated with the controller medication regimen and dose used during the randomized treatment period, which could be adjusted based on the medical judgment of the Investigator regarding of the patients' asthma control status.

2.1.2.2 Reliever medication

The reliever medication (ie, albuterol/salbutamol or levalbuterol/levosalbutamol) will not be dispensed or supplied by the Sponsor. All other reliever medications other than albuterol/salbutamol or levalbuterol/levosalbutamol should be avoided.

Patient(s)/parent(s)/caregiver(s)/legal guardian(s) may administer albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication by MDI as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

Salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use recorded in the electronic diary will be converted to number of puffs as shown on the following table:

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 daily = 7.5 mg ->12 puffs.

Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
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 daily = 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

2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint for this study is the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period.

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

- Use of systemic corticosteroids for ≥3 days; or

- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids

Two events will be considered as different if the interval between their start dates is equal or greater than 28 days.

The annualized rate of severe exacerbation events during the 52-week treatment period is defined as the number of severe exacerbation events with onset during the 52-week treatment period per patient-year. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and their additional off-treatment severe exacerbation events up to Visit 28(Week 52) will be included.

2.1.3.2 Secondary efficacy endpoint(s)

The key secondary endpoint of this study is the change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.

The other secondary efficacy endpoints include:

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

LOAC event during the study is defined as any of the following:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days or
- Increase in ICS dose ≥4 times than the dose at Visit 2 or
- A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The treatment period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to randomization (Day 1); or
- Severe exacerbation event

Two events will be considered as different if the interval between their start dates is equal or greater than 28 days.

If a patient has an event during the 52-week treatment period, regardless the patient is on the study treatment or discontinues the study treatment but remains in the study, the time to first severe exacerbation event/first LOAC event is defined as (onset date of the first severe exacerbation/LOAC event – randomization date +1).

If a patient has no severe exacerbation event/LOAC event during the study up to Visit 28/Week 52, then the patient will be considered as free of event till the date of visit at Visit 28/Week 52 or the last contact date, whichever happens earlier.

2.1.3.3 Disease-specific Efficacy Measures

2.1.3.3.1 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with the ATS/ ERS guidelines (1). Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable and/or acceptable maneuvers, an explanation should be recorded.

For pre-bronchodilator measured parameters, including FEV1, peak expiratory flow (PEF), FVC and FEF 25-75%, will be assessed at Visit 1 (Screening), Visit 2 (randomization), and every subsequent visit. Reversibility/Post-bronchodilator FEV1

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

Post-bronchodilator FEV1 is assessed at Visit 1 (Screening), Visit 2 (randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 14 (Week 24), Visit 20 (Week 36), Visit 28 (Week 52/EOT), and Visit 31 (Week 64/EOS).

2.1.3.4 Disease-specific, Daily Efficacy Assessments

2.1.3.4.1 Electronic Diary/PEF meter

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

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

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

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

Baseline AM PEF will be the mean AM measurement recorded for the 7 days prior to the first dose of investigational product, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to the first dose of investigational product. Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1. There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available. In case less than 4 days' measurement is available during the 7 days prior to randomization, the baseline AM/PM PEF is the mean of the 4 AM/PM PEF prior to and closest to randomization during the whole screening period. Calculation of periodical average of post-baseline AM/PM PEF is specified in Section 2.5.2.

2.1.3.4.2 Asthma Symptom Numerical Rating Scale (NRS) Score

Parent(s)/caregiver(s)/legal guardian(s) will record overall symptom scores in an electronic diary/PEF meter twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Symptoms experienced during the night will be recorded upon arising (AM symptom score). Baseline symptom scores will be the mean AM and mean PM scores recorded for the 7 days prior to randomization. The baseline AM/PM symptom score will be computed following the same algorithm used for baseline AM/PM PEF. Scores range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms. There is no global score, just an AM score and a PM score. A Minimal clinically important difference (MCID) of 0.35 is being used (2).

2.1.3.4.3 Use of Reliever Medicine

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

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The baseline reliever med use will be calculated as follows: The mean of reliever puffs taken in each of the 7 diary days (minimum 4 diary days) prior to randomization, including the diary day that ends with the morning diary completed on the randomization day. A diary day cannot be included in the calculation if it is not complete, meaning if an evening or morning diary is missing for that diary day. Out of the 7 diary days, if less than 4 are incomplete, the baseline reliever use is the mean of reliever puffs in each of the complete dairy days. If 4 or more diary days are incomplete, the baseline reliever use is the mean of reliever puffs taken in the closest 4 diary days with complete reliever use information prior to randomization. Calculation of periodical average of post-baseline use of reliever puffs is specified in Section 2.5.2.

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

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

2.1.3.5.1 Asthma Control Questionnaire–Interviewer Administered

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

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

The Asthma Control Questionnaire–Interviewer Administered, 7-question version (ACQ-7-IA) has 7 questions, with the first 5 items of ACQ-7 (ACQ-5-IA score) addressing the most common asthma symptoms: 1) frequency in past week awoken by asthma during the night, 2) severity of asthma symptoms in the morning, 3) limitation of daily activities due to asthma, 4) shortness of breath due to asthma and 5) wheeze. And with 2 questions on overall reliever medication use 6) short-acting bronchodilator use, and – after spirometry assessment – current asthma status: 7) predicted bronchodilator use of FEV1 (pre-bronchodilator use, % and % predicted use).

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

After spirometry assessment, patients and/or parent(s)/caregiver(s)/legal guardian(s) are asked to recall how their asthma and/or their child's asthma Clinic staff scores the % predicted FEV1 on a 7-point scale (see Appendix E).

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

A global score is calculated: the questions are equally weighted and the ACQ-7-IA score is the mean of the 7 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-7-IA, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the MCID defined by the developer.

Based on the manual of ACQ (3), any more than one missing value is not acceptable. 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.

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

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

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

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

Missing scores will be handled in the same way as for ACQ-7 score.

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

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

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

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

- Symptoms (10 items: 4, 6, 8, 10, 12, 14, 16, 18, 20, and 23)
- Activity limitation (5 items: 1, 2, 3, 19, and 22)
- Emotional function (8 items: 5, 7, 9, 11, 13, 15, 17, and 21)

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

To have a valid overall score, it is not acceptable to have more than three missing responses or more than one missing response per domain. For the symptoms domain score, only one missing value is acceptable. For the activity limitation and emotional function domain scores, no missing value is acceptable. For responses with more than acceptable amount of missing value(s), the overall or the domain score will be considered as missing. For responses with amount of missing value(s) within accept range, the missing score will be interpolated using the previous completions of the questionnaire following the similar algorithm used for ACQ.

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

2.1.3.5.3 Paediatric Asthma Caregiver's Quality of Life Questionnaire

The PACQLQ was designed as a 13-item questionnaire for the parent(s)/caregiver(s)/legal guardian(s) of children ≥7 years old and <12 years of age at Randomization Visit 2, and each item is rated on a 7-point scales ranging from 1 to 7, higher scores indicating better quality of life, in order to capture the impact of the child's asthma on their quality of life and which aspects were most troublesome to the parent(s)/caregiver(s)/legal guardian(s) during the time prior to this assessment (see Appendix J).

The PACQLQ has 2 domains. The domains and the number of items in each domain are as follows:

- Activity limitation (4 items: 2, 4, 6, and 8)
- Emotional function (8 items: 1, 3, 5, 7, 9, 10, 11, 12, and 13)

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

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

PRQLQ-IA (see Appendix I) is an interviewer-administered questionnaire developed to measure HRQoL signs and symptoms that are most problematic in children ≥6 years to <12 years old, as a result of perennial or seasonal allergic rhinitis. The 23-item PRQLQ-IA responses are based on 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Higher scores indicated more health-related quality of life impairment (lower scores better). The instrument takes approximately 7 minutes to complete. The minimally important difference (MID) of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (4).

The PRQLQ-IA has 5 domains. The domains and the number of items in each domain are as follows:

- Activity limitations (4 items: 16, 21, 22, and 23)
- Eye symptoms (4 items: 5, 6, 7, and 8)
- Nose symptoms (4 items: 1, 2, 3, and 4)
- Practical problems (5 items: 9, 10, 11, 12, and 20)
- Other symptoms (6 items: 13, 14, 15, 17, 18, and 19)

The overall score is calculated as the mean score of all items. And the score for each domain is calculated as the mean score of the items in each of the domains. No interpolation will be performed for missing scores.

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

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

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

2.1.4 Safety endpoints

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 exam.

Observation period

The observation period will be divided into 4 epochs:

The **screening** epoch is defined as the time from the signed informed consent date up to the first IMP administration.

The **treatment** epoch is defined as the time from the first administration of the IMP to the last administration of IMP + 14 days or till rollover to the LTS14424 study whichever is earlier.

The **residual treatment** epoch is defined as the time from the last administration of the IMP + 15 days to the last administration of IMP + 98 days or till rollover to the LTS14424 study whichever is earlier.

The treatment-emergent adverse event period will consist of the **treatment** and **residual treatment** epochs.

The **post-treatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the end of the study (defined as last protocol-planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of IMP
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period

All adverse events (including serious adverse events and adverse events with pre-specified monitoring/special interests) 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 OR specify version if already known from project specifics.

Adverse events of special interests (AESI) and other selected AE groupings will be searched based on the criteria in 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)	SMQ hypersensitivity (20000214) narrow search) and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	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 (Intensity='Severe' or Serious='Y')
Parasitic infection	The Infection Type 'Parasitic' was checked on eCRF page "Infection Defined as AESI Complementary Form"
Opportunistic infection	The Infection Type 'Opportunistic' was checked on eCRF page "Infection Defined as AESI Complementary Form"
Potentially drug-related liver 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 NIMP	The question "Is the event a Symptomatic Overdose with NIMP?" is answered "Yes" on the eCRF page "Adverse Event".

AE Grouping	Criteria
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)
Conjunctivitis (narrow company medical query)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis)
Conjunctivitis (broad company medical query)	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'

In addition, AESIs reported by the investigator in CRF will be summarized separately.

2.1.4.2 Deaths

The deaths observation periods are per the observation periods defined above

- Death on-study: deaths occurring during the on-study observation period
- 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 international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 8 (Week 12), Visit 14 (Week 24), Visit 20 (Week 36), Visit 28 (Week 52), Visit 31 (Week 64) and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, red blood cell count, platelet count
  - **White blood cells**: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism**: glucose, total cholesterol, total protein, creatine phosphokinase
  - **Electrolytes**: sodium, potassium, chloride, bicarbonate
  - **Renal function**: creatinine, blood urea nitrogen, uric acid

- **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), albumin
  - **Hepatitis screen**: Hepatitis virus tests will be performed at Screening Visit 1, including hepatitis B surface antigen (HBs Ag), hepatitis B Surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab). In case of results showing HBs Ag (negative), HBs Ab (negative) and HBc Ab (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the investigator believes the patient is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the investigator believes the patient is a false positive
- **HIV screen**: anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1
- **Anti-nuclear antibody (ANA)** will be tested at Visit 1

- Serum immunoglobulins: quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and IgA will be tested at Visit 2, Visit 14 (Week 24), and Visit 28 (Week 52)

Urine samples will be collected as follows:

- **Urinalysis** (limited to Visit 1(Week -4±1), Visit 8 (Week 12), Visit 14 (Week 24), Visit 20 (Week 36), Visit 28 (Week 52), and Visit 31 (Week 64)): Urine dipstick analysis specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory
- **Pregnancy test:** A urine pregnancy test will be performed at Screening (Visit 1) in female patients of childbearing potential who have commenced menstruating, and a urine dipstick pregnancy test will be performed at Visit 2 prior to randomization, Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 10 (Week 16), Visit 12 (Week 20), Visit 14 (Week 24), Visit 16 (Week 28), Visit 18 (Week 32), Visit 20 (Week 36), Visit 22 (Week 40), Visit 24 (Week 44), Visit 26 (Week 48), Visit 28 (Week 52), and Visit 31 (Week 64). Those female patients who commence initial menstruation during the study will be similarly monitored with urine dipstick pregnancy tests and contraception consulting for the duration of the study

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), and will include height (cm) and body weight (kg), measured at the Screening and Randomization Visits (Visits 1 and 2) and every subsequent visit. Height will be measured with a proper stadiometer at every visit. Stadiometer measurements will

be made without patient wearing shoes. Vital signs will be measured at clinic visits, in sitting position, using the same arm at each visit, and prior to administration of investigational product.

2.1.4.5 Electrocardiogram variables

One recording of a standard 12-lead electrocardiogram (ECG) will be performed at Screening, Visit 28 (Week 52/EOT), and Visit 31 (Week 64/EOS). ECGs were recorded automatically by the device at the Investigator site.

2.1.4.6 Physical Examination

Physical examinations will be performed at Screening, Visit 14 (Week 24), Visit 28 (Week 52/EOT), and Visit 31 (Week 64/EOS) and will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities, including menstruation status. All deviations from normal will be recorded, including those attributable to the patient's disease.

2.1.5 Pharmacokinetic variables

Predose blood samples will be collected for determination of functional dupilumab concentration in serum on Visit 2 (Week 0), Visit 5 (Week 6), Visit 8(Week 12), Visit 14 (Week 24), Visit 28 (Week 52) and Visit 31 (Week 64).

2.1.6 Anti-drug antibody (ADA) variables

Anti-dupilumab antibody (ADA) (including neutralizing antibodies) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Visit 8(Week 12), Visit 14 (Week 24), Visit 28 (Week 52) and Visit 31 (Week 64) will be provided. Patients who discontinue early from treatment or patients who choose not to participate in the LTS study visit may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall clinical presentation at that time.

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

a) 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.

b) Indeterminate Response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay

c) 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 values (Titer value category)

- Low (Titer <1000)
- 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.

2.1.7 Pharmacodynamic/genomics endpoints

Serum total IgE, antigen-specific IgE, antigen-specific IgG4 panel, and Thymus and Activation-Regulated Chemokine (TARC) will all be assayed at Visit 2(Week 0), (TARC only Visit 8 (Week 12)), Visit 14 (Week 28), and EOT (Week 52).

Fractional exhaled nitric oxide (FeNO) will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 3 (Week 2),Visit 4 (Week 4), Visit 5 (Week 6) , Visit 6 (Week 8) , Visit 7 (Week 10), Visit 8 (Week 12), Visit 10 (Week 16), Visit 12 (Week 20), Visit 14 (Week 24), Visit 16 (Week 28), Visit 18 (Week 32) , Visit 20 (Week 36) , Visit 22 (Week 40) , Visit 24 (Week 44), Visit 26 (Week 48), Visit 28 (Week 52), Visit 29 (Week 56), Visit 30(Week 60), Visit 31(Week 64).

Blood eosinophil counts from hematology assays will be collected at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 8 (Week 12), Visit 14 (Week 24), Visit 20 (Week 36), Visit 28 (Week 52), Visit 31(Week 64) and early termination.

[redacted]

2.1.8 Humoral immune response to vaccines

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

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

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

2.1.9 Health economic endpoints

The Health Care Resource Utilization (HCRU) questionnaire (questions on use of reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, school days' loss, etc), as integrated part of the e-CRF, will be administered at Visit 2, Visit 8, Visit 14, Visit 20, Visit 26, Visit 28 and Visit 31, and will additionally be used to asses HCRU in the event of any asthma exacerbation: severe asthma exacerbation event or evidence of LOAC (for detailed definitions see Section 2.1.3.1).

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for patient study status.

Screened patients are defined as any patients that have signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

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

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who did not complete the 52-week treatment as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Patients who withdraw from study prior to Week 52
- Patients who withdraw from study prior to Week 52 by main reason for study discontinuation.
- Patients who withdraw from study
- Patients who rolled over to the LTS14424 study
- Patients who withdraw from study by main reason for study discontinuation
- Death at last study contact

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator. Reasons for treatment discontinuation, including due to the COVID-19 pandemic, will be supplied in tables giving numbers and percentages by treatment group. This summary will be provided by treatment group and may also be further subgrouped by region/stratum as applicable.

All critical or major deviations will be summarized in tables giving numbers and percentages of deviations by deviation category for each treatment group. Critical or major deviations that are related to the COVID-19 pandemic will be summarized in a similar manner.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

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

All randomization and 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 randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Stratification error
Patient switched to another site

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population, but will be included in the safety population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

2.3.1 Efficacy populations

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

Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb.

Baseline blood eosinophils ≥0.3 Giga/L population is defined as the randomized patients with baseline blood eosinophils ≥0.3 Giga/L.

Baseline blood eosinophils ≥0.15 Giga/L population is defined as the randomized patients with baseline blood eosinophils ≥0.15 Giga/L.

Baseline FeNO ≥20 ppb population is defined as the randomized patients with baseline FeNO ≥20 ppb.

All efficacy endpoints will be analyzed based on both the population with a Type 2 inflammatory asthma phenotype and the population with baseline blood eosinophils ≥0.3 Giga/L. For selected efficacy endpoints, the analysis will be done for all four efficacy populations. For detailed analysis plan, refer to Appendix M. For the analysis of primary efficacy endpoint, the testing hierarchy will start with the patients with baseline blood eosinophils ≥0.3 Giga/L population for the US and US reference countries; For EU and EU reference countries, the testing hierarchy will start with the Type 2 inflammatory asthma phenotype population (patients with baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb). For more details about multiplicity consideration, refer to Section 2.4.4.4.

Patients will be analyzed in the treatment group to which they are randomized.

For PRO endpoints which are only valid on specific subpopulations of patients, only patients within the subpopulation will be analyzed according to their randomized treatment group. Such subpopulations include patients of age ≥7 years old at randomization for PACQLQ(S) and patients with history of allergic rhinitis for PRQLQ-IA.

If a patient is unblinded during the study, only data obtained before the unblinding will be included in the efficacy analyses.

2.3.2 Safety population

The safety population is defined as:

- All patients who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment patients actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.
- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be dupilumab group.
- If a patient is unblinded during the study, all safety data from the patient regardless of before or after unblinding will be included in the safety analyses according to the treatment patients actually received before the unblinding.

All analyses will be provided by treatment regimens as Dupilumab vs placebo. No planned analysis based on the subcategory of dose level will be provided.

2.3.3 Population for pharmacokinetics, immunogenicity, and pharmacodynamics analyses

The PK population will consist of all patients in the safety population with at least one non-missing serum concentration data. Patients will be analyzed according to the treatment actually received.

The ADA population will consist of all patients in the safety population who had at least one non-missing ADA results (either 'ADA negative' or 'ADA positive') after first dose of the study treatment. Patients will be analyzed according to the treatment actually received.

Biomarkers will be analyzed in the exposed population, consisting of patients in the safety population.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

The demographics, baseline characteristics and medical history will be presented for the population with Type 2 inflammatory asthma phenotype, population with baseline blood eosinophils ≥0.3 Giga/L, population with baseline blood eosinophils ≥0.15 Giga/L, population with baseline FeNO ≥20 ppb and full ITT population.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of full ITT population in the primary analysis for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical and surgical history will be summarized by treatment group and 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 incidence across treatment groups. Atopic medical history will be summarized separately.

No statistical testing on demographic and baseline characteristic data will be performed. P-values will not be calculated.

No specific description of either efficacy or safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each efficacy or safety analysis.

2.4.2 Prior or concomitant medications

The general prior and concomitant medications, and controller medications will be presented for the population with Type 2 inflammatory asthma phenotype, and population with baseline blood eosinophils ≥0.3 Giga/L, and full ITT population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) 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 will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medication received during first IMP to last IMP +14 days and concomitant medication received during first IMP to last IMP +98 days will be summarized separately. The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the dupilumab group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, inhaled corticosteroid in combination with other controllers and reliever medications will be summarized separately. Number of patients who have their controller medications permanently stepped-up during the study according to protocol will also be summarized and the time to first permanent step-up will also be summarized with descriptive statistics.

2.4.2.1 ICS in combination with other controllers

ICS and other asthma controller medications will be identified as the medications reported on the 'Prescribed Asthma Controller Medications' eCRF page.

Prior asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the overall treatment group.

Concomitant asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the dupilumab group.

The total daily dose of ICS in asthma controller medication at randomization will be classified as medium-dose or high-dose according to Appendix C. If a patient takes more than one medication containing ICS, the ICS dose of different products will be standardized according to equivalent dose specified in Table 5. The equivalent dose is determined based on the thresholds in Appendix C. After conversion, the total daily dose for inhaled corticosteroid will be calculated and classified as medium or high dose.

Table 5 - Equivalent dose for inhaled corticosteroids for children (≥6-11 years)

Inhaled corticosteroid	Conversion Factor to Fluticasone propionate (DPI)		
	Low	Medium	High
BECLOMETASONE DIPROPIONATE (CFC)	1	1	1
BECLOMETASONE DIPROPIONATE (HFA)	2	2	2
BUDESONIDE (DPI)	1	1	1
BUDESONIDE (HFA)	1	1	1
BUDESONIDE (nebules)	0.4	0.4	0.4
CICLESONIDE (HFA)	2.5	2.5	2.5
FLUNISOLIDE (HFA)	1.25	1.25	1.25
FLUTICASONE PROPIONATE(HFA)	1	(200+x*2)/3	0.8
MOMETASONE FUROATE	10/11	10/11	10/11
TRIAMCINOLONE ACETONIDE	0.25	-200+x/2	1/3

HFA=hydrofluoroalkane, DPI= Dry Powder Inhaler
x: the actual dose level of the corresponding inhaled corticosteroid
Example:
1): when the dose of FP(HFA) is 500 mcg, the corresponding dose of FP(DPI) will be 200/3 + 500*2/3=400 mcg.
2): when the dose of TRIAMCINOLONE ACETONIDE is 1200 mcg, the corresponding dose of FP(DPI) will be (-200 + 1200/2) = 400 mcg.

2.4.2.1.1 Compliance

During the study, the daily intake of each prescribed asthma controller medication will be recorded on the electronic diary every evening. Compliance for the controller medications with ICS component and overall compliance to all prescribed controller medications will be calculated for each patient. For each day, a patient is considered as compliant to the prescribed controller medication with ICS component if the actual dose of each controller medication with ICS component is same as or greater than the prescribed dose. Similarly, a patient is considered as compliant to all controller medication if the actual dose of each controller medication is same as or greater than the prescribed dose. Note that if the prescribed dose has been stepped-up based on protocol specified criteria, the compliance post dose increase will be calculated based on the updated prescribed controller medication dose.

Compliance for controller medication(s) with ICS component is defined as the **number of days** when the patient is compliant to the prescribed controller medication(s) with ICS component divided by the number of days the patient stays in the treatment period (from first dose to last dose + 14 days). **Overall controller medication(s) compliance** is defined as the **number of days** when the patient is compliant to all prescribed controller medication divided by the number of days the patient stays in the treatment period. Since it is required by the protocol that a 12 hours washout is required before spirometry tests, the calculation of overall controller medication compliance for patients with prescribed LABA will exclude the data from the spirometry test days.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment for Safety population, population with Type 2 inflammatory asthma phenotype, and population with baseline blood eosinophils ≥0.3 Giga/L (Section 2.3.1).

2.4.3.1 Extent of investigational medicinal product exposure

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

Duration of IMP exposure is defined as last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations (see Section 2.5.3 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, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

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.

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 defined in Section 2.1.4.

Above-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a higher dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Under-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a lower dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Treatment compliance 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. In addition, numbers and percentages of patients with at least 1 above-planned dose administration will also be provided, as well as numbers and percentages of patients with 0, (0, 20%], and >20% underplanned dose administrations.

Cases of overdose of IMP (defined as at least twice the intended dose during an interval of less than 11 days) will be summarized by numbers and percentages of patients with at least 1 over dose by treatment group. Different overdose intense by dose interval, ie, 1 day, 2 days, etc., will also be summarized. More generally, dosing irregularities will be listed as being described in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

All efficacy endpoints will be analyzed based on both the population with Type 2 inflammatory asthma phenotype and patients with baseline blood eosinophils ≥0.3 Giga/L populations.

Some selected efficacy endpoints will be also analyzed for full ITT population, as well as the Patients with baseline blood eosinophils ≥0.15 Giga/L population, and the patients with baseline FeNO ≥20 ppb. For more details, refer to Appendix M.

2.4.4.1 Analysis of primary efficacy endpoint(s)

Primary statistical model and adjustment for covariates

The primary analysis of the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period is to assess the efficacy of dupilumab. In this primary approach, for the patients who prematurely discontinue treatment, their off-treatment measurements up to Week 52 or the study withdrawal whichever comes earlier will be included for the analysis. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits. If a patient stays in study until the end of the 52-week treatment period, all severe exacerbation events that happen up to Visit 28 will be included in the primary analysis, regardless whether the patient is on-treatment or not, and the observation duration is defined as from randomization to Visit 28. If a patient withdraws from the study prior to the end of the 52-week treatment period, all observed severe exacerbation events up to the last contact date will be included in the analysis, and the observation duration is defined as from randomization to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation and up to Week 52. This estimand compares

the rate of severe exacerbation for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo.

The annualized rate of severe exacerbation events as defined in Section 2.1.3.1 will be analyzed using a negative binomial regression model. The analysis for the annualized severe exacerbation rate will be performed in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.3 Giga/L, baseline blood eosinophils ≥0.15 Giga/L, baseline FeNO ≥20 ppb and full ITT populations.

When performing the analysis for the annualized severe exacerbation rate in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.15 Giga/L or full ITT population, the model will include the total number of events that occur during the observation period defined above as the response variable, with the treatment arm, age, baseline weight (≤30kg, >30kg), region, baseline eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of severe exacerbation events within 1 year prior to the study as covariates. When performing the primary endpoint analysis in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates. When performing the primary endpoint analysis in the baseline FeNO ≥20 ppb population, the baseline FeNO level will be removed from the model covariates.

Treatment groups, baseline weight, region, baseline eosinophil level, baseline FeNO level, and baseline ICS dose level will be treated as categorical variables. Age and number of severe exacerbation events within 1 year prior to the study will be treated as continuous variables. Log transformed observation duration will be the offset variable. In the case where the negative binomial regression model may not converge, a categorical variable for the number of severe exacerbation events within 1 year prior to study (1, 2, more than 2) will replace the corresponding continuous variable in the model. A similar approach will also be applied to other analyses for severe exacerbation endpoint if applicable.

Comparisons of the annualized event rates between dupilumab and placebo will be derived by testing dupilumab group versus placebo. The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals will be derived from the negative binominal model.

Sample SAS code can be found below:

```
proc glimmix data=event;
  class weight eosblgpn1 fenoblgrn ics trt01pn cntygr1n;
  model numevents=trt01pn age weight eosblgpn1 fenoblgrn ics cntygr1n asmanum
        /offset=logdur dist=negbin link=log solution;
run;
```

If the model fails to achieve convergence, different estimation algorithms will be applied following the order: default→LAPLACE→QUAD; if the non-convergence issue still exists, other handling may be considered. The adjustment will be added to the footnote of the corresponding outputs.

The gross estimated annualized event rates will also be presented by each treatment group. Mean cumulative function plot will be provided for descriptive purpose.

The primary estimand for the primary endpoint used in the aforementioned statistical analysis method is the treatment policy estimand. Details about the intercurrent events strategy and missing data handling in this primary estimand are presented in as below Table 6.

Table 6 - Protocol amendment statistical changes

Endpoint Category (estimand)	Estimand			
	Endpoint	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary**
Primary objective: The primary objective is to evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma				
Primary endpoint[a] (treatment policy)	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period.	Patients with Type 2 inflammatory asthma phenotype for EU and EU reference countries Patients with baseline blood eosinophils ≥ 0.3 Giga/L for US and US reference countries	The intercurrent events will be handled as follows: Discontinuation of study treatment before Week 52: Off-study treatment data up to Week 52 will be included in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: Discontinuing the study follow-up before Week 52: Analyses will be censored at the time of study discontinuation.	In patients with Type 2 inflammatory asthma phenotype, the primary endpoint will be analyzed using negative binomial regression model, with the treatment group, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of severe asthma exacerbation events prior to the study as covariates, and log-transformed exposure will be used as the offset. The adjusted annualized severe exacerbation rate of each arm, relative risk between treatment and placebo arms, 95% confidence interval and P value will be reported. In patients with baseline blood eosinophils ≥0.3 Giga/L, the analysis will remain same as above except that the covariate of baseline eosinophil level will be removed.

Estimand of clinical efficacy of dupilumab versus placebo with treatment adherence

An analysis to assess the efficacy of dupilumab if patients adhere to the treatment as directed is also specified. In this approach, the severe exacerbation events reported after the premature treatment discontinuation will be excluded from the analysis. Any exacerbation obtained after the first permanent stepping-up of background asthma medication (following at least two severe exacerbation per protocol) will also be excluded from the analysis. The supportive analysis for the primary endpoint will be performed in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations. A negative binomial model with the same set of covariates as specified for the primary endpoint analysis in each of the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations will be used. This model will include severe exacerbation events occurring during the treatment epoch before any permanent treatment regimen change (including permanent IMP discontinuation and/or step-up of controller medication) as the response variable and the log transformed duration of the treatment epoch or from randomization to first permanent treatment regimen change whichever is shorter will be the offset variable. This approach defines the estimand to be the efficacy of dupilumab with treatment adherence.

Handling of missing data

If patients withdraw from the study before Visit 28 (Week 52), severe exacerbation events that may occur after study discontinuation will not be observed. These patients are considered as patients with missing data for the severe exacerbation endpoint. Number of patients with missing data, reasons and timing for patient withdrawals will be summarized by treatment groups. Summary statistics of selected demographic and baseline disease characteristics will be provided for patients with missing data and patients with complete data separately. Graphical summaries of the dropout patterns such as Kaplan-Meier plots of time to study discontinuation with different reasons of discontinuation may be provided to examine if there is any different missing pattern between treatment groups. In addition, the following sensitivity analyses will be conducted to assess the robustness of the conclusion drawn based on the main model for the primary analysis to the missing data:

- *Pattern mixture model (PMM-MI with logistic regression model)*

  For each patient with partial missing data of severe exacerbation events, the unobserved number of events after study discontinuation up to Week 52 will be imputed on monthly basis. Since the definition of severe exacerbation in Section 2.1.3.1 requires the start dates of 2 consecutive severe exacerbation events experienced by one patient to depart at least 28 days from each other, each patient is possible to have a maximum of one event per month that is defined as 28 days. A logistic regression model therefore can be used to impute whether a patient has an event or not for each of the corresponding unobservable months. This imputation will be repeated multiple times. A final statistical inference will be obtained by using Rubins' formula to combine the binomial regression results based on each of the imputed datasets. Details of the PMM model are described in Appendix D.

- *Control-based PMM*

  Similar to aforementioned PMM model except that the individual monthly mean probability will be calculated based on observations in placebo arm only in the logistic regression, with adjustment of missing observation duration.

- *Tipping point analysis*

  Similar to aforementioned PMM model except that if a patient with missing data is on dupilumab, the odds in the logistic model for each unobservable month will be increased, and vice versa if the patient is on placebo, the odds will be decreased. This adjustment will artificially lower the predicted event rates in placebo group and increase the predicted event rates in Dupilumab group. For each increasing/decreasing ratio, a p-value can be obtained based on the imputed dataset with this specific ratio. A sequence of different ratios will be explored until p-value becomes >0.05.

The missing data sensitivity analyses for the primary endpoint analysis will be performed in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations. For each of the above methods, a negative binomial model will be fitted using the complete dataset composed of observed and imputed data, including the total number of observed and imputed events during the 52 weeks as the response variable. When performing the sensitivity analyses in the population with Type 2 inflammatory asthma phenotype, the model will include the treatment group, age, baseline weight (≤30kg, >30kg), region (pooled country), baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. When performing the sensitivity analyses in the population with baseline blood eosinophils ≥0.3 Giga/L, the baseline eosinophil level will be removed from the model covariates. Log transformed observation duration will be the offset variable.

More details of the imputation and analyses methods are provided in Appendix D.

Sensitivity analysis related to COVID-19 Pandemic

To assess missing data due to COVID-19 pandemic, missing data from patients who were discontinued from the study before Week 52 due to COVID-19 will be imputed using a manner similar to pattern mixture model as mentioned above except breaking down the 'Other' discontinuation reason into 'Due to COVID-19 or not' when defining the missing patterns.

Subgroup analyses

To assess the consistency of treatment effects across the subgroup levels, subgroup analyses will be performed for the annualized rate of severe exacerbation event during the 52-week treatment period by:

- Gender (Male, Female)
- Region (Latin America, Eastern Europe, and Western Countries)
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, all the other)
- Background ICS dose levels at randomization (medium, high)

- Baseline blood eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L; <0.15 Giga/L, ≥0.15 Giga/L; <0.15 Giga/L, ≥0.15 - <0.3 Giga/L, ≥0.3 - <0.5 cells/µL, ≥0.5 cells/µL)
- Baseline FeNO level (<20 ppb, ≥20 – <35 ppb, ≥35 ppb)
- Eos-FeNO Quadrant (0.15-20) 1 (H-H): Baseline blood eosinophil level ≥0.15 Giga/L and Baseline FeNO ≥20 ppb
- Eos-FeNO Quadrant (0.15-20) 2 (H-L): Baseline blood eosinophil level ≥0.15 Giga/L and Baseline FeNO <20 ppb
- Eos-FeNO Quadrant (0.15-20) 3 (L-H): Baseline blood eosinophil level <0.15 Giga/L and Baseline FeNO >=20 ppb
- Eos-FeNO Quadrant (0.15-20) 4 (L-L): Baseline blood eosinophil level <0.15 Giga/L and Baseline FeNO <20 ppb
- Eos-FeNO Quadrant (0.3-20) 1 (H-H): Baseline blood eosinophil level ≥0.3 Giga/L and Baseline FeNO ≥20 ppb
- Eos-FeNO Quadrant (0.3-20) 2 (H-L): Baseline blood eosinophil level ≥0.3 Giga/L and Baseline FeNO <20 ppb
- Eos-FeNO Quadrant (0.3-20) 3 (L-H): Baseline blood eosinophil level <0.3 Giga/L and Baseline FeNO >=20 ppb
- Eos-FeNO Quadrant (0.3-20) 4 (L-L): Baseline blood eosinophil level <0.3 Giga/L and Baseline FeNO <20 ppb
- Background controller type at randomization (ICS only, ICS + LABA)
- Baseline predicted FEV1% (<80%, ≥80%)
- Baseline predicted FEV1% (<median, ≥median)
- Baseline ACQ-7-IA (≤2, >2)
- Baseline weight (≤30, >30 kg)
- Atopic medical condition (Yes, No)
- Baseline Total IgE (<median, ≥median)
- Baseline Total IgE (<100 IU/mL, ≥100 IU/mL)
- Age at onset of asthma (0 - <2, 2-<6, >=6)
- Number of severe asthma exacerbation prior to the study as defined in Section 2.1.1 (<=1, =2, >2)

Additional EOS-FeNO Quadrant analysis will be performed using alternative cut-off value for the baseline FeNO:

- Eos-FeNO Quadrant (0.15-35) 1 (H-H): Baseline blood eosinophil level ≥0.15 Giga/L and Baseline FeNO ≥35 ppb
- Eos-FeNO Quadrant (0.15-35) 2 (H-L): Baseline blood eosinophil level ≥0.15 Giga/L and Baseline FeNO <35 ppb

- Eos-FeNO Quadrant (0.15-35) 3 (L-H): Baseline blood eosinophil level <0.15 Giga/L and Baseline FeNO >=35 ppb
- Eos-FeNO Quadrant (0.15-35) 4 (L-L): Baseline blood eosinophil level <0.15 Giga/L and Baseline FeNO <35 ppb

A patient is considered to have ongoing atopic medical condition if he/she has any of the following: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline serum total IgE ≥100 IU/mL and at least one positive aeroantigen specific IgE (≥0.35 IU/mL) at baseline.

The aforementioned subgroup analyses (except for the baseline eosinophil levels and baseline FeNO levels) will be performed in the Type 2 inflammatory asthma phenotype population and baseline blood eosinophils ≥0.3 Giga/L population; and, the subgroup analyses concerning the baseline blood eosinophil level and baseline FeNO level will be performed in the full ITT population. The annualized rate of severe exacerbation events as defined in Section 2.1.3.1 will be analyzed using a negative binomial regression model.

When performing the subgroup analysis in the Type 2 inflammatory asthma phenotype population or the full ITT population, the model will include the total number of events that occur during the observation period defined above as the response variable, with the treatment arm, age, baseline weight (≤30kg, >30kg), region, baseline blood eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of severe exacerbation events within 1 year prior to the study as covariates. When performing the subgroup analysis in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates. Furthermore, in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.3 Giga/L, or full ITT population, when performing the subgroup analysis that is defined by age, baseline weight, region, baseline blood eosinophil level, baseline FeNO level, baseline ICS dose level, or number of severe exacerbation events within 1 year prior to the study, the covariate that defines the subgroup will be removed from the model covariates.

Treatment groups, baseline weight, region, baseline eosinophil level, baseline FeNO level, and baseline ICS dose level will be treated as categorical variables. Age and number of severe exacerbation events within 1 year prior to the study will be treated as continuous variables. Log transformed observation duration will be the offset variable. In the case where the negative binomial regression model may not converge, a categorical variable for the number of severe exacerbation events within 1 year prior to study (1, 2, more than 2) will replace the corresponding continuous variable in the model.

Treatment by subgroup interaction and its p-value will be derived from a negative binomial model. This model will include the total number of events occurring during the observation period as the response variable, with the treatment groups, age, baseline weight, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, number of severe exacerbation events within 1 year prior to the study, subgroup (if different than the aforementioned covariates) and treatment by subgroup interaction as covariates. Log transformed observation duration will be

the offset variable. If quantitative treatment by subgroup interaction is detected with nominal p-value <0.05 for any subgroup factor, the Gail-Simon test will be performed to evaluate possible qualitative interaction. Summary statistics of severe exacerbations will be provided within each subgroup. Forest plot of relative risks and corresponding CIs and forest plot of risk differences and corresponding CIs comparing dupilumab vs. placebo for the subgroups will be provided.

Treatment-by-Type 2 biomarker interaction

To examine the ability of FeNO to predict the treatment effect of dupilumab independent of blood eosinophil levels for the primary endpoint, treatment-by-biomarker interactions will be tested using negative binomial regression models that include the total number of severe exacerbation events during 52-week treatment period as the response variable, and with the following different sets of model covariates, respectively. A threshold value of 0.15 will be utilized for the nominal p value of interaction test.

[redacted]

2.4.4.2 Analyses of key secondary efficacy endpoints

Statistical analysis methods for the key secondary endpoints are presented below.

2.4.4.2.1 Change from baseline in percentage predicted pre-bronchodilator (pre-BD) FEV_1 at Week 12

Primary statistical model and adjustment for covariates

The analysis of change from baseline in % predicted pre-BD FEV1 at Week 12 is to assess the efficacy of dupilumab regardless of treatment adherence. The absolute change from baseline in % predicted FEV1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The analysis for change from baseline in % predicted pre-BD FEV1 will be performed in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.3 Giga/L, baseline blood eosinophils ≥0.15 Giga/L, baseline FeNO ≥20 ppb and full ITT populations.

When performing the key secondary endpoint analysis in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.15 Giga/L, and full ITT populations, the model will include change from baseline in % predicted FEV1 values up to Week 12 as response variables, and treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. When performing the key secondary endpoint analysis in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates. When performing the key secondary endpoint analysis in the baseline FeNO ≥20 ppb population, the baseline FeNO level will be removed from the model covariates.

Treatment group, baseline weight, region, baseline eosinophil level, baseline FeNO level, ethnicity, baseline ICS dose level, and visit will be treated as categorical variables. For patients who discontinue the treatment before Week 12, they will be asked and encouraged to return to the clinic for all remaining study visit and the additional off-treatment % predicted FEV1 values measured up to Week 12 will be included in the primary analysis. For patients who withdraw from the study before Week 12, % predicted FEV1 values will be missing after study discontinuation. No imputation will be performed for missing values in the primary analysis. This estimand

compares the change from baseline in % predicted pre-BD FEV1 for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo.

An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in % predicted FEV1 at Week 12 will be derived from the mixed-effect model. Difference in LS mean change from baseline, the corresponding 95% CI and the p-value with Kenward-Roger adjustment will be provided for comparison for dupilumab against placebo. In addition, descriptive statistics including number of patients, mean, standard error and LS mean of change from baseline will be provided.

A sample SAS code can be found below:

```
proc mixed data=adsd.adre method=reml;

        where paramcd='FEV1PP'and ATPT='PRE-BRONCHODILATOR' and avisitn ge 3 and
avisitn le 8 and ittfl='Y';

        class subjid weight eosblgpn1 fenoblgpn ics trt01pn avisitn cntygr1n ethnicity;

        model chg = trt01pn weight ics eosblgpn1 fenoblgpn cntygr1n ethnicity avisitn
trt01p*avisitn base base*avisitn/ddfm=kr residual;

        repeated avisitn/type=un subject=subjid;

        lsmeans trt01pn*avisitn /pdiff cl;

    estimate 'dupilumab vs Placebo at Week 12 Visit 8'

    trt01pn -1 1 trt01pn*avisitn   0 0 0 0 0 -1 0 0 0 0 0 1/cl;

 run;
```

The primary estimand for the key secondary endpoint is summarized as in below Table 7.

Table 7 - Summary of primary estimand for key secondary endpoint

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary**
Primary objective: The primary objective is to evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma				
Key secondary endpoint (treatment policy)	Change from baseline in pre-bronchodilator % predicted forced expiratory volume in 1 second (FEV1) at Week 12	Type 2 inflammation phenotype; Patients with baseline blood eosinophils ≥ 0.3 Giga/L population	The intercurrent events will be handled as follows: Discontinuation of study treatment before Week 12: Off-study treatment data up to Week 12 will be included in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: In addition, missing data will be imputed latently by MMRM based on missing at random assumption	In patients with Type 2 inflammatory asthma phenotype, the key secondary endpoint will be will be analyzed using MMRM with change from baseline in % predicted FEV1 values up to Week 12 as response variable, and treatment, age, baseline weight, region, sex, ethnicity, baseline height, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. The LS mean of each group, difference of LS means between treatment and placebo arms, 95% confidence internal and P value will be reported. In patients with baseline blood eosinophils ≥ 0.3 Giga/L, the analysis will remain same as above except that the covariate of baseline eosinophil level will be removed.

Estimand of clinical efficacy of dupilumab versus placebo with treatment adherence

To assess the treatment effect when the patients adhere to the study treatment as directed, on-treatment % predicted pre-BD FEV1 measurements will be analyzed using the similar MMRM model as for the key secondary endpoint analyses, using the same estimation algorithm. The model will include on-treatment change from baseline in % predicted pre-BD FEV1 values up to Visit 8 (Week 12) as response variables. A % predicted pre-BD FEV1 value is considered as on-treatment if it's measured before or on the last dose date + 14 days. The on-treatment analyses for the key secondary endpoint will be performed in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations. The same set of covariates as specified for the key secondary endpoint analyses in each of the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations will be used in the MMRM model for the on-treatment analyses. Measurements obtained during off treatment period will be considered as missing.

Sensitivity analyses with different censoring methods for pre-BD FEV1 potentially confounded by systemic corticosteroid use

In addition, two sets of sensitivity analyses with different methods of handling % predicted pre-BD FEV1 measurements confounded by the systemic corticosteroid use will be performed:

- Censoring method 1: The % predicted pre-BD FEV_1 measurements collected from systemic corticosteroid start date to systemic corticosteroid end date + 14 days will be excluded in order to reduce the confounding effect of systemic corticosteroids
- Censoring method 2: All % predicted pre-BD FEV_1 measurements collected on and after first day of systemic corticosteroid use will be excluded

The above two censoring methods will be applied to the key secondary endpoint analyses and the on-treatment analysis for the key secondary endpoint.

Handling of missing data

If a patient misses scheduled % predicted pre-BD FEV1 measurement during the first 12-week treatment, or withdraws from the study before Visit 8 (Week 12), he/she will have missing % predicted pre-BD FEV1 data from these time points up to Week 12. Descriptive statistics of % predicted pre-BD FEV1 by visit up to Week 12 will be summarized for patients with some missing data and patients with complete data up to Week 12 separately. Number of patients with missing % predicted pre-BD FEV1, reasons and timing for missing % predicted pre-BD FEV1 will be summarized by treatment groups. In addition, the following sensitivity analyses will be conducted to assess the robustness of the conclusion drawn based on the main model for the key secondary endpoint analyses to the missing data:

- *Pattern mixture model-multiple imputation (PMM-MI)*

  Missing % predicted pre-BD FEV1 values will be imputed multiple times with adjustment for covariates including treatment, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, baseline % predicted FEV1 value and reason of treatment discontinuation. Each of the complete datasets will be analyzed using the ANCOVA model with change from baseline in % predicted pre-BD FEV1 at Week 12 as the response variable, treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and baseline % predicted pre-BD FEV1 value as covariates. Then the SAS MIANALYZE procedure will be used to generate statistical inference by combining results using Rubin's formula.

- *Control based PMM-MI*

  The analysis is similar as the standard PMM-MI described above, except that it assumes that after withdrawal from the study, patients from the dupilumab groups would exhibit the same future evolution of % predicted pre-BD FEV1 as patients on the placebo who were not exposed to dupilumab.

- *Tipping point analysis*

  First, missing values will be imputed by PMM-MI as illustrated above. The imputed values in placebo group will then be shifted by adding a sequence of positive values and the imputed values in dupilumab group will be shifted by subtracting a sequence of positive values. For each combination of the shift parameters, each of the imputed and shifted datasets will be analyzed with the ANCOVA model and their results will be combined using Rubin's formula to generate statistical inference. LS mean difference between dupilumab and placebo in change from baseline in % predicted pre-BD FEV1 at Week 12 and the corresponding p-values will be provided for each combination of shift parameters.

The missing data sensitivity analyses for the key secondary endpoint analysis will be performed in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations. When performing the sensitivity analyses in the population with Type 2 inflammatory asthma phenotype, the model will include treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. When performing the sensitivity analyses in the population with baseline blood eosinophils ≥0.3 Giga/L, the baseline eosinophil level will be removed from the model covariates.

More details of the imputation and analyses methods are included in Appendix D.

Subgroup analysis

To assess the consistency of treatment effects across the subgroup levels, subgroup analyses will be conducted for the change from baseline in % predicted pre-BD FEV1 at Week 12 in the same set of subgroups as defined for the primary endpoint of annualized rate of severe exacerbation events. The subgroup analyses (except for the baseline eosinophil levels and baseline FeNO levels) will be performed in the Type 2 inflammatory asthma phenotype population and baseline blood eosinophils ≥0.3 Giga/L population; and, the subgroup analyses for the baseline blood eosinophil level and baseline FeNO level will be performed in the full ITT population. The same MMRM model for the key secondary endpoint will be applied for the subgroup analyses.

When performing the subgroup analysis in the Type 2 inflammatory asthma phenotype population or the full ITT population, the model will include change from baseline in % predicted FEV1 values up to Week 12 as response variables, and treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. When performing the subgroup analysis in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates. Furthermore, in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.3 Giga/L, or full ITT population, when performing the subgroup analysis that is defined by age, baseline weight, region, gender, baseline blood eosinophil level, baseline FeNO level, baseline ICS dose level, or baseline % predicted FEV1, the covariate that defines the subgroup will be removed from the model covariates.

Treatment-by-subgroup interaction at Week 12 and its p-value will be derived from an MMRM model. If quantitative treatment by subgroup interaction at Week 12 is detected with nominal p-value <0.05 for any subgroup factor, the Gail-Simon test will be used to test the qualitative interaction. Summary statistics of change from baseline in % predicted pre-bronchodilator FEV1 will be provided within each subgroup. Forest plot of LS mean difference and corresponding CIs comparing dupilumab vs placebo for the subgroups will be provided.

Distribution of change from baseline in percent predicted pre-BD FEV1

Water fall plots of change from baseline in % predicted FEV1 at Week 12 and Week 52 will be presented in the Type 2 inflammatory asthma phenotype population and baseline blood eosinophils ≥0.3 Giga/L population.

Treatment-by-Type 2 biomarker interaction

To examine the ability of FeNO to predict the treatment effect of dupilumab independent of blood eosinophil levels for the key secondary endpoint, the treatment-by-biomarker interactions will be tested with MMRM model, which includes change from baseline in % predicted FEV1 values up to Week 12 as response variables, and with the following different sets of model covariates, respectively. A threshold value of 0.15 will be utilized for the nominal p value of interaction test.

Biomarker covariate and treatment -by-biomarker interaction	Model covariates
Baseline biomarker as categorical variable:	
Baseline FeNO group (<20 ppb, >=20 ppb), and treatment-by-baseline FeNO group interaction	MMRM with the treatment arm, baseline weight (≤30kg, >30kg), region, ethnicity, baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline % predicted FEV1 value -by-visit interaction, and treatment-by-baseline FeNO group interaction as covariates.
Baseline eosinophil group (<0.15 Giga/L, >=0.15 Giga/L), and treatment-by- baseline eosinophil group interaction	MMRM with the treatment arm, baseline weight (≤30kg, >30kg), region, ethnicity, baseline eosinophil level (<0.15 Giga/L, ≥0.15 Giga/L), baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline % predicted FEV1 value -by-visit interaction, and treatment-by- baseline eosinophil group interaction as covariates.
Baseline FeNO group (<20 ppb, >=20 ppb), baseline eosinophil group (<0.15 Giga/L, >=0.15 Giga/L), and treatment-by-baseline FeNO group interaction	MMRM with the treatment arm, baseline weight (≤30kg, >30kg), region, ethnicity, baseline eosinophil level (<0.15 Giga/L, ≥0.15 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline % predicted FEV1 value -by-visit interaction, and treatment-by-baseline FeNO group interaction as covariates.
Baseline FeNO group (<20 ppb, >=20 ppb), baseline eosinophil group (<0.15 Giga/L, >=0.15 Giga/L), treatment-by-baseline FeNO group interaction, and treatment-by- baseline eosinophil group interaction	MMRM with the treatment arm, baseline weight (≤30kg, >30kg), region, ethnicity, baseline eosinophil level (<0.15 Giga/L, ≥0.15 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline % predicted FEV1 value -by-visit interaction, and treatment-by- baseline eosinophil group interaction, and treatment-by-baseline FeNO group interaction as covariates.

Baseline biomarker as continuous variable:	
Baseline FeNO value, and treatment-by-baseline FeNO value interaction	MMRM with the treatment arm, baseline weight (≤30kg, >30kg), region, ethnicity, baseline FeNO value, baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline % predicted FEV1 value -by-visit interaction, and treatment-by-baseline FeNO value interaction as covariates.
Baseline eosinophil value, and treatment-by- baseline eosinophil value interaction	MMRM with the treatment arm, baseline weight (≤30kg, >30kg), region, ethnicity, baseline eosinophil value, baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline % predicted FEV1 value -by-visit interaction, and treatment-by- baseline eosinophil value interaction as covariates.
Baseline FeNO value, baseline eosinophil value, and treatment-by-baseline FeNO value interaction	MMRM with the treatment arm, baseline weight (≤30kg, >30kg), region, ethnicity, baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline % predicted FEV1 value -by-visit interaction, baseline eosinophil value, baseline FeNO value, and treatment-by-baseline FeNO value interaction as covariates.
Baseline FeNO value, baseline eosinophil value, treatment-by-baseline FeNO value interaction, and treatment-by- baseline eosinophil value interaction	MMRM with the treatment arm, baseline weight (≤30kg, >30kg), region, ethnicity, baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline % predicted FEV1 value -by-visit interaction, baseline eosinophil value, baseline FeNO value, treatment-by- baseline eosinophil value interaction, and treatment-by-baseline FeNO value interaction as covariates.

Slope analysis of post-bronchodilator % predicted FEV1

For post-bronchodilator % predicted FEV1, the rate of change in post-bronchodilator % predicted FEV1% (termed as % predicted FEV1 slope) will be compared between dupilumab and placebo in the Type 2 inflammatory asthma phenotype population and baseline blood eosinophils ≥0.3 Giga/L population. Change from baseline in post-bronchodilator % predicted FEV1 after Week 4 and after Week 8 will be analyzed correspondingly using linear mixed-effects model with treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, time since randomization, and treatment-by-time interaction, baseline post-bronchodilator % predicted FEV1 value as covariates in the Type 2 inflammatory asthma phenotype population; when performing the slope analysis in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates Intercept and time since randomization will be treated as random effects in this mixed-effects model.

2.4.4.3 Analyses of secondary efficacy endpoints

2.4.4.3.1 Change from baseline for continuous endpoints

Change from baseline in ACQ-7-IA Week 24 will be analyzed using MMRM model including change from baseline up to Week 24 as response variables, regardless if the patient is on treatment or not when the endpoint is measured. Change from baseline in FeNO at Week 12 will be analyzed using MMRM including change from baseline up to Week 12 as response variables, regardless if the patient is on treatment or not when the endpoint is measured. The analyses for the secondary endpoints of ACQ-7-IA and FeNO will be performed in the Type 2 inflammatory

asthma phenotype, baseline blood eosinophils ≥0.3 Giga/L, baseline blood eosinophils ≥0.15 Giga/L, baseline FeNO ≥20 ppb and full ITT populations. When performing these analyses in the Type 2 inflammatory asthma phenotype, baseline blood eosinophils ≥0.15 Giga/L or full ITT population, the MMRM models will include treatment, age, baseline weight, region (pooled country), baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value, and baseline-by-visit interaction as covariates. When performing these analyses in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates. When performing these analyses in the baseline FeNO ≥20 ppb population, the baseline FeNO level will be removed from the model covariates. An MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time-points in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations, with including the same set of model covariates as specified for the secondary endpoint analyses. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparison between dupilumab and placebo along with descriptive statistics.

In the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations, change from baseline for other continuous endpoints at all time-points will be analyzed using MMRM model including measurements up to Week 52. The model will include change from baseline of these endpoints from all available planned time points up to Week 52 as response variables, regardless if the patient is on treatment or not when the endpoint is measured. When performing these analyses in the Type 2 inflammatory asthma phenotype population, treatment, age, baseline weight, region (pooled country), baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value and baseline-by-visit interaction will be the model covariates. When performing these analyses in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates. Ethnicity will be included as the covariate only in the models for spirometry parameters, specifically. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparison between dupilumab and placebo along with descriptive statistics.

In addition to the MMRM analyses for change from baseline in ACQ-7, ACQ-5, and AQLQ total score a responder analysis will also be performed for these endpoints at Week 12, 24, 36 and 52, in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations. For ACQ-7 score, a logistic regression model will be used to compare percentage of patients who reached MCID (responders) in dupilumab and placebo group at the time points aforementioned correspondingly. Patients with change from baseline in ACQ-7 ≤ -0.5 will be considered as responders. Patients with change from baseline in ACQ-7 > -0.5 or with missing value will be considered as non-responders. When performing the analyses in the Type 2 inflammatory asthma phenotype population, the logistic model will include treatment, age, baseline weight, region (pooled country), baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and baseline ACQ-7 score as covariates. When performing the analyses in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates. Odds ratio of being a responder comparing dupilumab and placebo group will be provided along with the corresponding 95% CI and p-value. Descriptive statistics

including number and percentage of responders will also be provided. Responder analysis for ACQ-5 and AQLQ global score will be performed in the same way. For ACQ-5, a patient is considered as a responder if change from baseline in ACQ-5 score ≤ -0.5, or as a nonresponder if change from baseline in ACQ-5 score > -0.5 or missing. For AQLQ global score, a patient is considered as a responder if change from baseline in AQLQ global score ≥0.5, or as a non-responder if change from baseline <0.5 or missing.

2.4.4.3.2 Time to event variables

A Cox regression model and Kaplan-Meier method will be used to assess treatment differences in time to events (defined in Section 2.1.3.2) in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations.

When performing the time-to-event analyses in the Type 2 inflammatory asthma phenotype population, the model will include the time to the first event as the dependent variable, and treatment groups, age, baseline weight (≤30kg, >30kg), region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. When performing the time-to-event analyses in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates. Hazard ratio will be estimated for the comparison between dupilumab and placebo. The Kaplan-Meier method will be used to derive the probabilities that a patient would experience events up to Week 12, 24, 36 and 52 per each treatment group. Kaplan-Meier curves will be generated; quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% point-wise confidence intervals.

Sample SAS codes can be found as below:

proc phreg data=timeto;

class weight eosblgpn eosblgpn1 fenoblgpn ics trt01pn cntygr1n /param=GLM;

*model aval*CNSR(1) =trt01pn weight age eosblgpn1 fenoblgpn ics cntygr1n asmanum;*

contrast 'dupilumab vs Placebo rate ratio' trt01pn –1 1

run;

For these secondary endpoints, the primary estimand and details about the intercurrent events strategy and missing data handling are presented in

Table 8 as below. Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (ie, count, continuous, proportion, time-to-event).

Table 8 - Summary of primary estimand for secondary endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary**
Primary objective: The primary objective is to evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma				
Secondary endpoint (treatment policy)	Time to first severe exacerbation event during 52-week treatment period	Type 2 inflammation phenotype; Patients with baseline blood eosinophils ≥0.3 Giga/L population	The intercurrent events will be handled as follows: Discontinuation of study treatment before Week 52: Off-study treatment data up to Week 52 will be included in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: Discontinuing the study follow-up before Week 52: Analyses will be censored at the time of study discontinuation.	In patients with Type 2 inflammatory asthma phenotype, this time-to-event endpoint will be analyzed using the Cox proportional hazards model, include the time to the first event as the dependent variable, and treatment groups, age, baseline weight, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. The hazards ratio, its 95% confidence interval and p-value will be reported. Kaplan-Meier curves will be also provided. In patients with baseline blood eosinophils ≥0.3 Giga/L, the analysis will remain same as above except that the covariate of baseline eosinophil level will be removed.
Secondary endpoint (treatment policy)	Proportion of participants who reached MCID (responders) defined as change from baseline in ACQ-7 ≤ -0.5 at Week 12, 24, 36 or 52.	Type 2 inflammation phenotype; Patients with baseline blood eosinophils ≥0.3 Giga/L population	The intercurrent events will be handled as follows: Discontinuation of study treatment before the visit to be analyzed: Off-study treatment data wil be included in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: In addition, having missing data at the visit to be analyzed, patients will be considered as non-responders	In patients with Type 2 inflammatory asthma phenotype, this endpoint will be analyzed using logistic regression with treatment, age, baseline weight, region (pooled country), baseline eosinophil level, baseline FeNO level, baseline ICS dose, level, and baseline ACQ-7 score as covariates. The number (n) and percentage (%) of responders of each arm, odds ratio between treatment and placebo arms, 95% confidence internal and P value will be reported. In patients with baseline blood eosinophils ≥0.3 Giga/L, the analysis will remain same as above except that the covariate of baseline eosinophil level will be removed.

2.4.4.4 Multiplicity issues

To control the type-I error rate for the analysis of efficacy endpoint, a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 5% level.

To match the approved indication in adults and adolescents, for the US and US reference countries, the testing hierarchy will start with baseline blood eosinophils ≥0.3 Giga/L population. For EU and EU reference countries, the testing hierarchy will start with Type 2 inflammatory asthma phenotype population. The complete list of the endpoints with their testing order is specified in Table 9 (For US and US reference countries) and Table 10 (for EU and EU reference countries).

For US and US reference countries:

Table 9 - Hierarchical testing order for US and US reference countries:

Endpoints	Population	Test Order
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.3 Giga/L	1st
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.15 Giga/L	2nd
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb)	3rd
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.	Patients with baseline blood eosinophils ≥0.3 Giga/L	4th
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.	Patients with baseline blood eosinophils ≥0.15 Giga/L	5th
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb)	6th
Change in ACQ-7-IA at Week 24	Patients with baseline blood eosinophils ≥0.3 Giga/L	7th
Change in ACQ-7-IA at Week 24	Patients with baseline blood eosinophils ≥0.15 Giga/L	8th
Change in ACQ-7-IA at Week 24	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb)	9th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Baseline FeNO ≥20 ppb	10th
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12	Baseline FeNO ≥20 ppb	11th
Change in ACQ-7-IA at Week 24	Baseline FeNO ≥20 ppb	12th

Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Full ITT	13th
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.	Full ITT	14th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.3 Giga/L and High ICS at baseline	15th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.15 Giga/L and High ICS at baseline	16th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb) with High ICS at baseline	17th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Baseline FeNO ≥20 ppb with High ICS at baseline	18th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Full ITT with High ICS at baseline	19th
Change from baseline in FeNO at Week 12	Patients with baseline blood eosinophils ≥0.3 Giga/L	20th
Change from baseline in FeNO at Week 12	Patients with baseline blood eosinophils ≥0.15 Giga/L	21st
Change from baseline in FeNO at Week 12	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb)	22nd
Change from baseline in FeNO at Week 12	Baseline FeNO ≥20 ppb	23rd
Change from baseline in FeNO at Week 12	Full ITT	24th

For EU and EU reference countries:

Table 10 - Hierarchical testing order for EU and EU reference countries

Endpoints	Population	Test Order
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb)	1st
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.15 Giga/L	2nd
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.3 Giga/L	3rd
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb)	4th

Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.	Patients with baseline blood eosinophils ≥0.15 Giga/L	5th
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.	Patients with baseline blood eosinophils ≥0.3 Giga/L	6th
Change in ACQ-7-IA at Week 24	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb)	7th
Change in ACQ-7-IA at Week 24	Patients with baseline blood eosinophils ≥0.15 Giga/L	8th
Change in ACQ-7-IA at Week 24	Patients with baseline blood eosinophils ≥0.3 Giga/L	9th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Baseline FeNO ≥20 ppb	10th
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12	Baseline FeNO ≥20 ppb	11th
Change in ACQ-7-IA at Week 24	Baseline FeNO ≥20 ppb	12th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Full ITT	13th
Change from baseline in pre-bronchodilator % predicted FEV1 at Week 12.	Full ITT	14th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb) with High ICS at baseline	15th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.15 Giga/L and High ICS at baseline	16th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.3 Giga/L and High ICS at baseline	17th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Baseline FeNO ≥20 ppb and High ICS at baseline	18th
Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Full ITT and High ICS at baseline	19th
Change from baseline in FeNO at Week 12	Type 2 inflammatory asthma phenotype (Baseline blood eosinophils ≥0.15 Giga/L or Baseline FeNO ≥20 ppb)	20th
Change from baseline in FeNO at Week 12	Patients with baseline blood eosinophils ≥0.15 Giga/L	21st
Change from baseline in FeNO at Week 12	Patients with baseline blood eosinophils ≥0.3 Giga/L	22nd
Change from baseline in FeNO at Week 12	Baseline FeNO ≥20 ppb	23rd
Change from baseline in FeNO at Week 12	Full ITT	24th

2.4.4.5 Additional efficacy analysis(es)

2.4.4.5.1 Analysis of additional PROs

Change from baseline in additional PRO endpoints listed in Section 2.1.3.5 will be analyzed using the same MMRM model for the key secondary endpoint analysis as described in Section 2.4.4.2.1 in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations defined in Section 2.3.1. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparison between dupilumab and placebo along with descriptive statistics.

2.4.4.5.2 Analysis of systemic corticosteroid (SCS)

SCS exposure in the dupilumab versus placebo exposed groups will be evaluated by total SCS intake in days, number of courses of SCS, and time to first SCS use. This will be evaluated in the population with the Type 2 inflammatory asthma phenotype and the population with baseline blood eosinophils >/= 0.3 Giga/L. Total SCS intake in days, and number of courses during the treatment period, will be summarized by treatment groups of Dupilumab and placebo with the treatment duration defined as in Section 2.4.4.1. A course of SCS is considered continuous if treatment is separated by less than 7 days.

For patients who discontinue treatment, data collected during the off- treatment period will also be used.

Descriptive statistics including number of subjects, mean, standard deviation, min, and max will be provided together with annualized number of courses or annualized total dose. The annualized number of courses of SCS intake during the treatment period will be analyzed using a negative binomial regression model. The model will include the number of courses of SCS intake during the treatment period as the response variable, and same set of covariates as defined in Section 2.4.4.1.

Time to the first use of SCS during the 52-week placebo-controlled treatment period will be analyzed as time to event variable using same method as stated in Section 2.4.4.3.2 in both the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L population.

2.4.4.5.3 Annualized rate of Loss of asthma control (LOAC)

If a patient stays in the study until the end of the 52-week treatment period, all LOAC events that happen up to Week 52 visit will be included in the analysis, regardless whether the patient is on-treatment or not, and the observation duration is defined as from randomization to Week 52 visit. If a patient withdraws from the study prior to the end of the 52-week treatment period, all observed LOAC events up to the last contact date will be included in the analysis, and the observation duration is defined as from randomization to the last contact date. Patients who prematurely discontinue treatment will have off-treatment measurements included in the analysis up to either Week 52 or study withdrawal, whichever comes earlier.

The annualized rate of LOAC events will be analyzed using negative binomial regression model in the Type 2 inflammatory asthma phenotype and baseline blood eosinophils ≥0.3 Giga/L populations. This model includes the total number of events that occur during the observation period defined above as the response variable, with the treatment arm, age, baseline weight (≤30kg, >30kg), region, baseline eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of severe exacerbation events within 1 year prior to the study as covariates. When performing the analysis in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level will be removed from the model covariates.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group actually received.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2.

- Analysis of TEAE as defined in Section 2.4.5.1
  - Analysis of all treatment-emergent adverse events
  - Analysis of all treatment-emergent serious adverse event(s)
  - Analysis of all treatment-emergent adverse event(s) leading to permanent treatment discontinuation or drug interruption
  - Analysis of adverse events of special interest (AESI) and other selected AE groupings
  - Death
- Change in blood eosinophil as defined in Section 2.4.5.3

Unless otherwise specified, following common rules will be applied:

- The baseline value is defined as the last available value before the first dose of IMP
- 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 for this age group (PCSA version dated May 2014 [Appendix A])
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population. Number (%) of patients

with at least 1 PCSA will be summarized regardless of baseline PCSA status and also by baseline PCSA status

- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. 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 end of treatment. If this value is missing, this endpoint value will be the closest value prior to the end of treatment epoch. The worst value is defined as the nadir and /or the peak post-baseline (up to the end of treatment epoch or EOT) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned
- All safety values including unscheduled measurements will be assigned to the appropriate safety analysis visit window defined in Section 2.5.4

2.4.5.1 Analyses of adverse events

General information

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment adverse events will be described separately.

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 pretreatment or treatment-emergent. 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 pretreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Sorting will be based on results for the dupilumab group.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
    - Treatment-emergent adverse event
    - Serious treatment-emergent adverse event

  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation

- Overview of exposure adjusted incidence rate of treatment-emergent adverse events, summarizing number of patients with an event per 100 patient years with any:
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse events by primary system organ class, showing number (%) of patients with at least 1 treatment-emergent adverse event, sorted by internationally agreed order of primary system organ class
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- Exposure adjusted incidence rate of all treatment-emergent adverse events by primary SOC and PT, showing the number of patients with at least 1 treatment-emergent adverse event per 100 patient-years
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- Number (%) of patients experiencing treatment-emergent adverse event(s) presented by primary and secondary SOC, HLGT, HLT, and PT sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Incidence rate of all common TEAEs (PT >= 2%) with >= 1% higher incidence in one of the groups compared to any other by primary SOC and PT. The relative risk ratio of qualifying TEAEs along its 95% confidence interval will be presented.
- A listing of all treatment-emergent adverse events will be presented

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 with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted 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 the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- Exposure adjusted incidence rate of serious treatment-emergent adverse events by primary SOC and PT, showing the number of patients with at least 1 serious treatment-emergent adverse event per 100 patient-years
- A listing of all treatment-emergent serious adverse events will be presented

Analysis of all treatment-emergent adverse event(s) leading to permanent treatment discontinuation or drug interruption

- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC and PT, showing number (%) of patients with at least one TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC
- Exposure adjusted incidence rate of treatment-emergent adverse events leading to permanent treatment discontinuation by primary SOC and PT, showing the number of patients with at least 1 treatment-emergent adverse event leading to permanent treatment discontinuation per 100 patient-years

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

- All treatment-emergent adverse events, by selected standardized MedDRA query (SMQ) and PT or by laboratory values (as in ALT elevation), showing the number (%) of patients with at least 1 PT, sorted by decreasing incidence of PTs within each SMQ
- For each AESI,
  - Number (%) of patients with any specific treatment emergent AESI
  - Number (%) of patients with any specific serious AESI (regardless of treatment emergent status)
  - Number (%) of patients with any specific treatment emergent serious AESI

  - Number (%) of patients with any specific AESI leading to death
  - Number (%) of patients with any specific treatment emergent AESI leading to permanent study drug discontinuation
  - Number (%) of patients with any specific treatment emergent AESI by maximum intensity, corrective treatment, and final outcome
  - Number of specific treatment emergent AESI adjusted by the exposure duration
  - Number of patients with any specific treatment emergent AESI adjusted by the exposure duration
- Number of patients with any specific treatment emergent AESI adjusted by the exposure duration at risk. For each AESI, Kaplan-Meier estimates of cumulative incidence at Week 12, 24, 36 and 52 and K-M plot may be provided to depict the course of onset over time if the number of events is large enough
- Number (%) of patients with injection site reactions by the related injection
- Number (%) of patients with different number of injection site reactions

Analysis of pretreatment adverse events

- All pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All serious pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to permanent treatment discontinuation by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

If only a few patients have pretreatment adverse events leading to permanent treatment discontinuation, a listing will be presented instead of the summary table above.

Subgroup analysis for adverse events

Analysis of adverse events will be performed for below subgroups of interest based on safety population:

- 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)
- Baseline ICS level (Medium, High)

The subgroup analysis of adverse events includes:

- Overview of treatment emergent AE
- Treatment emergent AE by primary SOC and PT
- Treatment emergent SAE by primary SOC and PT
- Treatment emergent AE leading to permanent treatment discontinuation by primary SOC and PT
- AESI by category

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, poststudy)
- Deaths in nonrandomized patients or randomized but not treated patients
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

A listing of deaths will be provided.

2.4.5.3 Analyses of laboratory variables

The analyses of laboratory data will be performed in the safety population. The summary statistics (including number, mean, median, Q1, Q3, standard deviation, 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 postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For each continuous parameters listed in Section 2.1.4.3, mean changes from baseline with the corresponding standard error will be plotted over time in each treatment group. This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

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

For parameters for which no PCSA criteria are 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 PCSAs will be provided.

Drug-induced liver injury

If there is any imbalance in the incidence of liver-related adverse events across the treatment groups, analysis of liver-related adverse events will be performed.

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group.

Time to onset of the initial ALT and AST elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) (time to first observation of ALT >3 x ULN or total bilirubin >2 x ULN, whichever comes first) will be analyzed using Kaplan-Meier estimates, presented by treatment group. Consideration should be given to the impact of the spacing of scheduled tests. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin and creatine phosphokinase, serum creatinine, complete blood count, HCV RNA.

Summarize the normalization by parameter (to ≤1 x ULN or return to baseline) of elevated liver function tests by categories of elevation (3 x, 5 x, 10 x, 20 x ULN for ALT and AST, 1.5 x ULN for alkaline phosphatase, and 1.5 x and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized despite treatment continuation of IMP, or normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category.

Change in Blood Eosinophil

Mean and median changes from baseline in eosinophil with the corresponding standard error will be plotted over time in each treatment group for patients with baseline blood eosinophil <0.5 Giga/L and patients with baseline blood eosinophil >=0.5 Giga/L. Number (%) of patients with post-baseline peak blood eosinophil >= 1 Giga/L, >=3 Giga/L and >=5 Giga/L will also be summarized in each treatment group and by baseline blood eosinophil status (All, <0.5 Giga/L,>=0.5 Giga/L).

2.4.5.4 Analyses of vital sign variables

The analyses of vital sign data will be performed in the safety population. The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

2.4.5.5 Analyses of electrocardiogram variables

The analyses of electrocardiogram (ECG) data will be performed in the safety population. The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all ECG variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, V28 (EOT) and V31(EOS) and ETD, last on-treatment and/or worst on-treatment value) by treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

2.4.6 Analyses of pharmacokinetic, immunogenicity, and pharmacodynamic variables

The PK/ADA analyses will be based on the PK/ADA population as defined in Section 2.3.3.

2.4.6.1.1 Analyses of serum concentrations of SAR231893 (REGN668)

Serum concentrations of SAR231893 (REGN668) will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time by each dose regimen group and overall treatment group. If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. For drug-treated patients, where concentration values are below the lower limit of quantification (LLOQ), one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three significant figures. For patients in the placebo group,

concentration values are below the LLOQ will be taken into account with a plasma concentration considered equal to 0.

2.4.6.1.2 Analyses of ADA variables

The following summary will be provided by each dose regimen group and overall treatment group:

- Number (%) of patients negative in ADA assay at all times
- Number (%) of patients with pre-existing ADA
- Number (%) of patients with treatment-emergent ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent ADA, and patients with persistent, indeterminate and transient ADA response
- Number (%) of patient with transient treatment-emergent ADA
- Number (%) of patients with persistent treatment-emergent ADA
- Number (%) of patients with indeterminate treatment-emergent ADA
- Number (%) of patients with treatment-boosted ADA.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-boosted ADA
- The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) of the ratio of peak post-baseline titer to baseline titer for patients with treatment-boosted ADA
- Listing of ADA peak titer levels and neutralizing antibody status (y/n) for the positive ADA samples
- Number (%) of patients with neutralizing antibody status

Kinetics of treatment-emergent ADA response

Number (%) of patients with ADA treatment-emergent ADA positive response at each visit will be summarized by each dose regimen group and overall treatment group.

Plot of percentage of patients with ADA treatment-emergent ADA positive response at each visit will be provided by each dose regimen group and overall treatment group.

Impact of ADA on PK

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and serum concentration of dupilumab may be explored for each dupilumab dose group. Plot of serum concentration of functional SAR231893 (REGN668) versus visit will be provided by ADA classifications for each dupilumab dose group.

Impact of ADA on clinical efficacy

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and following efficacy endpoints may be explored for each dupilumab dose group:

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

Impact of ADA on clinical safety

Association of safety versus ADA status may be analyzed in the ADA population. The safety assessment may focus on the following events:

- Severe injection site reactions last longer than 24 hours or serious injection site reactions
- Hypersensitivity reactions (SMQ hypersensitivity narrow search and confirmed by medical review)
- Anaphylactic reactions (SMQ anaphylactic reaction narrow search)

In response to AESI like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgment of the medical investigator and/or medical monitor.

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent and treatment-boosted) and safety may be explored.

2.4.6.2 Pharmacodynamics/genomics analyses

All biomarkers listed in Section 2.1.7 will be summarized in the exposed population defined as patients who actually received at least 1 dose or part of a dose of the IMP. Baseline values will be the last value collected prior to the first IMP. For randomized but not treated patients, baseline value will be the last value collected prior to the randomization. Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) of biomarkers at baseline will be summarized.

For all parameters including 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 by treatment group and time point. Values reported as below the LLQ (lower limit of quantitation) will be imputed as a value one half of the LLQ.

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 LLQ as the threshold.

Summary plots (mean +/- standard error of the mean) on values at each visit, absolute changes from baseline and percent changes from baseline will be provided for each biomarker by treatment group.[redacted]

2.4.7 Analyses of vaccine response

For patients who receive vaccination, vaccine IgG titers in serum prior and after vaccination will be summarized by treatment groups with descriptive statistics by treatment group and vaccine types.

Number of patients who receive vaccination and number of patients who are eligible to receive vaccination and the type of vaccination received will also be summarized by descriptive statistics.

2.4.8 Analyses of health economics variables

Analyses of health care resource utilization will be performed under the responsibility of the Health Economics Outcomes Research (HEOR) department of Sanofi.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age is calculated as:

Integer part of (informed consent date -birth date)/365.25

Age of onset of asthma is calculated as:

Integer part of (asthma onset date - birth date)/365.25

Time since first diagnosis of asthma (years) is calculated as:

(Year of randomization -Year of first diagnosis of asthma) + (month of randomization - month of first diagnosis of asthma)/12

Time since last asthma exacerbation (months) is calculated as:

(Year of randomization - Year of last asthma exacerbation)×12 + (month of randomization - month of last asthma exacerbation)

BMI is calculated as:

Weight in kg / (height^2 in meters)

Renal function formulas

For patients ≥6 and <12 years old, CLcr value will be derived using the equation of GFR Bedside Schwartz

$$\text{GFR (mL/min/1.73 m2)} = k \times \text{height (cm)} / \text{sCr (mg/dL)},$$

where the coefficient k=0.55.

2.5.2 Data handling conventions for secondary efficacy variables

Calculation of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations per day is the sum of number of inhalations recorded in one diary day including the evening diary and the following day's morning diary.

Periodical average of daily efficacy endpoints at designated study days

For the daily efficacy endpoints, the time period used to calculate the periodical average at each designated study day is summarized in Table 11. Randomization day is used as the reference day (Day 1).

[redacted]

[redacted]

2.5.3 Missing data handling for safety analysis

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.

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 the Investigational Product Administration report form page. If this date is missing, the exposure duration should be left as missing.

The last dose injection should be clearly identified in the case report form 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 randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose injection 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 of adverse events

If the severity 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.

2.5.4 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 administration. Selected safety variables will be summarized by the analysis window define in Table 12 for the by visit descriptive analysis. All available values from central lab 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. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 12 - Time window for safety endpoints

		Time windows for						
Visit	**Target Day**	**Vital signs**	**ECG endpoints**	**Clinical lab testing (serum)**	**Urinalysis**	**Urine Pregnancy test**	**Serum immunoglobulins**	**Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy**
Visit 1 (Week -4±1)	-28±7	<-14	1-	<-14	1-	<-14	1-	1-
Visit 2 (Week 0)	1	-14-1-		-14-1-		-14-1-		
Visit 3 (Week 2)	15	1+-21						
Visit 4 (Week 4)	29	22-35				1+-42		
Visit 5 (Week 6)	43	36-49						
Visit 6 (Week 8)	57	50-63				43-70		
Visit 7 (Week 10)	71	64-77						
Visit 8 (Week 12)	85	78-98		1+-126	1+-126	71-98		
Visit 10 (Week 16)	113	99-126				99-126		
Visit 12 (Week 20)	141	127-154				127-154		
Visit 14 (Week 24)	169	155-182		127-210	127-210	155-182	1+-266	
Visit 16 (Week 28)	197	183-210				183-210		

		Time windows for						
Visit	Target Day	Vital signs	ECG endpoints	Clinical lab testing (serum)	Urinalysis	Urine Pregnancy test	Serum immunoglobulins	Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy
Visit 18 (Week 32)	225	211-238				211-238		
Visit 20 (Week 36)	253	239-266		211-308	211-308	239-266		
Visit 22 (Week 40)	281	267-294				267-294		
Visit 24 (Week 44)	309	295-322				295-322		
Visit 26 (Week 48)	337	323-350				323-350		
Visit 28 (Week 52)	365	351-378	1+-406	309-406	309-406	351-378	267-406	
Visit 29 (Week 56)	393	379-406				379-406		
Visit 30 (Week 60)	421	407-434				407-434		
Visit 31 (Week 64)	449	>434-	>406	>406	>406	>434-	>406	

1-: up to 1st dose date/time; 1+: after 1st dose date/time;

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the randomization day. If a patient receives IMP prior to the randomization by mistake, the reference date of efficacy assessment will be the date of the first IMP administration for that patient. For the primary analyses, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 13. 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. For the on-treatment sensitivity analyses, only scheduled measurements collected during the treatment epoch will be assigned to a time window.

Table 13 - Time window for efficacy variables

Visit	Target Day	Time windows for			
		Pre-bronchodilator Spirometry, ACQ-IA	Post-bronchodilator spirometry	PAQLQ(S)-IA, PACQLQ(S)-IA PRQLQ-IA	EQ-5D-Y
Visit 1 (Week -4±1)	-28±7	<-14			
Visit 2 (Week 0)	1	-14-1^{-}	1^{-}	1^{-}	1^{-}
Visit 3 (Week 2)	15	1^{+}-21	1^{+}-21		
Visit 4 (Week 4)	29	22-35	22-42		
Visit 5 (Week 6)	43	36-49			
Visit 6 (Week 8)	57	50-63	43-70		
Visit 7 (Week 10)	71	64-77			
Visit 8 (Week 12)	85	78-98	71-126	1^{+}-126	
Visit 10 (Week 16)	113	99-126			
Visit 12 (Week 20)	141	127-154			
Visit 14 (Week 24)	169	155-182	127-210	127-210	1^{+}-266
Visit 16 (Week 28)	197	183-210			
Visit 18 (Week 32)	225	211-238			
Visit 20 (Week 36)	253	239-266	211-308	211-308	
Visit 22 (Week 40)	281	267-294			
Visit 24 (Week 44)	309	295-322			
Visit 26 (Week 48)	337	323-350			
Visit 28 (Week 52)	365	351-378(spirometry) 351-406(ACQ-IA)	309-406	309-406	267-406
Visit 29 (Week 56)	393	379-406(spirometry only)			
Visit 30 (Week 60)	421	407-434(spirometry only)			
Visit 31 (Week 64)	449	>434(spirometry) >406(ACQ-IA)	>406	>406	>406

1^{-}: up to randomization and before 1st dose date/time; 1^{+}: after randomization or 1st dose date/time

For the pharmacokinetics, immunogenicity, and pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP administration if the patient is treated with study treatment, or the randomization date if the patient is not treated. Pharmacokinetics /pharmacodynamics variables will be summarized by the analysis window defined in Table 14 for the by visit descriptive analyses. All available values of 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. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 14 - Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target day	Time windows for				
		TARC	Exhaled NO	Systemic drug concentration	Anti-drug antibodies	Total IgE/Antigen-specific IgE/IgG 4 panel
Visit 1 (Week -4±1)	-28±7					
Visit 2 (Week 0)	1	1^-	1^-	1^-	1^-	1^-
Visit 3 (Week 2)	15		1^+-21			
Visit 4 (Week 4)	29		22-35			
Visit 5 (Week 6)	43		36-49	1^+-63		
Visit 6 (Week 8)	57		50-63			
Visit 7 (Week 10)	71		64-77			
Visit 8 (Week 12)	85	1^+-126	78-98	64-126	1^+-126	
Visit 10 (Week 16)	113		99-126			
Visit 12 (Week 20)	141		127-154			
Visit 14 (Week 24)	169	127-266	155-182	127-266	127-266	1^+-266
Visit 16 (Week 28)	197		183-210			
Visit 18 (Week 32)	225		211-238			
Visit 20 (Week 36)	253		239-266			
Visit 22 (Week 40)	281		267-294			
Visit 24 (Week 44)	309		295-322			
Visit 26 (Week 48)	337		323-350			
Visit 28 (Week 52)	365	267-406	351-378	267-406	267-406	>267
Visit 29 (Week 56)	393		379-406			
Visit 30 (Week 60)	421		407-434			
Visit 31 (Week 64)	449	>406	>434	>406	>406	

1^-: up to 1st dose date/time or randomization if patient is not treated; 1^+: after 1st dose date/time or randomization date if patient is not treated;

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries, but will be used for computation of baseline, worst value and PCSAs.

2.5.6 Pooling of centers for statistical analyses

Due to the large number of centers, the randomization is stratified by country. Due to small sample size in some countries, the countries will be pooled into regions as defined below for the analyses:

- East Europe: Poland, Hungary, Romania, Lithuania, Turkey, Russia and Ukraine
- Western Countries: Australia, Canada, Italy, South Africa, Spain, and USA
- Latin America: Argentina, Brazil, Colombia, Chile and Mexico

2.5.7 Statistical technical issues

All statistical technical issues have been described in each associated sections.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database lock is planned based on the time when all randomized patients complete Week 52 visit or discontinue from the study before Week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR. Additional data between database lock and last patient completing last visit will be summarized in CSR addendum. In reality, because all patients have completed the follow-up visits shortly after the Week 52 visit of the last patient, the originally planned two DBLs will be integrated into one single final DBL. In this case, there will be one clinical study report, which will summarize all the data in the integrated DBL, instead of the originally planned one CSR plus one CSR addendum.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

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

2. Juniper E. Asthma control questionnaire: Background, administration and analysis. 2012; QOL Technologies, West Sussex, UK.

3. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324-43.

4. Juniper EH, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol. 1994;47(1):81-7.

7 LIST OF APPENDICES

Appendix A Potentially clinically significant abnormalities 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 ≥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 ≥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 ≥140 bpm and increase from baseline ≥20 bpm	
	6 to <12 years old (Children)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
	12 to 16/18 years old (Adolescents)	≤50 bpm and decrease from baseline ≥20 bpm ≥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	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
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	
QTc	Birth/0 to <12 years old (Neonates, Infants, Children)	Absolute values (ms) Borderline: 431-450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	**To be applied to QTcF** *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) Prolonged*: >450 ms (Boys); >470 ms (Girls) Additional: ≥500 ms AND Increase from baseline	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
		Borderline: Increase from baseline 30-60 ms 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 ≥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 ≥98 mmHg and increase from baseline ≥20 mmHg	
	24 months/2 years to <6 years old (Children)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥101mHg and increase from baseline ≥20 mmHg	
	6 to <12 years old (Children)	≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg	
	12 to 16/18 years old (Adolescents)	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119mmHg and increase from baseline ≥20 mmHg	
DBP	Birth/0 to 27 days old (Neonates)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥50mHg and increase from baseline ≥10 mmHg	
	28 days/1 month to 23 months old (Infants)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥54mHg and increase from baseline ≥10 mmHg	
	24 months/2 years to <6 years old (Children)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥59mHg and increase from baseline ≥10 mmHg	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72mHg and increase from baseline ≥10 mmHg	
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78mHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP : St — Su ≤ - 20 mmHg DBP : St — Su ≤ - 10 mmHg	
Temperature	All age ranges	Rectal, ear or temporal artery: ≥100.4 °F/38.0 °C Oral or pacifier: ≥99.5 °F/37.5 °C 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 >60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	<24 per minutes >40 per minutes	
	24 months/2 years to <6 years old (Children)	<22 per minutes >34 per minutes	
	6 to <12 years old (Children)	<18 per minutes >30 per minutes	
	12 to 16/18 years old (Adolescents)	<12 per minutes >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 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 By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥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 By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥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)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Total Bilirubin	All age ranges	≥1.3 ULN	CF = mg x 1.7 = µmol 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 Based on normal range: 0 to 0.4 mg/dL
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 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 (Adolescents)	≥132µmol/L or 1.5mg/dL	
Creatinine Clearance	All age ranges	50 % of normal <60 ml/min/1.73m2 (After 1 year old)	Based on GFR Bedside Schwartz Formula 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 ≥8.0 mg/dL or 476 µmol/L	CF = mg x 5.95 = µmol Based on normal ranges: 2.4 to 6.4 mg/dL

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
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 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 ≥115 mmol/L or 115 mEq/L	CF = 1 Based on normal range: 98 to 106
Sodium	All age ranges	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	CF = 1 Based on normal range : 134 to 146
Potassium	Birth/0 to 27 days old (Neonates)	≤3.0 mmol/L or 3.0 mEq/L ≥7.0 mmol/L or 7.0 mEq/L	CF = 1 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 ≥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 ≥5.5 mmol/L or 5.5 mEq/L	
Bicarbonate	All age ranges	≤16 mmol/L or 16 mEq/L ≥30 mmol/L or 30 mEq/L	CF = 1 Based on normal range: 18 to 26
Calcium total	All age ranges	≤2.0 mmol/L or 8.0 mg/dL ≥2.9 mmol/L or 11.6 mg/dL	CF = mg x 0.025 = mmol 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 ≥1.4 mmol/L or 5.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 4.0 to 5.1 mg/dL

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Total Cholesterol	All age ranges	≥6.20 mmol/L or 240 mg/dL	CF = g x 2.58 = mmol 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) CF = g x 1.14 = mmol 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 to32 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 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 Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
CRP	All age ranges	>2 ULN or >10 mg/L (if ULN not provided)	Based on normal ranges: <6 mg/L
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 >25.0 GIGA/L or 25,000 /mm3	To be used if no differential count available 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 >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 >16.0 GIGA/L or 16,000 /mm3	
	6 to <12 years old (Children)	<5.0 GIGA/L or 5,000 /mm3 >17.0 GIGA/L or 17,000 /mm3	
	12 to 16/18 years old (Adolescents)	<4,5 GIGA/L or 5,000 /mm3 >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 >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 >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 >9.5 GIGA/L or 9,500 /mm3	
	6 to <12 years old (Children)	<1.0 GIGA/L or 1,000 /mm3 >8.0 GIGA/L or 8,000 /mm3	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
	12 to 16/18 years old (Adolescents)	<0.6 GIGA/L or 600 /mm3 >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) <1.5 GIGA/L or 1,500 /mm3 (2-7 days old) <1.25 GIGA/L or 1,250 /mm3 (>7 day-1 month old) >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) <1.2 GIGA/L or 1,200 /mm3 (3-24 months) >1 ULN	
	24 months/2 years to <6 years old (Children)	<1.2 GIGA/L or 1,200 /mm3 >1 ULN	
	6 to <12 years old (Children)	<1.2 GIGA/L or 1,200 /mm3 >1 ULN	
	12 to 16/18 years old (Adolescents)	<1.2 GIGA/L or 1,200 /mm3 >1 ULN	
Eosinophils	All age ranges	>0.5 GIGA/L or 500 /mm3 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 $\geq$0.31 mmol/L or 2 g/dL	CF = g x 1.55 = mmol 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 $\geq$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 $\geq$0.31 mmol/L or 2 g/dL	
Hematocrit	Birth/0 to 27 days old (Neonates)	<0.39 l/l or 40 % >0.61 l/l or 47 %	CF = % x 0.01 = l/l 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 % >0.42 l/l or 42 %	
	24 months/2 years to <16/18 years old (Adolescents)	<0.32 l/l or 32 % >0.47 l/l or 47 %	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Platelets	All age ranges	<100 GIGA/L or 100,000 /mm3 >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 List of commonly used asthma controller therapies

ICS	ICS/LABA	LABA	Anti-leukotrienes	Long-acting muscarinic antagonist (LAMA)	Methylanthines
Beclomethasone dipropionate CFC	Fluticasone Propionate / Salmeterol	Salmeterol	Montelukast	Tiotropium	Aminophylline
Beclomethasone dipropionate HFA	Fluticasone Propionate / Formoterol	Formoterol	Pranlukast	Glucopyrronium bromide	Theophylline
Budesonide DPI	Fluticasone Furoate / Vilanterol	Bambuterol	Zafirlukast	Aclidinium bromide	Dyphylline
Budesonide HFA	Budesonide /Formoterol	Clenbuterol	Zileuton	Umeclidinium	Oxtryphylline
Budesonide nebules	Mometasone Furoate / Formoterol	Tulobuterol			Diprophylline
Ciclesonide HFA	Beclometasone Dipropionate and Formoterol	Vilanterol			Acebrophylline
Flunisolide HFA		Olodaterol			Bamifylline
Fluticasone propionate HFA		Indacaterol			Doxofylline
Fluticasone propionate DPI					
Mometasone furoate					
Triamcinolone acetonide					
Fluticasone furoate					

Appendix C Low, medium and high dose inhaled corticosteroids- Children (6-11 years)

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–<440	≥440
Triamcinolone acetonide	400–800	>800–1200	>1200

CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; nebules = nebulized solution
Source: Adapted from Global Initiative for Asthma (GINA) 2015 guidelines with the addition of Budesonide HFA and Flunisolide information

Appendix D Handling of missing data

Annualized severe exacerbation events during the 52-Week period

- ***Pattern mixture model (PMM)***
  Step 1. The 52-week observation period is partitioned into monthly (4-week) segments. In the analysis, for each patient, in each month, an imputation flag (imputefl) will indicate whether the patient needs imputation in that month.

  Step 2. ***Calculation of observed monthly mean of event count***

  Within each month, the logistic regression model will be fitted to the observed data to model coefficient estimates and the estimated variance-covariance matrix, with adjusting for the planned treatment group, age, baseline weight (≤30kg, >30kg), region (pooled country), baseline eosinophil level (removed for the baseline eosinophils ≥0.3 Giga/L population), baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. From the posterior distribution of the model coefficients, we randomly draw 40 sets of iid samples. As a result, for each patient and in each month, 40 estimated probabilities can be obtained by using the 40 samples of coefficients and the patient's covariates values.

  Step 3. ***Imputation of event count after study withdrawal***

  If a patient withdraws from the study at the kth ($1 \leq k < 28$) day of Month i prior to Week 52, and experienced a severe exacerbation within the first k days, this patient will be considered as "observed" (imputefl=0) up to Month i and will need imputations (imputefl=1) from Month $i+1$ to Month 13 (Week 52).

  If a patient withdraws from the study at the kth ($1 \leq k < 28$) day of Month i prior to Week 52, and has no severe exacerbation in Month i, this patient will be considered as "observed" (imputefl=0) up to Month $i-1$ and will need imputations (imputefl=1) from Month i to Month 13 (Week 52).

  For a patient who needs imputation from Month $i+1$ to Month 13, in each month, 40 independent random samples will be respectively drawn from 40 estimated Bernoulli distributions, whose probabilities are obtained in Step 2. For each patient who early withdraws from the study, 40 sets of complete event count data can be obtained by summing the observed event count prior to withdrawal and each series of imputed binary events after withdrawal up to Week 52.

Step 2 and 3 can be realized by using PROC MI in SAS. Sample code can be found below:

```
proc mi data=dd seed=9816388 nimpute=40 out=outdata;
by month;
class outcome trt01pn weight eosbgp1n cntygr1 icsgrp fenoblgrn ;
monotone reg (asmanum/details)
logistic (outcome=trt01pn age weight eosbgp1n cntygr1 icsgrp fenoblgrn asmanum/details
DESCENDING);
var eosbgp1n cntygr1 age icsgrp trt01pn fenoblgrn asmanum outcome;
run;
```

Step 4. A negative binomial model with the same set of covariates as in the primary endpoint analysis will be fitted with 40 sets of complete datasets obtained in Step 3, so as to obtain 40 sets of treatment effect estimates and p-values accordingly. Log transformed observation duration will be the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 18 (Week 52). At last, the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 4 can be realized by using PROC MIANALYZE in SAS. Sample code can be found below

```
proc mianalyze data=rr_conv;
by Label;
modeleffects Estimate;
stderr StdErr;
ods output ParameterEstimates=rr_pooled;
run;
proc mianalyze data=aer_conv;
by TRT01PN;
modeleffects Estimate;
stderr;
ods output ParameterEstimates=aer_pooled;
run;
```

- ***Control-based PMM***

  All steps are the same as the aforementioned approach except in **Step 2**: the individual monthly mean probability will be calculated based on observations in placebo arm only, with adjustment of missing observation duration.

- ***Tipping point analysis***
  The tipping point analysis for severe exacerbation events will use the similar approach as PMM-MI with tipping values for the odds

Step 1. ***Estimation for the monthly binary event probability using observed data***

Within each month up to Week 52, the logistic regression model will be fitted to the observed data to obtain the model coefficient estimates and the estimated variance covariance matrix, with adjusting for the planned treatment group, age, baseline weight (≤30kg, >30kg), region (pooled country), baseline eosinophil level (removed for the baseline eosinophils ≥0.3 Giga/L population), baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. From the posterior distribution for the model coefficients, we randomly draw 40 sets of iid samples. As a result, for each patient and in each month, 40 estimated binary event probabilities can be obtained by using the 40 samples of coefficients and the patient's covariate values.

Step 2. ***Tip on the monthly binary odds (the probability of have an event in the month over the probability of being event-free in the month)***

Within each month, for the patients from the placebo group(s) and need imputation in that month, the estimated odds for binary event will be deflated by decreasing a positive amount; for the patients from the treatment group(s) and need imputation in that month, the estimated odds for binary event will be inflated by increasing a positive amount. After the deflation/inflation, 40 sets of binary event probabilities can be obtained for the placebo and treatment groups, respectively.

Step 3. ***Multiple Imputation of binary event by month after study withdrawal***

For a patient who needs imputation from Month i+1 to Month 13, in each month, 40 independent random samples will be respectively drawn from 40 estimated Bernoulli distributions, whose probabilities are obtained in Step 2.

For each patient who early withdraws from the study, 40 sets of complete event count data can be obtained by summing the observed event count prior to withdrawal and each series of imputed binary events after withdrawal up to Week 52.

Step 4. A negative binomial model with the same set of covariates as in the primary analysis will be fitted to the 40 sets of complete datasets obtained in Step 3, so as to obtain 40 sets of treatment effect estimates and p-values accordingly. Log transformed observation duration will be the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 18 (Week 52). Then, the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 2, 3 and 4 will be repeated iteratively until the p-value for combined treatment effect of dupilumab compared to placebo estimated in Step 4 is >0.05.

Change from baseline in % predicted pre-BD FEV1 at Week 12

Pattern mixture model-multiple imputation (PMM-MI)

Step 1. Monotone missing pattern was induced by Markov Chain Monte Carlo (MCMC) method using PROC MI: for patients who have missing values at intermediate visits, but have value at subsequent visits, the intermediate missing values were imputed assuming a multivariate normal distribution over observations from all visits. 40 datasets with a monotone missing pattern will be obtained using this method.

Step2. For each of the imputed dataset with monotone missing pattern obtained in Step 1, the remaining missing data will be imputed using the regression method for the monotone pattern with adjustment for covariates including response variable, treatment groups, baseline weight (≤30kg, >30kg), region (pooled country), ethnicity, baseline eosinophil level (removed for the baseline eosinophils ≥0.3 Giga/L population), baseline FeNO level, baseline ICS dose level, and baseline % predicted pre-BD FEV1 and missing pattern defined by reason of treatment discontinuation. All available data in the monotone missing pattern data will be used. 40 fully imputed datasets are obtained.

Step 3. Each of the 40 complete datasets will be analyzed using an ANCOVA model with change from baseline in % predicted pre-BD FEV1 at Week 12 as the response variable, treatment, baseline weight (≤30kg, >30kg), region (pooled country), ethnicity, baseline eosinophil level (removed for the baseline eosinophils ≥0.3 Giga/L population), baseline FeNO level, baseline ICS dose level, and baseline % predicted pre-BD FEV1 value as covariates. Then the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Control based PMM-MI

The analysis is similar as the standard PMM-MI described above, except **Step 2**. To implement control-based imputation, we broke the imputation process into a sequence of PROC MI, where each call is to impute missing values at one time-point only. The steps are as follows:

Step 2.1 Call PROC MI to impute values for the first time-point *t* with missing values. The input dataset include data up to time-point *t* for all Placebo patients and patients on Dupilumab with missing values at time-point *t*.

Step 2.2 Repeat Step 2.1 for all the following time-points sequentially. Data imputed in the previous step will be included for imputation of missing values at time-point *t+1*.

Tipping point analysis

Step 1. 40 imputations will be performed to generate 40 completed data sets following Step 1 and 2 for PMM-MI.

Step 2. The imputed % predicted FEV_1 values in Dupilumab group are subtracted by a positive amount *d* for each imputed data sets.

Step 3. The imputed % predicted FEV_1 values in placebo group are added by a positive amount *p* for each imputed data sets.

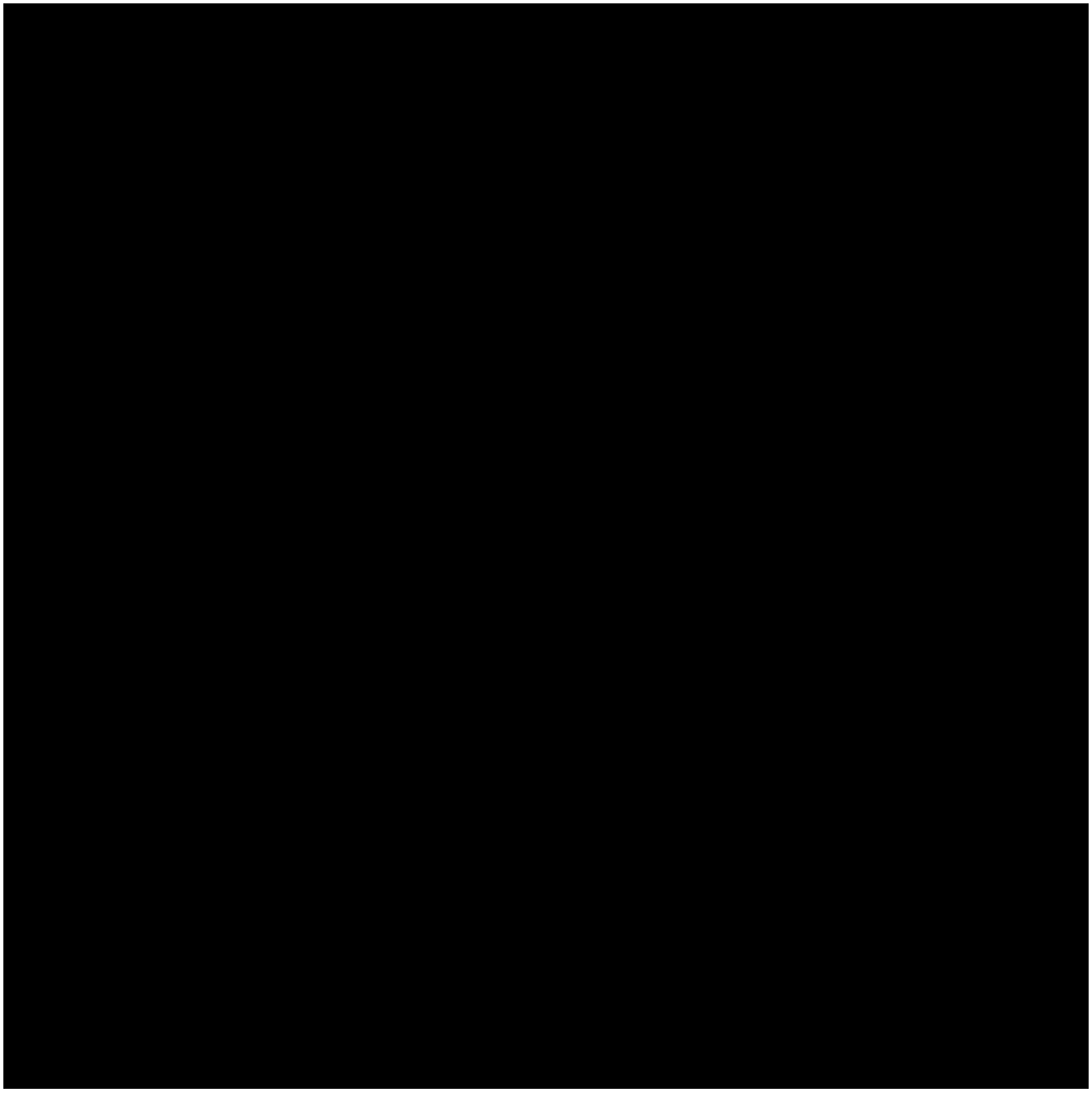
Step 4. Change from baseline in % predicted pre-BD FEV1 will be analyzed using the ANCOVA model as described in the PMM-MI for each of the 40 complete datasets. Then the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 2 and Step 3 will be repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated in Step 4 is >0.05.

Appendix E Asthma Control Questionnaire-Interviewer Administered (ACQ-IA) for Children 6 to <12 years

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

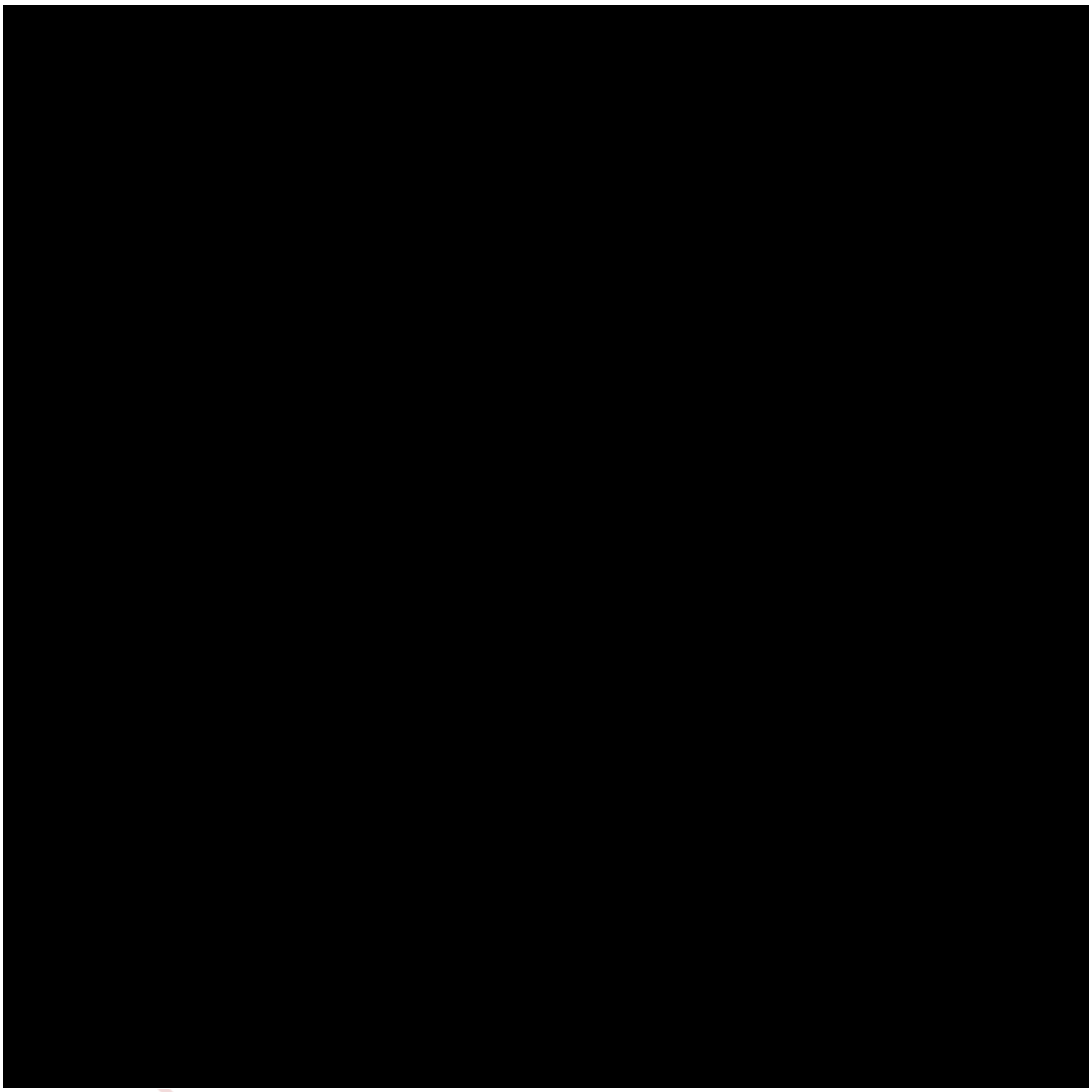
JULY 2011



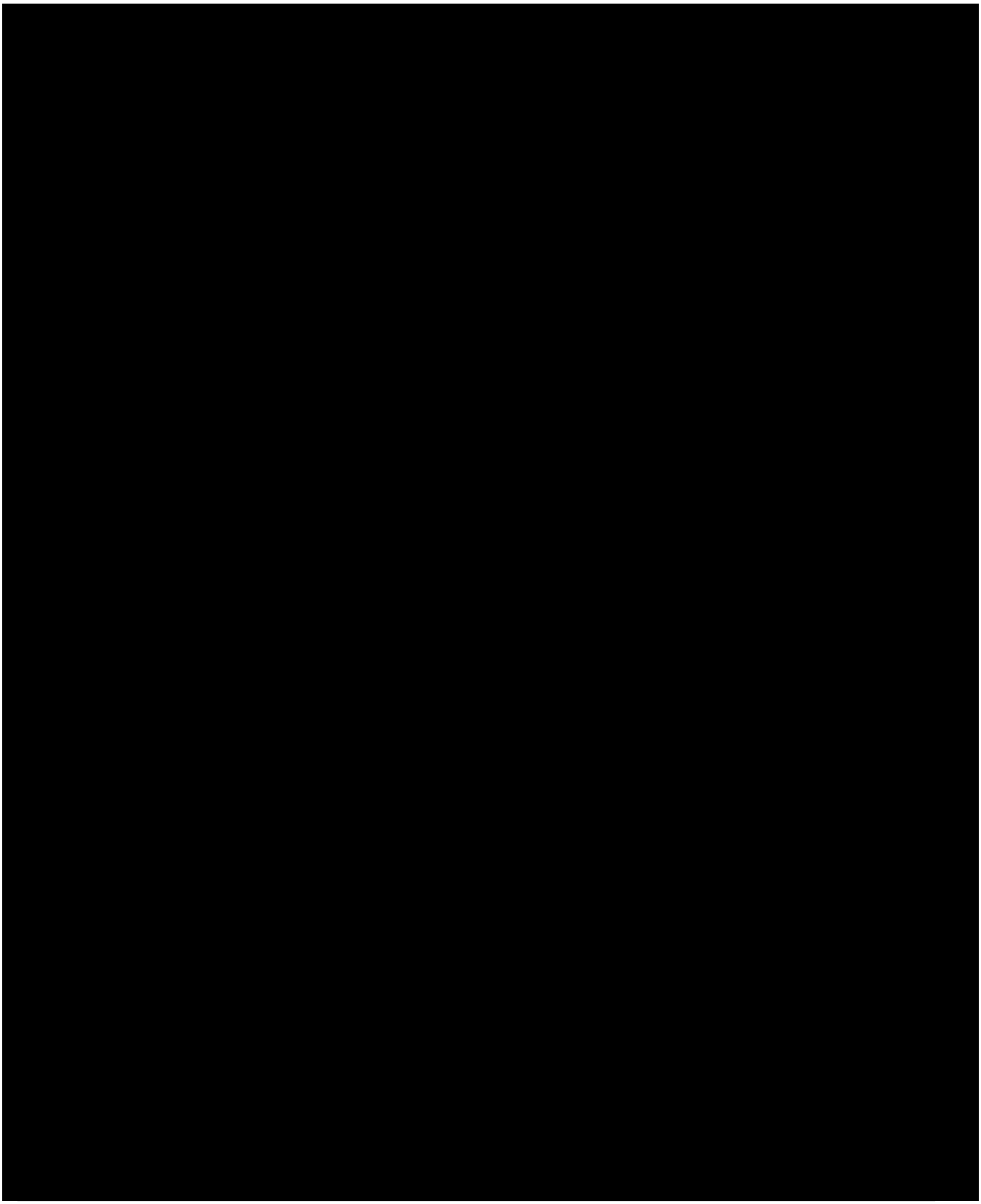
[redacted]

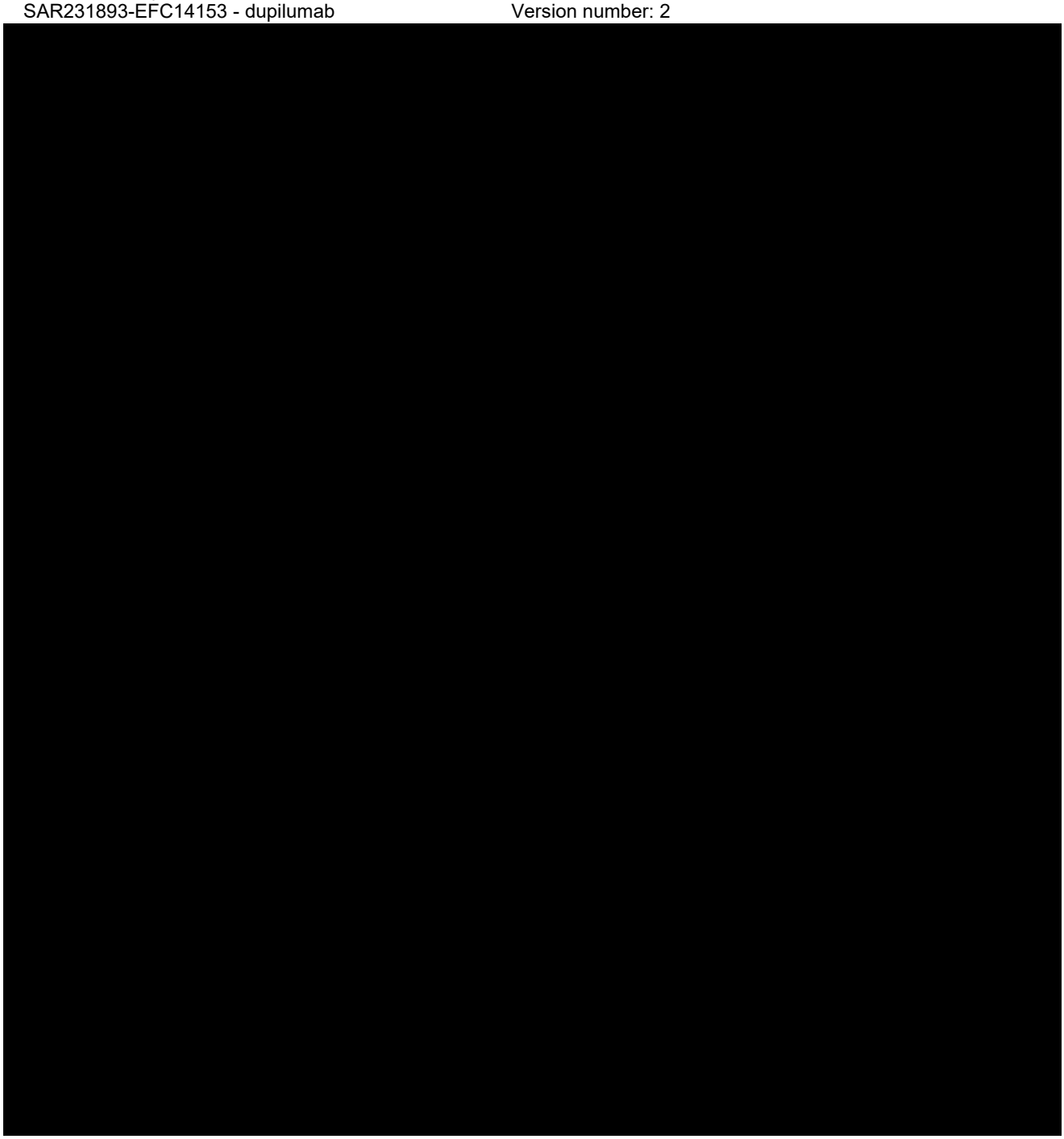
Appendix F Asthma Symptom Score Numerical Rating Scale (NRS)

Appendix G Paediatric Asthma Quality of Life Questionnaire With Standardised Activities(PAQLQ[S])



JANUARY 2001





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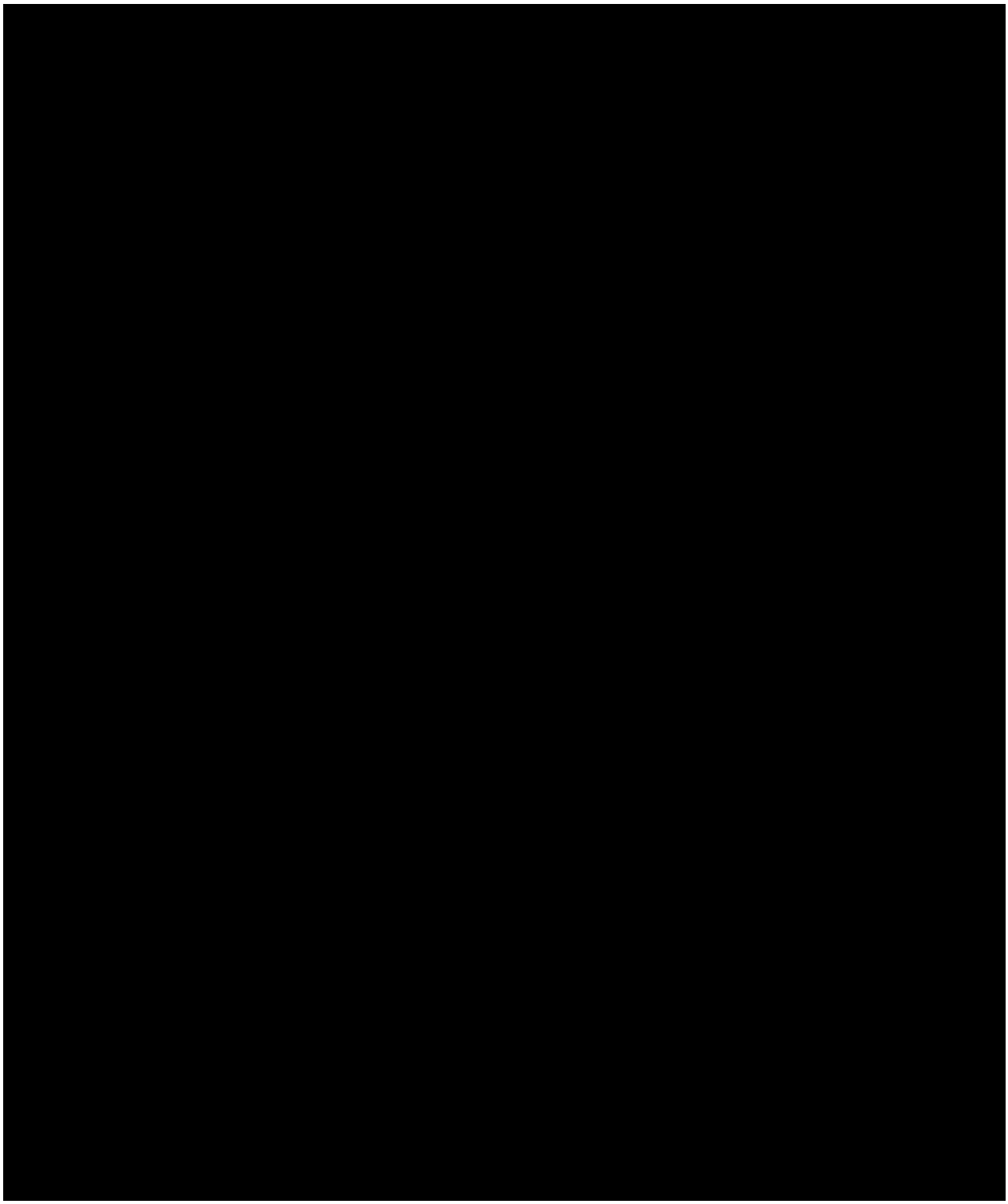
Appendix H EuroQual Questionnaire (EQ-5D-5Y) – for Children



[redacted]

Appendix I Pediatric Rhinoconjunctivitis Quality of Life Questionnaire– Interviewer Administered (PRQLQ-IA) – for Children with Comorbid Allergic Rhinitis

[redacted]

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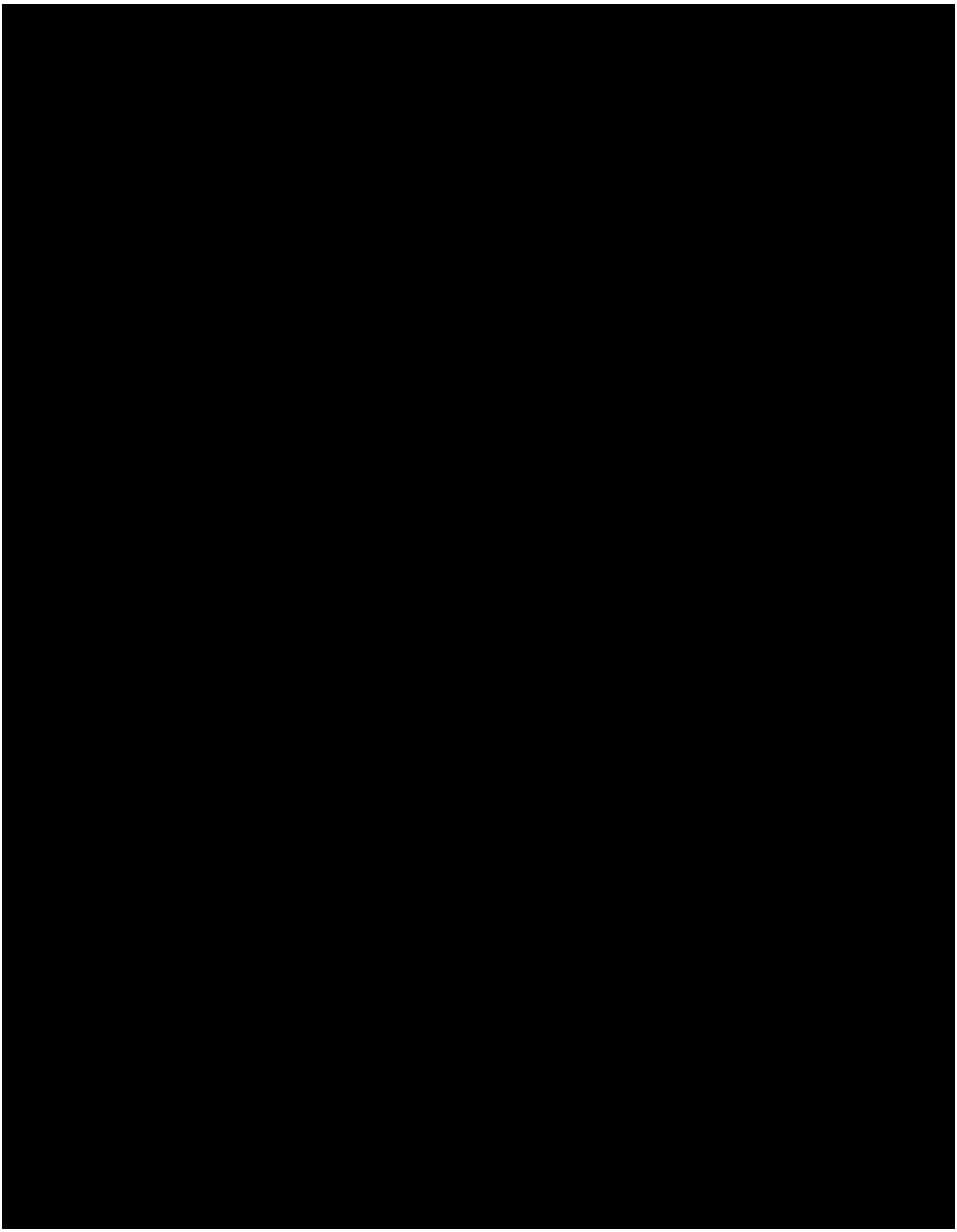
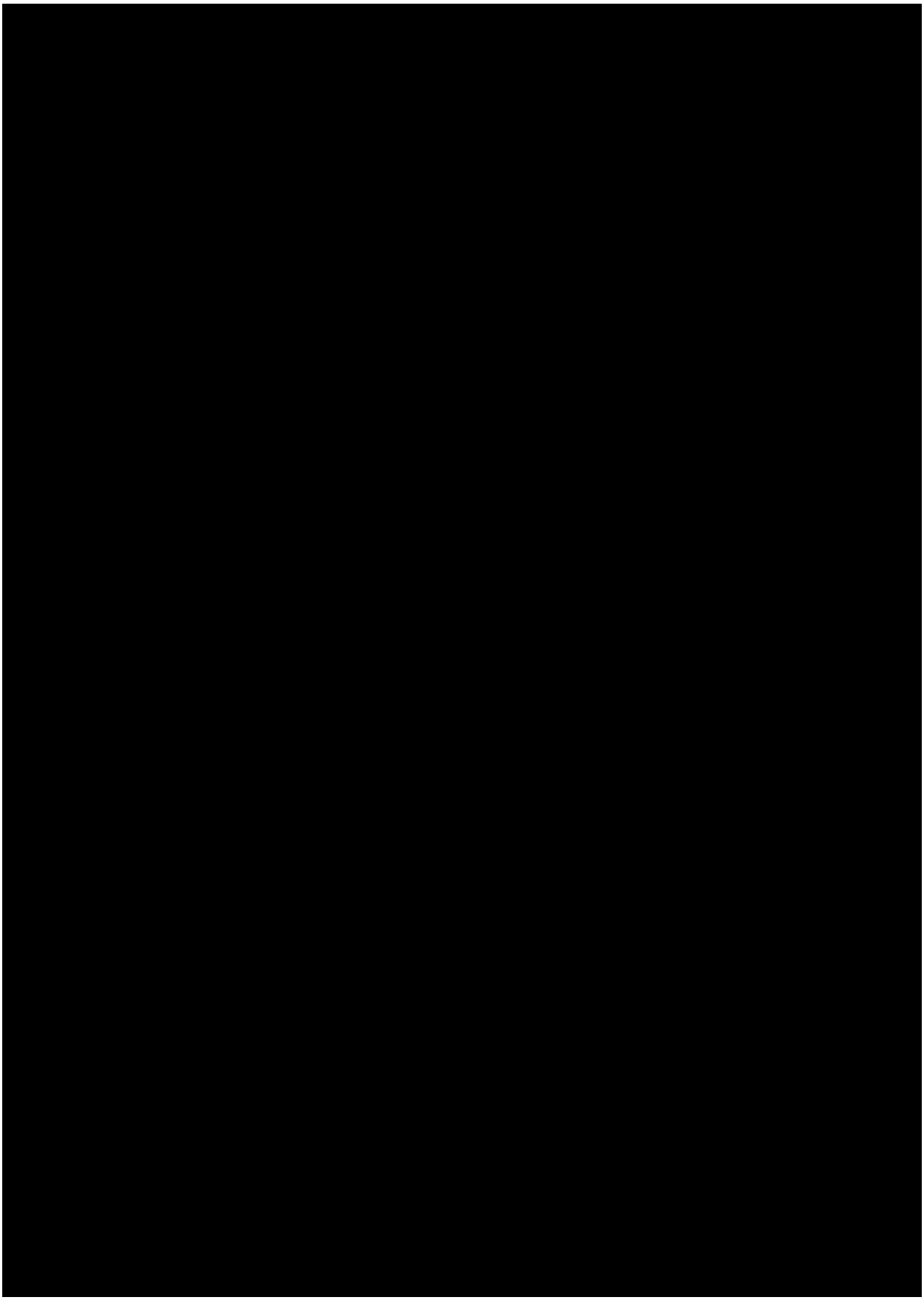
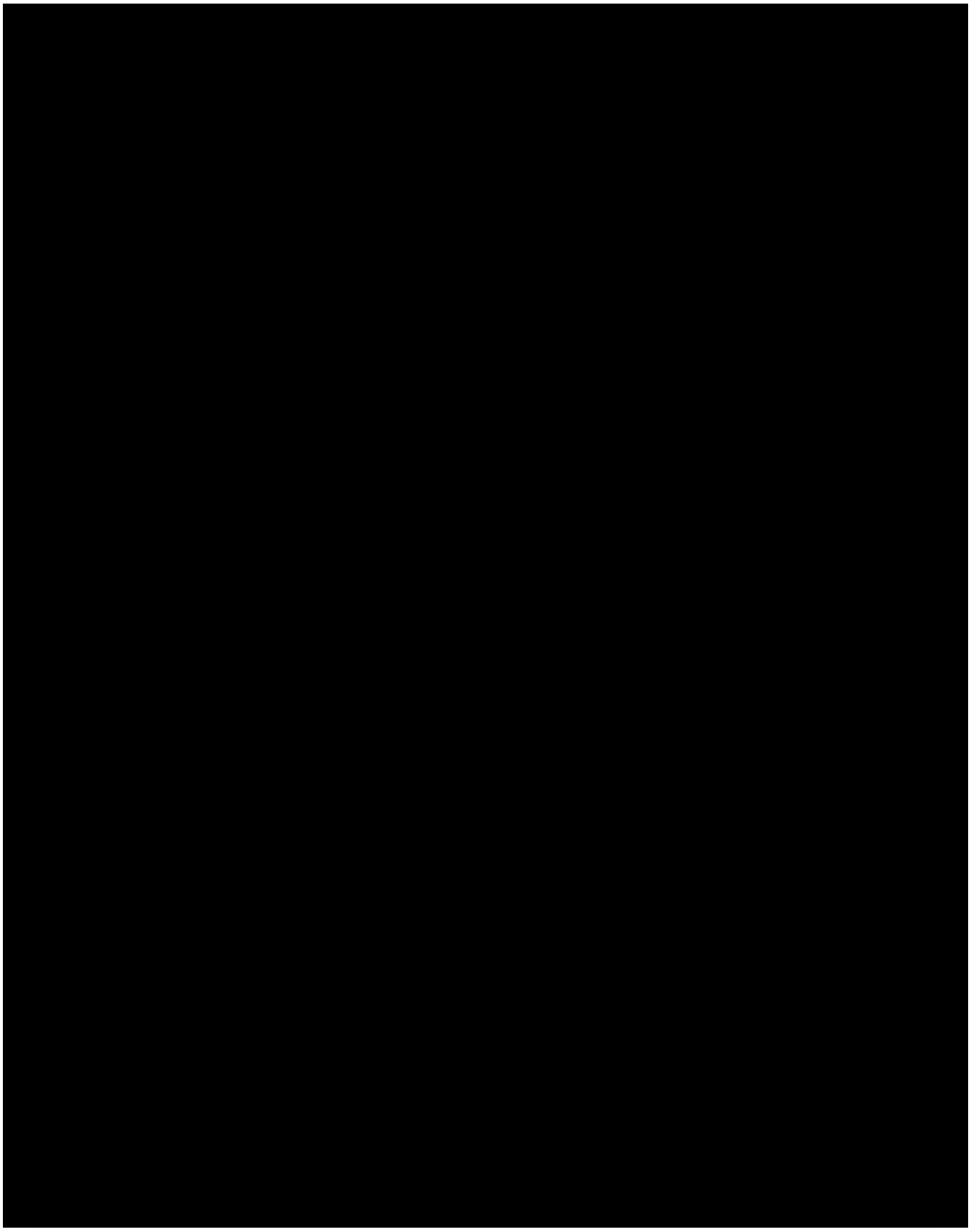
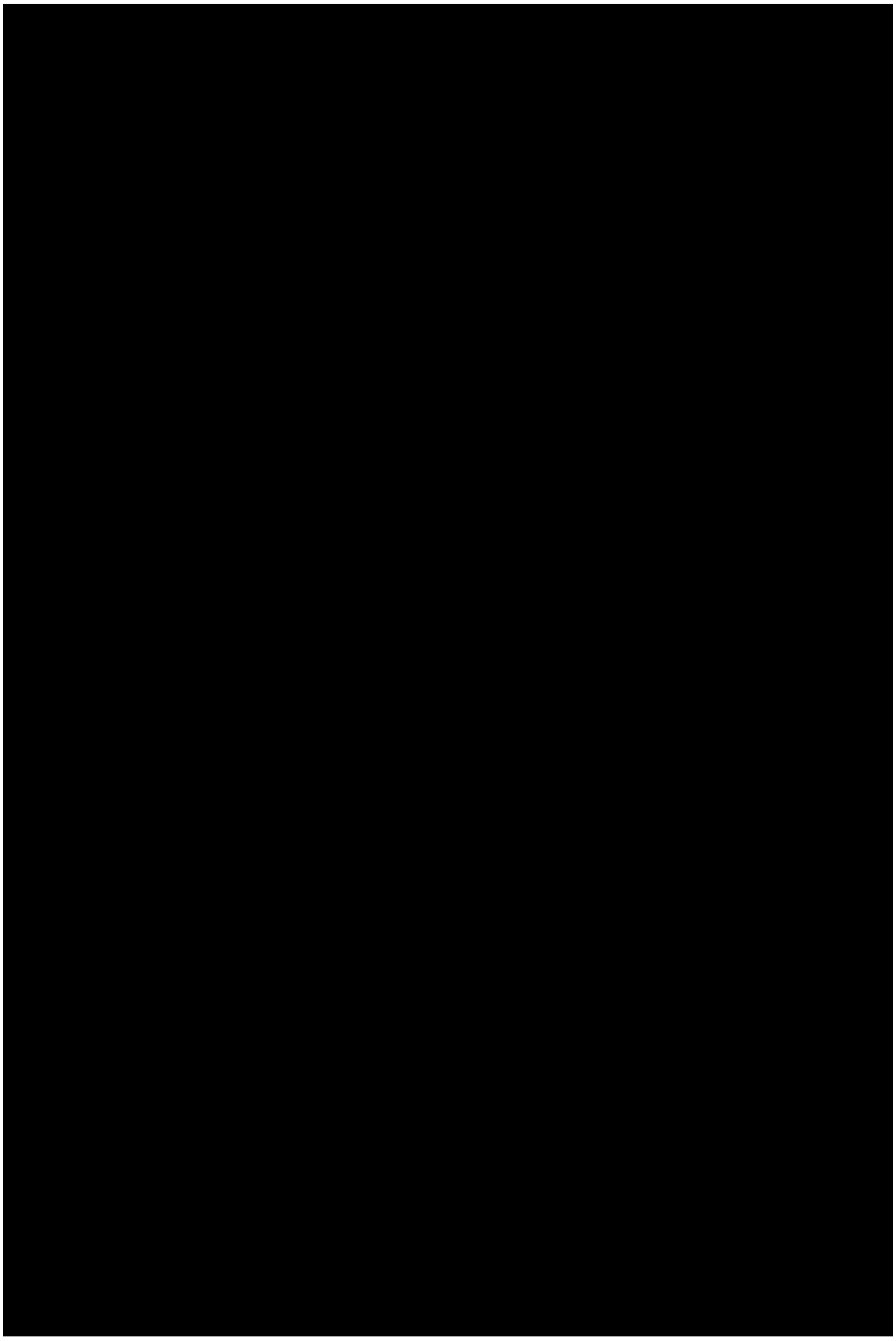
MAY 1999





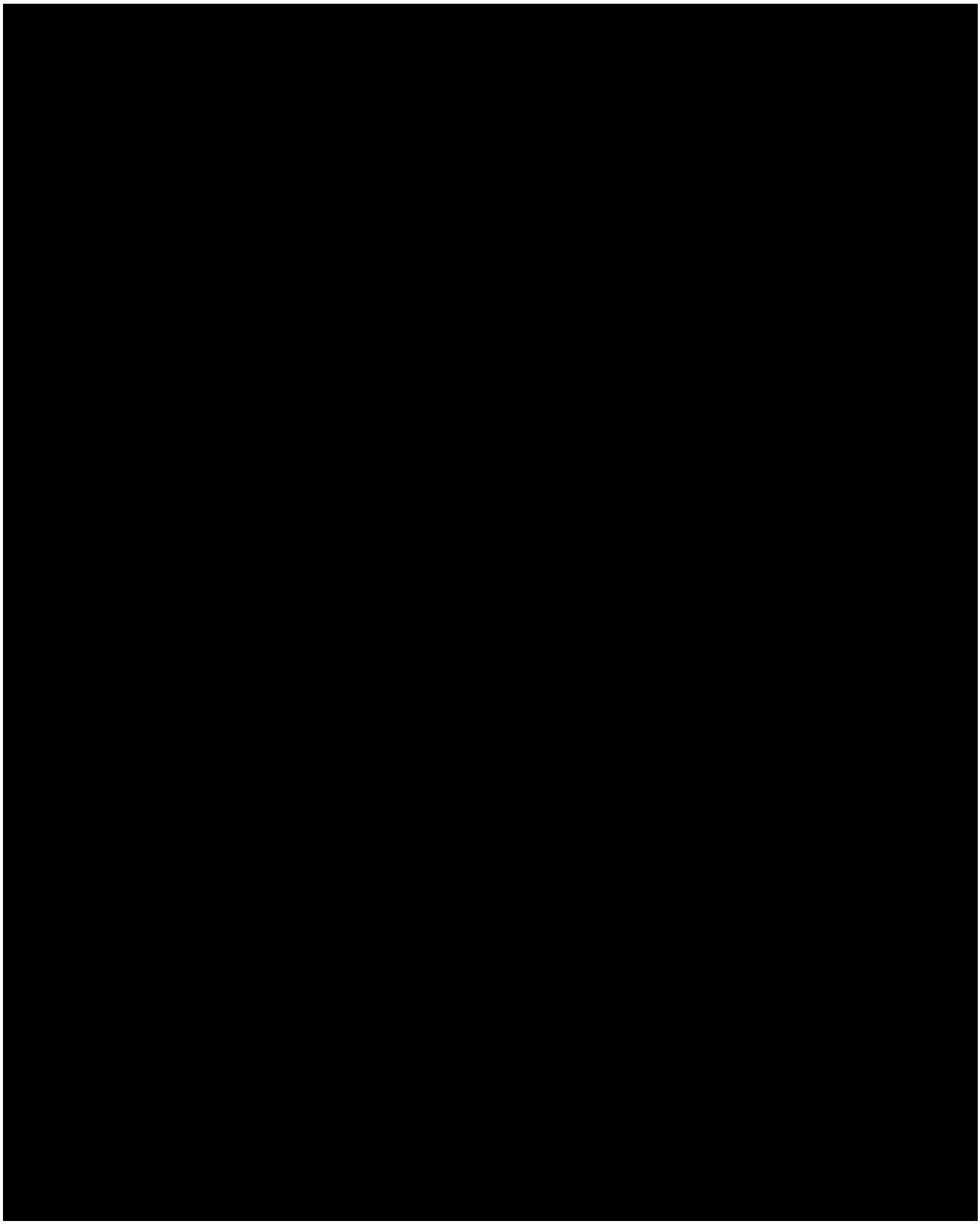


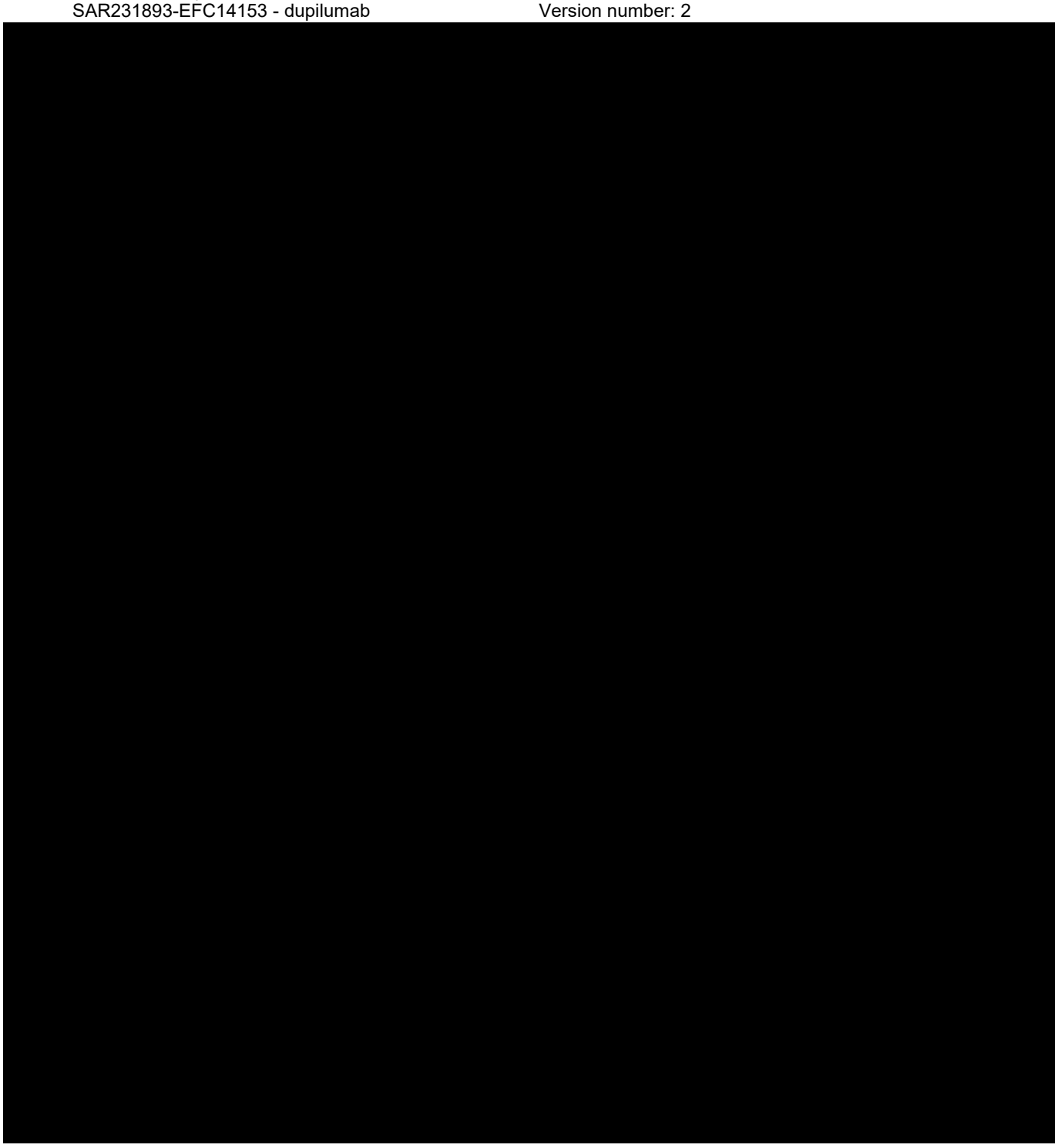


Appendix J Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ)

[redacted]

JANUARY 2001





Appendix K 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.

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 L List of opportunistic infections

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis – Note that all cases should be collected as AEs (or SAEs if requirements met), however, only cases which are NOT cutaneous (systemic or mucous membranes involved) unless involvement is extensive, will be considered as AE with pre-specified monitoring.
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (severe/disseminated)
- Herpes Zoster
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)

This list is indicative and not exhaustive

Appendix M Summary of the planned analyses by population

Section	Analyses	Type 2 inflammatory asthma phenotype	Baseline Eosinophils ≥0.3 Giga/L	Baseline Eosinophils ≥0.15 Giga/L	Baseline FeNO ≥20 ppb	Full ITT	Safety	PK /ADA
Disposition	Patient disposition	Y	Y			Y		
Demographics and baseline characteristics	Demographics, baseline characteristics, baseline biomarkers, atopic medical history	Y	Y	Y	Y	Y		
	Others					Y		
Medication	Prior, concomitant and controller medications	Y	Y			Y		
IMP Exposure	IMP compliance and dosing	Y	Y				Y	
Efficacy	Annualized severe exacerbation rate during 52-week treatment period	Y	Y	Y	Y	Y		
	Change from baseline in % predicted FEV1 at Week 12	Y	Y	Y	Y	Y		
	Change from baseline in % predicted FEV1 up to Week 52	Y	Y	Y	Y	Y		
	Change from baseline in ACQ-7-IA at Week 24	Y	Y	Y	Y	Y		
	Annualized severe exacerbation rate during 52-week treatment period in patients with baseline high ICS dose	Y	Y	Y	Y	Y		
	Change from baseline in FeNO at Week 12	Y	Y	Y	Y	Y		
	On-treatment analysis, missing data sensitivity analyses, and subgroup analyses (except for EOS/FeNO) for endpoints of severe exacerbation and % predicted FEV1 at Week 12	Y	Y					
	Baseline EOS/FeNO subgroup analyses, and EOS-FeNO quadrant analyses for endpoints of severe exacerbation and % predicted FEV1 at Week 12					Y		
	LOAC, severe exacerbation leading to hospitalization/ER, time-to-event, other spirometry endpoints, PRO, change from baseline for continuous endpoints at all time points, and other efficacy endpoints	Y	Y					
	Systemic corticosteroid exposure	Y	Y	Y	Y			
Safety / Biomarker	The endpoints of AE, Laboratory, Vital sign, ECG, Eosinophils, and Biomarkers						Y	
PK/ADA	Endpoints of PK, ADA and NAb							Y

Signature Page for VV-CLIN-0551071 v2.0
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Approve & eSign	[redacted]	

Approve & eSign	[redacted]	