AMENDED CLINICAL TRIAL PROTOCOL 03

COMPOUND: DUPILUMAB/SAR231893

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

STUDY NUMBER: EFC14153

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NAMES AND ADDRESSES OF

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	18-Oct-2019, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 02	All	18-Jun-2018, version 1 (electronic 5.0)
Protocol Amendment 03	All	18-Jun-2018, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	Brazil	02-Feb-2018, version 1 (electronic 1.0)
Protocol Amendment 02	Brazil	02-Feb-2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	All	10-Mar-2017, version 1 (electronic 1.0)
Protocol Amendment 01	All	10-Mar-2017, version 1 (electronic 1.0)
Original Protocol		04-Aug-2016, version 1 (electronic 1.0)

AMENDED PROTOCOL 03 (18 October 2019)

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

OVERALL RATIONALE FOR THE AMENDMENT

To change the study primary efficacy analysis population from an overall uncontrolled persistent asthma population to the subpopulation with evidence of either asthma with an eosinophilic phenotype or, more broadly, asthma with type 2 inflammatory phenotype. This is to be consistent with the observed efficacy seen in the pivotal Study EFC13579 (QUEST) as well as approved label indications for adults and adolescents with asthma.

Protocol amendment summary of change table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary 11.3.1 Analysis population 11.4.2.1 Analysis of Primary Efficacy Endpoint(s) 11.4.2.2 Analyses of Secondary Efficacy Endpoints	Change of primary efficacy analysis population from full intent-to-treat (ITT) to patients with either "asthma with an eosinophilic phenotype" or with "asthma with type 2 inflammatory phenotype".	[redacted]
4 Introduction and Rationale	Description of type 2 inflammatory phenotype population	To support the change of primary efficacy analysis population

Clinical trial summary 1 Flow chart 1.1 Overview of study design 11.1 Determination of sample size	Change of study sample size.	The population of interest is asthma patients with either “asthma with an eosinophilic phenotype” or “asthma with type 2 inflammatory phenotype” based on the observed efficacy from the QUEST study and on the approved indications in different regions. With regard to these populations, the sponsor has designated a primary analysis population and additional secondary analysis populations based on these two populations of interest. The sponsor has updated the sample size needed to demonstrate efficacy based on these definitions for the primary analysis populations. [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.

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary 11.4.2.3 Multiplicity considerations	To specify that different hierarchy orders are to be used for US and US reference countries and EU and EU reference countries.	[redacted]
Clinical trial summary 8.4 Method of assigning patients to treatment group 11.1 Determination of sample size	Removal of the limit in enrolling patients according to background therapy with medium-dose ICS or blood eosinophil count level	[redacted]

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary	To describe the Planned Database lock	To define a date for database lock when all randomized patients complete the week 52 visit or discontinue from the study before week 52.
Clinical trial summary 9.3.1.3 Biomarker endpoints 9.4.1 Exploratory endpoints	To classify FeNO as a secondary endpoint instead of an exploratory endpoint.	Based on the strong pharmacodynamics effect of FeNO on QUEST, the Sponsor anticipates similar effect in this population and feels appropriate to investigate it as secondary endpoint.
1.2 Study flow chart footnote y 9.2.3.5 Clinical Laboratory Safety Variables	To describe the fasting status	Fasting status will be described as no intake of any food or drink except for water for at least 8 hours.
1.2 Study Flow Chart; footnote m 8.1.4 Dosing schedule	To allow for home dosing start after Visit 9	IMP home administration is allowed at any visit following Visit 9 after parents have been trained and PI has allowed.
Clinical trial summary 7.1 Inclusion Criteria	To clarify that ACQ 5 data collected on V2 can be used for inclusion criterion 01	To clarify that ACQ 5 value at V2 shall be considered for the evidence of uncontrolled asthma described in inclusion criterion 01
9.2.2.4.1.1 ACQ-7-IA (Asthma Control Questionnaire–Interviewer Administered, 7-question version)	To clarify how ACQ-7 value is calculated for statistical analysis	To add the information that for statistical analysis, ACQ-7 global score is calculated by sponsor using the BMS post central reading value for %predicted FEV1 for the question 7 of the questionnaire.
[redacted]	[redacted]	[redacted]
10.3.5 Procedure and Consequence for Patient Withdrawal from Study	To remove a sentence on the possible hurdle to public health value of the study in case of study withdrawal	To remove the sentence due to the change in Protocol template

CLINICAL TRIAL SUMMARY

COMPOUND: Dupilumab	**STUDY No.: EFC14153**
TITLE	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.
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVES	**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 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 assess the dupilumab systemic exposure and incidence of anti-drug antibodies (ADA). • 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 **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
STUDY DESIGN	**General Design** Multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study assessing the effect of dupilumab administered subcutaneously (SC) for a maximum of 52 weeks in children 6 to <12 years of age with uncontrolled asthma. **Periods** 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

	Screening Period Prior to and during the Screening Period, patients must be on one of the following: stable-dose background therapy of medium-dose ICS with second controller medication (ie, long-acting β2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1. The Screening Period will be of 4 (±1) weeks in duration. **Randomized Treatment Period** Patients are randomized to either dupilumab or matching placebo administered SC for a maximum treatment duration of 52 weeks. During the Randomized Treatment Period, patients continue the stable dose(s) of controller medication used during the Screening Period. For patients experiencing a deterioration of asthma during the study, the ICS dose may temporarily be increased up to 4-fold (recorded as a loss of asthma control [LOAC] event) for a maximum of 10 days, as indicated and upon recommendation of the physician and/or Investigator. Treatment may then be changed to systemic corticosteroids (severe exacerbation event) or revert back to the original ICS dose depending on asthma symptom progression. Patients may be placed on systemic corticosteroids at any time as clinically indicated based on the presence of symptoms consistent with a severe asthma exacerbation event, as per the Investigator's judgment. If a patient experiences 2 or more severe asthma exacerbation events anytime during the study, a permanent change (ie, step up in medium- to high-dose ICS or addition of second controller for patients on high-dose ICS monotherapy) on their stable-dose background controller medication may occur, as indicated and upon recommendation of the physician and/or Investigator. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for study visits and participate in assessments according to the visit schedule until the end of the study (EOS) with a ±5 day window or up to recovery or stabilization of any adverse event (AE). At the time of permanent treatment discontinuation, patients will perform the early treatment discontinuation (ETD) visit with all the assessments defined for the end-of-treatment (EOT) Visit 28. Patients who permanently discontinue early from treatment will not be eligible for the 1-year long-term extension study. For patients who permanently discontinue the study, under exceptional circumstances where there is no possibility for a patient and parent(s)/caregiver(s)/legal guardian(s) to come to the site for the scheduled follow-up visit, a phone contact may be made after Sponsor's approval is given. During that phone contact, at least information about AEs, concomitant medication and asthma exacerbation events must be collected, and the schedule for these calls should still reflect the visit schedule. Patients who discontinue early from treatment may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall assessment of antibody titers and clinical presentation at the time of discontinuation.

	Post-treatment Period After completing the treatment period, patients are evaluated for 12 weeks (± 5 days) in the post-treatment period. During this follow-up period, patients continue treatment with their stable dose of controller medication or it can be modified based on their level of asthma control, as determined by the Investigator. Eligible patients who complete the Randomized Treatment Period will be offered the opportunity to participate in the 1-year long-term extension study with dupilumab. Patients subsequently enrolled in the 1-year long-term extension study will not participate in the post-treatment period of this trial.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Children 6 to <12 years of age, with an Investigator diagnosis of persistent asthma for ≥12 months prior to Screening, based on clinical history and examination, pulmonary function parameters according to Global initiative for asthma (GINA) 2015 Guidelines and the following criteria: - Existing background therapy of medium-dose ICS with second controller medication (ie, LABA, LTRA, LAMA, or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1. - Pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≤95% of predicted normal or pre-bronchodilator FEV1/forced vital capacity (FVC) ratio <0.85 at Screening and Baseline Visits. - Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puff inhalations with metered-dose inhaler [MDI]) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication if tolerated by the patient). **Note:** A maximum of 3 visits to meet the qualifying criterion of reversibility may be made during the screening period and prior to the patient's randomization. **Note:** Documented reversibility or positive airway hyperresponsiveness to methacholine within 12 months prior to Screening V1 is considered acceptable. - Must have experienced, within 1 year prior to Screening Visit 1, any of the following events: a) Treatment with a systemic corticosteroid (SCS, oral or parenteral), as prescribed by a healthcare professional for worsening asthma at least once or, b) Hospitalization or emergency room visit for worsening asthma. - Evidence of uncontrolled asthma, with at least one of the following criteria during the 4 (±1)-week Screening Period: a) Asthma Control Questionnaire–Interviewer Administered (ACQ-IA) ACQ-5 score ≥1.5 on at least one day of the Screening Period including V2.

	b) Use of reliever medication (ie, albuterol/salbutamol or levalbuterol/levosalbutamol), other than as a preventive for exercise induced bronchospasm, on 3 or more days per week, on at least one week during the Screening Period. c) Sleep awakening due to asthma symptoms requiring use of reliever medication at least once during the Screening Period. d) Asthma symptoms 3 or more days per week on at least one week during the Screening Period. **Exclusion Criteria:** E 01. Patients <6 or ≥12 years of age. E 02. Patients <16 kg body weight (bw). E 03. Any other chronic lung disease (cystic fibrosis, bronchopulmonary dysplasia, etc) which may impair lung function. E 04. A subject with any history of life threatening asthma (ie, extreme exacerbation that requires intubation). E 05. Co-morbid disease that might interfere with the evaluation of IMP
Total expected number of patients	Approximately 402 patients will be randomized in a 2:1 ratio to receive dupilumab (268) or placebo (134).
STUDY TREATMENT(s)	
Investigational medicinal product(s)	Dupilumab (SAR231893/REGN668) or matching placebo
Formulation:	Dupilumab for children ≤30 kg bw at randomization: 150 mg/mL in pre-filled syringe to deliver a once every 2 weeks (q2w) dose of 100 mg in a 0.67 mL subcutaneous injection. Dupilumab for children >30 kg bw at randomization: 175 mg/mL in pre-filled syringe to deliver a once q2w dose of 200 mg in a 1.14 mL subcutaneous injection. Placebo: Matching placebo in a prefilled syringe to deliver a once q2w dose of placebo in a 0.67 or 1.14 mL subcutaneous injection for children with ≤30 or >30 kg bw at randomization, respectively.
Route(s) of administration:	Subcutaneous (SC) injection
Dose Regimen	Randomized 2:1 to the following regimens: • Dupilumab 200 or 100 mg SC once q2w for children with bw >30 kg or ≤30 kg, respectively. • Placebo SC q2w After randomization, dose regimen will not be adjusted for patient's age or weight during the Randomized Treatment Period of this study.
Noninvestigational medicinal products (Background Therapy) **Formulation:**	**Inhaled corticosteroid in combination with a second controller medications** Screening Period Prior to and during the Screening Period, patients must be on stable-dose background therapy of medium-dose ICS with a second controller medication (ie, long-acting β2 agonist (LABA), long acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA) or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller.

	Randomized Treatment Period During this period, patients will continue taking their controller medication(s) For patients experiencing deterioration of asthma during the study, the ICS dose may temporarily be increased up to 4-fold (recorded as LOAC event) for a maximum of 10 days, as indicated and upon recommendation of the physician and/or Investigator. Treatment may then be changed to systemic corticosteroids (severe exacerbation event) or revert back to the original ICS dose depending on asthma symptom progression. Patients may be placed on SCS at any time as clinically indicated based the presence of symptoms consistent with a severe asthma exacerbation event, as per the Investigator's judgment. If a patient experiences 2 or more severe asthma exacerbation events anytime during the study, a permanent change (ie, step up in medium- to high-dose ICS or addition of second controller for patients on high-dose ICS monotherapy) on their stable-dose background controller medication may occur, as indicated and upon recommendation of the physician and/or Investigator. Post-treatment Period Upon completing the randomized treatment period, patients not continuing with the 1-year long-term extension study, will continue treatment with the controller medication regimen and dose used during the randomized period, which could be adjusted based on medical judgment of the patients' asthma control status. **Reliever Medication** Patients may use albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.
Route(s) of administration:	Oral inhalation by puff inhalation with MDI (eg, ICS, ICS combination, albuterol/salbutamol or levalbuterol/levosalbutamol; for other background controllers according to label)
Dose regimen:	ICS: medium to high-dose in combination with a second controller Reliever medication: Albuterol/salbutamol or levalbuterol/levosalbutamol: as needed
ENDPOINT(S)	**Primary Endpoint:** • Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period. **Key Secondary Efficacy Endpoint:** • Change from Baseline in pre-bronchodilator % predicted forced expiratory volume in 1 second (FEV1) at Week 12. **Secondary Endpoints:** Efficacy • Change from Baseline in pre-bronchodilator % predicted forced expiratory volume in 1 second (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 during 52-week treatment period.

	• Change from Baseline in other lung function measurements (absolute and relative FEV1, AM/PM peak expiratory flow (PEF), 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 • Change from Baseline at Weeks 2, 4, 8, 12, 24, 36, 52, and other time points assessed, in: - Morning/evening asthma symptom score (electronic diary) - PRO: • Asthma Control Questionnaire–Interviewer Administered (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. <u>Safety and tolerability</u> • Adverse events (AEs) • Vital signs (including height, weight) • Physical examination • Electrocardiogram (ECG) • Clinical laboratory tests <u>Systemic drug concentration, anti-drug antibodies and IgG responses to vaccination during drug treatment</u> • Serum functional dupilumab concentrations • ADA • IgG responses to vaccination with any vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza vaccine during dupilumab treatment (may be analyzed as exploratory endpoint if insufficient power). <u>Biomarkers</u> • Change from baseline in fractional exhaled nitric oxide (FeNO) at Week 12. **Exploratory endpoints:** • Change from baseline and blood biomarkers (thymus and activation regulated chemokine [TARC], serum total immunoglobulin E [IgE]). [redacted] • The proportion of patients requiring a permanent step up in background controller medication after 2 or more severe asthma exacerbation events.

	• The effect of dupilumab on additional PROs: - Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) score, for caregivers of children ≥7 years old at randomization - Pediatric Rhinoconjunctivitis Quality of Life Questionnaire – Interviewer Administered (PRQLQ-IA) score, in children 6 to <12 years old, with history of allergic rhinitis) - EuroQol 5 dimension youth questionnaire (EQ-5D-Y) for children • Change from Baseline in antigen-specific IgE, antigen-specific immunoglobulin G subtype 4 (IgG4) and ratio of IgE:IgG4 • Slope of % predicted FEV1 **Criteria for Asthma Exacerbations during the study:** Two types of asthma exacerbation are defined in this study, as outlined below: 1) 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 2) A LOAC event 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; • Increase in ICS dose ≥4 times than the dose at Visit 2; • 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 peak expiratory flow obtained over the last 7 days prior to randomization (Day1); • Severe exacerbation event • Two events will be considered as different if the interval between their start dates is equal or greater than 28 days.
ASSESSMENT SCHEDULE	• Screening Period (4 [±1] weeks) • Randomized Treatment Period (up to 52 weeks) • Post-treatment Period (12 weeks)
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size of this study was based on a comparison between dupilumab versus placebo with regard to the primary endpoint of annualized rate of severe exacerbations over 52 weeks of treatment for the 3 populations of interest: patients with baseline blood eosinophils ≥300 cells/µL, patients with baseline blood eosinophils ≥150 cells/µL, and patients with type 2 inflammatory phenotype (baseline blood eosinophils ≥150 cells/µL or baseline FeNO ≥20 ppb), with assuming the number of severe exacerbations follows a negative binomial distribution and a randomization ratio of 2:1. [redacted]

	[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 EFC13579 QUEST study. To achieve target sample size for each of the populations stated above, approximately 402 patients in the overall population (268 for dupilumab and 134 for placebo) need to be randomized assuming approximately 86% of the randomized patients with type 2 inflammatory phenotype (baseline blood eosinophils ≥150 cells/μL or baseline FeNO ≥20 ppb), assuming approximately 81% of the randomized patients have baseline blood eosinophils ≥150 cells/μL, and approximately 64% of the randomized patients have baseline blood eosinophils ≥300 cells/μL. Patients will be randomized (2:1 ratio) to receive dupilumab or matching placebo. After a patient is randomly assigned to dupilumab or matching placebo, the dosage of dupilumab or matching placebo for the patient, 200 or 100 mg SC once q2w, will be determined based on body weight >30 kg or ≤30 kg, respectively. Randomization will be stratified by ICS dose (medium-dose versus high-dose) and eosinophil count (<300 cells/μL versus ≥300 cells/μL) at Screening, and by region. **Analysis populations:** In order to confirm the efficacy of dupilumab with appropriate multiplicity control, there will be two primary analysis populations to evaluate the efficacy endpoints: 1) Population with type 2 inflammatory phenotype will be defined as randomized patients with baseline blood eosinophils ≥150 cells/μL or baseline FeNO ≥20 ppb (1). This multiplicity control will be applied to the analysis in countries that use the same or similar indication as approved in the EU. 2) Population with baseline blood eosinophil ≥300 cells/μL, which is defined as the randomized patients with baseline blood eosinophil ≥300 cells/μL, will be the primary analysis population that the

	sponsor uses for US and US reference countries, similar to the approach taken for evaluating these patients in the QUEST study. In addition, patients with baseline blood eosinophils ≥150 cells/μL will be tested in the hierarchy. This multiplicity will be used in countries with the same or similar indication wordings as approved in the US. The efficacy analyses will be conducted according to the treatment to which they are randomized. The analysis population for the safety endpoints will be the safety population, defined as all patients exposed to study medication, regardless of the amount of treatment administered and regardless of whether they are randomized. The safety analyses will be conducted according to the treatment patients actually received. **Analysis of the primary endpoint** The estimand of the dupilumab treatment effect compares the annualized rate of severe exacerbation for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo. In this primary approach, off-treatment measurements of patients who prematurely discontinue treatment will be included for the analysis. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits. If a patient stays in study till the end of 52-week treatment period, all severe exacerbation events that happen up to Week 52 will be included in the primary analysis, regardless if the patient is on-treatment or not. If a patient withdraws from study prior to the end of 52-week treatment period, all observed severe exacerbation events up to the last contact date will be included in the analysis, and the observation duration is defined as from randomization to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation and up to Week 52. The annualized rate of severe asthma exacerbation events will be analyzed using a negative binomial regression model. The analysis of the primary endpoint will be conducted in the type 2 inflammatory phenotype, baseline blood eosinophils ≥300 cells/μL, baseline blood eosinophils ≥150 cells/μL, baseline FeNO ≥20 ppb and full intent-to-treat (ITT) populations using appropriate multiplicity control. When performing the primary endpoint analysis in the type 2 inflammatory phenotype, baseline blood eosinophils ≥150 cells/μL or the full ITT populations, the model will include the total number of events of each patient occurring during the 52 weeks as the response variable, with the treatment group, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<300 cells/μL, ≥300 cells/μL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of severe asthma exacerbation events prior to the study as covariates. When performing the primary endpoint analysis in the baseline blood eosinophils ≥300 cells/μL population, the baseline eosinophil level will be removed from the model covariates. When performing the primary endpoint analysis in the baseline FeNO ≥20 ppb population, the baseline FeNO level will be removed from the model covariates. Severe asthma exacerbation event prior to the study is defined as treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once or hospitalization or emergency medical care visit for worsening asthma (as defined in this protocol). Log transformed observation duration will be the offset variable.

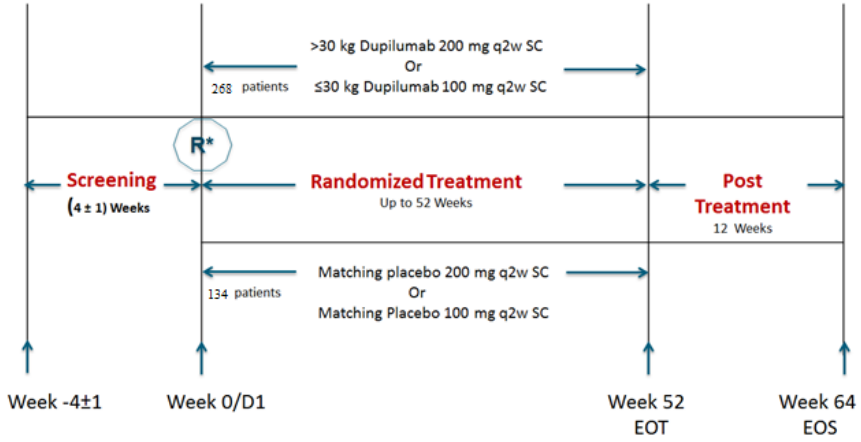
	A supportive analysis to assess the treatment effect of dupilumab if patients adhere to the treatment and background asthma medication as directed is also provided. In this approach, the severe exacerbation events reported after the premature treatment discontinuation will be excluded from the analysis. Any measurement obtained after the first permanent step up of background asthma medication will also be excluded from the analysis. The supportive analysis will be performed in the type 2 inflammatory phenotype and baseline blood eosinophils ≥300 cells/µL populations and will use a negative binomial model with the same set of covariates as specified for the primary analysis in the two populations. This model will include severe exacerbation events occurring during the treatment epoch before any permanent stepping-up of background asthma medication as the response variable and the log transformed duration of the treatment or from randomization to first permanent stepping-up of background asthma medication whichever is shorter will be the offset variable. The analysis of the primary endpoint will be conducted in the type 2 inflammatory phenotype, baseline blood eosinophils ≥300 cells/µL, baseline blood eosinophils ≥150 cells/µL, baseline FeNO ≥20 ppb, and full ITT populations using appropriate multiplicity control. **Multiplicity considerations** The hypothesis testing on the primary endpoint of annualized severe exacerbation rate will be controlled with a two-sided type I error of 0.05 by incorporating a sequential testing procedure as below: <u>For US and US reference countries</u>: 1st: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with baseline blood eosinophils ≥300 cells/µL. 2nd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with baseline blood eosinophils ≥150 cells/µL. 3rd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with type 2 inflammatory phenotype (baseline blood eosinophils ≥150 cells/µL or baseline FeNO ≥20 ppb). <u>For EU and EU reference countries</u>: 1st: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with type 2 inflammatory phenotype (baseline blood eosinophils ≥150 cells/µL or baseline FeNO ≥20 ppb). 2nd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with baseline blood eosinophils ≥150 cells/µL population. 3rd: Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period based on the patients with baseline blood eosinophils ≥300 cells/µL population. Multiplicity control for any secondary endpoints if considered will be specified in the SAP. Otherwise, nominal p-values will be provided. **Handling of missing data** If patients withdraw from the study before Week 52 with severe exacerbation events that may occur after study discontinuation, these patients are considered as patients with missing data on severe exacerbation. Number,

	reasons and timing of the missing data will be summarized by treatment groups. In the primary analysis, all observed data will be used regardless of treatment adherence or increase of asthma background medication. No imputation will be conducted for the missing severe exacerbation information after a patient prematurely withdraws from the study up to Week 52. In addition, sensitivity analyses based on pattern mixture model, placebo based pattern mixture model and tipping point analysis based on the same negative binomial model as being used in the primary analysis may be conducted to assess the robustness of the conclusion of the main model. Details of these sensitivity analyses will be described in the SAP. **Analysis of other secondary endpoints** The change from baseline for continuous endpoints will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline as response variables, and for treatment, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<300 cells/μL, ≥300 cells/μL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as covariates; unless otherwise specified (details will be documented in SAP). Sex, height, and ethnicity will also be included as covariates in the models for spirometry parameters. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method using the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline at Weeks 12 will be derived from the mixed-effect model with Kenward and Roger degree of freedom adjustment approach. Treatment comparisons at other timepoints, 8, 12, 24, 36 and 52 Week and other timepoints in between will also be provided from the mixed-effect model for descriptive purpose. Data up to Week 52 will be included as response variables. Time to first severe asthma exacerbation event and time to first LOAC will be analyzed using a Cox regression model with time-to-event as the dependent variable, and treatment, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<300 cells/μL, ≥300 cells/μL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of asthma events prior to the study as covariates. The estimated hazard ratio (dupilumab versus placebo) along with its 95% confidence interval will be presented. The Kaplan-Meier method will be used to derive the proportion of patients with a severe asthma exacerbation event at Weeks 12, 24, 36, and 52, specific to each treatment group. The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics. The analysis of safety variables will be performed based on the safety population. **Interim Analysis** There is no interim analysis planned for this study. **Planned database lock** The database lock is planned based on the time when all randomized patients reach complete week 52 visit or discontinue from the study before week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR (Clinical Study Report). Additional data between database lock and last patient completing last visit will be summarized in a CSR addendum.

DURATION OF STUDY PERIOD (per patient)	Total duration of study (per patient) is expected to be up to 68±1 weeks: • 4 (±1) weeks for screening • 52 weeks of treatment • 12 weeks of post-treatment follow-up

1 FLOW CHARTS

1.1 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

1.2 STUDY FLOW CHART

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

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

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

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

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

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

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

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

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

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

[redacted].

g Medical history, asthma-specific medical history (ie, family history of atopy & Ig E mediated disease [particularly maternal], premature birth and/or, low birthweight, exposure to tobacco smoke, recurring viral infections in early childhood), surgical history.

h Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puff inhalations with metered-dose inhaler [MDI]) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication if tolerated by the patient). Documented reversibility or positive airway hyper-responsiveness to methacholine within 12 months prior to Screening V1 is considered acceptable. If the subject does not meet this reversibility criterion at Screening V1, up to 2 additional assessment attempts can be performed at any time between Screening and Baseline Visit 2.

i A separate assent must be obtained from female patients at the earliest visit when the investigator is notified that the first menses have occurred.

j Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), height (cm) and body weight (kg) will be measured at the Screening and Randomization visits (Visits 1 and 2) and every subsequent visit. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

k Electronic diary/PEF meter is used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, oral steroid requirements, nocturnal awakenings due to asthma symptoms requiring the use of reliever medications, morning and evening asthma symptom NRS scores and AM and PM PEF. This device is dispensed at Visit 1 and information is downloaded from this device on the other indicated days.

l During the Randomized Treatment Period IMP administrations, every 2 week (q2w), will be performed by the Investigator at scheduled study site visits (must be separated by at least 11 days) up to Week 50. In the first 12 weeks (up to V8), patients will be monitored at the study site for a minimum of 30 minutes after injection of IMP, to assess any injection reactions (see Section 8.1.4 for more details). After randomization, dose regimen will not be adjusted for patient's age or weight until the randomized treatment will be completed.

m Home Dosing and training of parent(s)/caregiver(s)/legal guardian(s): For all visits scheduled only for IMP administration (ie, at Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50), parent(s)/caregiver(s)/legal guardian(s) may decide to do the injection of IMP at home (ie, home administration of IMP). These parent(s)/caregiver(s)/legal guardian(s) will be trained by the Investigator or designee to administer IMP, by demonstration at V2, V3, and V4 (injections performed by Investigator). After parent(s)/caregiver(s)/legal guardian(s) have successfully administered IMP under close supervision of the Investigator at V5-V8 (Weeks 6, 8, 10, and 12), the Investigator may approve them to perform home administration of IMP at all further visits that do not require a scheduled visit. It is possible to start home administration at any visit following V9, provided parent(s)/caregiver(s)/legal guardian(s) have been trained by the investigator or designee to administer IMP by demonstration at not less than 3 visits followed by a successful IMP administration under close supervision of the investigator or designee at not less than 3 visits.
However, if parent(s)/caregiver(s)/legal guardian(s) do not develop the comfort to inject the IMP at home, or the Investigator determines that injection by parent(s)/caregiver(s)/legal guardian(s) at home is not appropriate, alternative arrangements may be made: for example for qualified site personnel and/or healthcare professionals (eg, visiting nurse service) to administer IMP at these timepoints at the patient's home.

n Forced expiratory volume (FEV1), PEF, forced vital capacity (FVC), forced expiratory flow between 25% to 75% of vital capacity (FEF25%-75%) at all visits; pulmonary function tests should be performed in the morning if possible, but if it could only be done at a different time of the day, the spirometry should be done at approximately the same time of the day at each visit throughout the study. Spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.

o Treatment Period stability limits will be established for FEV1 and PEF. Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Visit 2 (Day1). There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available.

p Asthma Control Questionnaire–Interviewer Administered (ACQ-IA, for children 6 to <12 years), ACQ-7 and ACQ-5 scores and Paediatric Asthma Quality of Life Questionnaire With Standardised Activities–Interviewer Administered (PAQLQ(S)-IA) score, for children ≥7 years old at Randomization V2, are administered by the interviewer during the study visits at the clinical site. The ACQ-7 score will be used to follow up evaluations in all patients. The ACQ-5 (the first 5 items of the ACQ-7) score is used for eligibility evaluation at Screening V1 and Baseline V2 for all patients.

q Pediatric rhinoconjunctivitis quality of life questionnaire–Interviewer Administered (PRQLQ-IA): For those patients with comorbid allergic rhinitis, administered by the interviewer during the study visits at the clinical site.

r Biomarker set includes serum Thymus and Activation-Regulated Chemokine (TARC).

s Assessment of total IgE, antigen-specific IgE, antigen-specific IgG4, and ratio of IgE:IgG4.

t Systemic drug concentration samples are to be collected prior to dosing and in case of SAE and AESI.

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

[redacted]

w ADA samples are to be collected prior to dosing and in case of SAE and AESI.

x For female patients who have commenced menstruating (ie, are of child-bearing potential) at Screening, a urine pregnancy test is mandatory at the Screening Visit 1 with negative result obtained prior to randomization at Visit 2 (Week 0) and at every subsequent visits defined in the flowchart. For female patients who happen to commence menstruating after Screening, a negative urine dipstick pregnancy test will be obtained prior to administration of IMP.

y Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with five-part differential count, and total red blood cell count. Serum chemistry: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Patients' fasting (considering fasting as no intake of any food or drink except for water for at least 8 hours) or non-fasting status at blood sample collection will be recorded on the Central Laboratory Requisition Form. Clinical laboratory testing only at Screening Visit 1 will include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA).

z At Screening, parent(s)/caregiver(s)/legal guardian(s) will be asked to provide information on their child's vaccination schedule, and assess whether immunizing their children with any vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza (as per local medical practice) will result in vaccination during the study.
The timing of these vaccinations should be adjusted to fit into the IMP treatment period if appropriate. Any planned tetanus, diphtheria and pertussis vaccination should be administered between Visit 12 (Week 20) and Visit 18 (Week 32), as administration after Visit 18 (Week 32) may require an additional blood draw (refer to Section 9.3.1.2) for assessment. Any planned seasonal trivalent/Quadrivalent influenza should be administered between Visit 6 (Week 8) and Visit 18 (Week 32) as administration after Visit 18 (Week 32) may require an additional blood draw (refer to Section 9.3.1.2) for assessment.

aa Scheduled blood sample collection for pre- and post-vaccine antibody titers (ie, for IgG response assessment), for both vaccinations (ie, any tetanus, diphtheria and pertussis and/or seasonal trivalent/quadrivalent influenza) should be drawn within 8 weeks prior to vaccination and at 3-4 weeks (up to 6 weeks) after the respective vaccination(s); however, all blood titer samples must be drawn between Week 6 and Week 50 (ie, Visit 5 and Visit 27, respectively).
Depending on patient's vaccination schedule during the course of this study, every effort should be made to draw pre-vaccination titers at either Weeks 6, 12, or 24 (V5, V8, V14) of the Randomized Treatment Period, and to draw post-vaccination titers at either Weeks 12, 24, or 36 (V8, V14, V20) of the Randomized Treatment Period.
For patient(s) requiring urgent/emergency vaccination with any seasonal trivalent/quadrivalent influenza and/or any tetanus, diphtheria and pertussis vaccine (eg, flu season approaching, animal bite, emergency room standard procedures) please refer to Section 9.3.1.2.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACQ-7 IA:	Asthma Control Questionnaire–Interviewer Administered, 7-question version
ACQ-IA:	Asthma Control Questionnaire–Interviewer Administered
AD:	Atopic dermatitis
ADA:	Anti-drug antibodies
AE:	Adverse event(s)
AESI:	adverse events of special interest
ALP:	Alkaline phosphatase
ALT:	Alanine aminotransferase
ANA:	Anti-nuclear antibody
AST:	Aspartate aminotransferase
ATS:	American Thoracic Society
bw:	Body weight
CDC-NHANES:	Centers for Disease Control and Prevention-National Health and Nutrition Examination Survey
CDMS:	Clinical data management system
CPK:	Creatine phosphokinase
CSD:	Clinical Study Director
CV:	Curriculum vitae
CV%:	Coefficient of variation
CYP:	Cytochrome P450
DMC:	Data Monitoring Committee
DRF:	Discrepancy Resolution Form
DTP:	Duties and Taxes paid
EASI:	Eczema area and severity index
EC:	Ethics Committee
ECG:	Electrocardiogram
e-CRF:	Electronic-case report form
ELISA:	Enzyme-linked immunosorbent assay
EOS:	End of Study
EOT:	End-of-treatment
EQ-5D-Y:	EuroQol 5-dimensions questionnaire for children
ERS:	European Respiratory Society
ETD:	Early treatment discontinuation
FEF:	Forced expiratory flow
FeNO:	Fractional exhaled nitric oxide
FEV1:	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
GCP:	Good Clinical Practice
GINA:	Global initiative for asthma

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

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

4 INTRODUCTION AND RATIONALE

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products. For most asthma patients, a regimen of controller therapy and reliever therapy provides adequate long-term control.

The majority of children with asthma have mild or moderate disease and can obtain adequate asthma control through avoidance of triggering factors and/or with the help of medications, such as short-acting inhaled β2-receptor agonists, inhaled corticosteroids (ICS) and, when needed, addition of long-acting β2-receptor agonists and leukotriene receptor antagonists (LTRA). However, 2-5% of all asthmatic children have uncontrolled asthma despite maximum treatment with conventional medications (2). Children with such severe symptoms are heterogeneous with respect to trigger factors, pulmonary function, inflammatory pattern and clinical symptoms (3). These children have a reduced quality of life, account for a large proportion of the healthcare costs related to asthma and represent a continuous clinical challenge to the pediatrician.

Additionally, the long term adverse effects of systemic and ICS on bone metabolism, adrenal function, and growth in children lead to attempts to minimize the amount of corticosteroid usage. Lastly, the consequences of unresponsiveness to therapy or lack of compliance with therapy are evidenced by loss of asthma control (LOAC), which can be severe (ie, severe asthma exacerbation event) and possibly life-threatening. The poor response of some patients with asthma may reflect the number of cellular and molecular mechanisms operative in asthma. There is increasing interest in distinct phenotypes because targeted therapy is more likely to be successful in patients with similar underlying pathobiologic features (4). Recent therapeutic approaches in asthma have been focused on trying to control type 2 inflammation. A vast majority of 6-11 years old with asthma show evidence of type 2 inflammation characterized by upregulation of inflammatory cytokines, interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). The most recent GINA guidelines (1) for management of severe asthma report that for patients with severe asthma, type 2 inflammation can be identified by elevated peripheral eosinophils (≥150 cells/μL) and/or elevated FeNO (≥20 ppb), and/or sputum eosinophils ≥2%, and/or asthma that is clinically allergen-driven. Up-regulation of IL-4 and IL-13 activity has been implicated as an important inflammatory component of asthma disease progression. Dupilumab is under development as a potential novel treatment for asthma. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 heterodimeric receptors Type I (IL4-ligand only) and Type II (both IL-4 and IL-13 ligands). The binding of dupilumab to IL-4Rα results in blockade of downstream signaling initiated by both IL-4 and IL-13. For complete information regarding the preclinical and clinical evaluation of dupilumab to date, see the Investigator's Brochure.

4.1 RATIONALE

This is a Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study to be conducted in children 6 to <12 years of age with uncontrolled persistent asthma while on a

medium dose ICS, in combination with a second controller or high-dose ICS alone or in combination with a second controller. This study is designed to investigate the efficacy and safety profile of dupilumab over one year in a population of asthmatic children in need for an additional treatment to their current maintenance management. The presence of a placebo arm is appropriate for the objectives of this study since it will provide the most robust assessment of the efficacy and safety of dupilumab.

The proposed study design provides the opportunity to understand better the efficacy of dupilumab on multiple asthma domains including prevention of severe exacerbations, lung function and symptom control. The short and long term effects on lung function and symptom control will be evaluated.

4.2 RATIONALE FOR DOSE SELECTION

The dose regimens for pediatric patients aged 6 to <12 years are selected based on the observed efficacy and safety in the dose ranging study in adult asthma patients (Phase 2b study DRI12544), the PK characterization and safety observation in pediatric atopic dermatitis (AD) study (R668-AD-1412) of 6 to <18 years, as well as the available blinded safety data of EFC13579, the asthma pivotal study being conducted in adults and adolescents.

In the completed Phase 2b dose ranging study (DRI12544), dupilumab efficacy at 4 dose regimens (300 mg once every 4 weeks (q4w) and once every 2 weeks (q2w), and 200 mg q2w and q4w with a total dose on Day 1 of 600 mg for (the 300 mg regimen) and 400 mg (for the 200 mg regimen) respectively, was evaluated in patients with uncontrolled asthma while receiving a stable dose of medium to high-dose ICS/ Long-acting β2 agonist (LABA) in addition to their study treatment (placebo or dupilumab). Dupilumab demonstrated dose dependent improvement, compared with placebo, in the change from baseline in forced expiratory volume in 1 second (FEV1) at Week 12. In addition, consistent efficacy results in favor of dupilumab over placebo were observed in the majority of main secondary efficacy endpoints including annualized rate of severe exacerbation events. The maximum treatment effects were observed in the 200 mg and 300 mg q2w regimens. Exposure-response analyses further supported the maximal effect for both endpoints of FEV1 and severe exacerbation rate approached/achieved at the steady-state exposure of the two q2w regimens (mean steady-state trough concentrations of 28.3 and 58.5 mg/L, respectively). Dupilumab was observed to be safe and well tolerated across all dose regimens examined. Treatment-emergent adverse events (TEAEs) were reported in 79.1% patients in the dupilumab groups (75.3% to 82.8%) and 74.7% patients in the placebo group. The most frequently reported TEAEs included injection site reactions, respiratory tract infections and related symptoms, headache, and back pain. There was no apparent dose relationship for any particular TEAE except for injection site reactions, majority of which were mild in nature.

From the available blinded safety data of EFC13579, injection site erythema, nasopharyngitis, and upper respiratory tract infection were the 3 most commonly reported TEAEs among adolescents in this study. None of the TEAEs observed in the 26 adolescents dosed at the time of blinded analysis were severe or serious. No new safety signal was identified in these adolescent patients compared to adults. The top 3 most common TEAEs in adolescents were also the most common reported TEAEs in adults in this study and the DRI12544 study.

Study R668-AD-1412 was a Phase 2a, multicenter, open-label, ascending-dose, sequential-cohort study investigating the safety, tolerability, PK, immunogenicity, and efficacy of single-dose and repeat-doses of dupilumab administered subcutaneously (SC) in pediatric patients with moderate to severe AD (for adolescents 12 to <18 years old) or severe AD (for school-going children ≥6 to <12 years old) that was not adequately controlled with topical treatments. The 2 assessed dose regimens at 2 mg/kg and 4 mg/kg corresponds to the weight normalized dose in adults at 150 mg and 300 mg, respectively. Dupilumab administered as single and repeated weekly doses of 2 mg/kg and 4 mg/kg for 4 weeks was generally safe and well tolerated in both pediatric age groups included in that study. There was a higher incidence of TEAEs following single and repeated weekly administration of 4 mg/kg compared to 2 mg/kg in both age-groups. However, most of the adverse events (AE) were mild in intensity, transient in nature and not related to study drug. There were no new safety signals detected with dupilumab in the pediatric age 6 to <18 years. The most common AEs reported after both single doses and repeated weekly doses were nasopharyngitis and exacerbation of AD.

In study R668-AD-1412, dupilumab administered as a single dose of either 2 mg/kg or 4 mg/kg, in the Study R668-AD-1412, induced significant and rapid reduction of disease activity in patients at Week 2 (34% and 51% reduction in eczema area and severity index (EASI) score from baseline for 2 mg/kg and 4 mg/kg doses respectively. Repeated weekly doses of dupilumab led to a further improvement in disease severity in patients in both dose groups (67% and 70% reduction in EASI score from baseline for 2 mg/kg and 4 mg/kg doses, respectively, at Week 12). There did not appear to be a clear dose response, as the 2 dose groups showed similar efficacy on the various endpoints evaluated during the study.

The collective clinical data on the exposure versus efficacy and safety in the adults and pediatric population as observed to date supports a similar exposure-response relationship for efficacy and safety between the adult and pediatric populations down to 6 years of age and justify the approach of selecting EFC14153 dose regimen based on the criteria of matching adult efficacious and safe exposure.

Dupilumab PK is not affected by disease status/population in adults. Similar PK profile was observed between healthy subjects, and patients with AD or asthma. Thus, the same PK profile is anticipated in children with asthma and AD which supports the use of AD-1412 PK data for the pediatric asthma dose selection. The observed pediatric PK profile analysis showed general similarity in dupilumab PK profile between adults and children after accounting for body size difference. Similar to adults, body weight (bw) was the only statistically significant covariate of dupilumab PK identified in the pediatric population of 6 to 17 years, where clearance and volume of distribution decreases with decreasing bw following an allometric relationship. There was no significant impact of age and gender on dupilumab PK after adjustment of the bw effect.

A pediatric Pop PK model was developed using pediatric data alone (AD-1412) together with single IV dose PK data in healthy volunteers (AS-0907) to further evaluate the typical pharmacokinetics in the pediatric population, and to identify and quantify PK variability component in the pediatric population. The pediatric Pop PK model shares the same two-compartment model structure as that of adults with the first-order absorption, and parallel linear and nonlinear elimination (target-mediated disposition with quasi steady-state QSS approximation).

To determine the appropriate dose regimen, the population PK simulation was conducted using the pediatric Pop PK model and the pediatric demographic data of Centers for Disease Control and Prevention-National Health and Nutrition Examination Survey (CDC-NHANES) database. The NHANES population of 6 to 11 years is adequate to reflect the inter-subject variability to inform the dosage recommendation in the age group.

To account for body size difference in the pediatric population and taking into account the observed large therapeutic indices of dupilumab, a tiered fixed dosing regimen was chosen over weight based (mg/kg) dosing, as this approach offers a potential safety advantage of reducing the risk of dosing errors, as well as dosing convenience for patients by allowing self-administration using a prefilled syringe/device. The dosing regimen was selected as shown below:

Dupilumab 200 or 100 mg SC once q2w for children with bw >30 kg or ≤30 kg, respectively.

The predicted exposure at 200 mg q2w in children aged 6 to <12 years weighing more than 30 kg largely overlaps with the observed efficacious exposure in adults at 300 mg and 200 mg q2w and is expected to be well within the adult safe exposure of up to 300 mg qw. Similarly, the lower dose of 100 mg q2w in children less than 30 kg is predicted to provide comparable exposure to that in the heavier children and the adults. Moreover, the estimated range of steady-state C_{max} was generally within the range of pediatric exposure in 6 to <12 years observed in AD-1412 which was well tolerated and safe.

In summary, the proposed tiered dosing regimen (200 mg q2w weighing >30 kg and 100 mg q2w weighing ≤30 kg) for children aged 6 to <12 years is expected to provide significant clinical benefit and a safety profile similar to that of older patients.

5 STUDY OBJECTIVES

5.1 PRIMARY

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

5.2 SECONDARY

- 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 assess the dupilumab systemic exposure and incidence of anti-drug antibodies (ADA)
- 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.

5.3 OTHER

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 ICS or step up in the second controller medication regimen
- To evaluate the effect of dupilumab on additional PROs

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

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

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

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

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

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur when either:

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

6.3 INTERIM ANALYSIS

No interim analysis is planned for this study.

6.4 STUDY COMMITTEES

6.4.1 Data Monitoring Committee

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

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

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

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

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

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

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

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

bronchospasm, on 3 or more days/per week on at least one week during the Screening Period.

e) Sleep awakening due to asthma that required the use of reliever medication at least once during the Screening Period.

f) Asthma symptoms 3 or more days/week on at least one week during the Screening Period.

I 02. Willing and able to comply with clinic visits and study-related procedures.

I 03. With parent(s)/caregiver(s)/legal guardian(s) able to understand the study requirements.

I 04. Patients ≥6 years of age (or above an age determined by the Institutional Review Board [IRB]/Independent Ethics Committee [IEC] and in accordance with the local regulations and requirements) must provide written informed assent, and their parent(s)/caregiver(s)/legal guardian(s) must provide written informed consent.

I 05. Patients/parent(s)/caregiver(s)/legal guardian(s), as appropriate, must be able to understand and complete study-related questionnaires.

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion Criteria Related to Study Methodology

E 01. Patients <6 or ≥12 years of age

E 02. Patients <16 kg bw

E 03. Any other chronic lung disease (cystic fibrosis, bronchopulmonary dysplasia, etc) which may impair lung function.

E 04. A subject with any history of life-threatening asthma (eg, requiring intubation).

E 05. Co-morbid disease that might interfere with the evaluation of investigational medicinal product (IMP)

E 06. History of malignancy of any kind.

E 07. Inability to follow the procedures of the study (eg, due to language problems or psychological disorders).

E 08. Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days prior to Visit 1 or any other biologic therapy/immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, systemic lupus

erythematosus as well as other diseases) within 2 months or 5 half-lives prior to Visit 1, whichever is longer.

E 09. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or dose change from 1 month prior to Visit 1 or a plan to begin allergen immunotherapy or to change its dose during the Screening Period or the Randomized Treatment Period.

E 10. Exposure to another investigative antibody within a time period prior to Visit 1 that is less than 5 half-lives of the antibody. In case the half-life is not known, then the minimum interval since exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 1.

E 11. Patients receiving medications or therapy that are prohibited as concomitant medications (See Section 8.8.1).

E 12. Patients who have previously been treated in any clinical trial of dupilumab.

E 13. Patients or his/her parent(s)/caregiver(s)/legal guardian(s) is related to the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff thereof directly involved in the conduct of the study.

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

E 14. Non-compliance with use of the mandatory background therapy (ie, medium-dose ICS with a second controller medication [eg, LABA, LTRA, LAMA, or methylxanthines] or high-dose ICS alone or high-dose ICS with second controller), during the Screening Period, as defined as <80% of total number of prescribed doses of background medication taken during the Screening Period. Compliance is verified based on background medication use recorded on the patient electronic diary during the Screening Period.

E 15. Patient treated with SCS for diagnoses other than severe exacerbation of asthma, and/or high-potency topical steroids within 30 days before Screening Visit 1, during the Screening Period, and/or during the randomized treatment phase of this study.

E 16. Patient with history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to uncontrolled diabetes, active hepatitis, active or latent untreated tuberculosis, bronchiectasis. Patients with active tuberculosis, latent untreated tuberculosis or a history of incompletely treated tuberculosis will be excluded from the study unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing will be performed in every country according to their local guidelines as required by regulatory

authorities and/or ethic committees. Other conditions that are well controlled and stable will not prohibit participation if deemed appropriate per the Investigator's judgment.

7.2.3 Exclusion Criteria Related to the Current Knowledge of Sanofi Compound

E 17. For female patients who have commenced menstruating at any time during the study and are either:

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

E 18. Diagnosed with active parasitic infection (helminthes); suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.

E 19. History of human immunodeficiency virus (HIV) infection or positive HIV serology at Visit 1.

E 20. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per Investigator's judgment.

E 21. Evidence of acute or chronic infection requiring systemic treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1 or during the Screening Period, significant viral infections within 4 weeks before Visit 1 or during the Screening Period that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).

E 22. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, juvenile idiopathic arthritis, inflammatory bowel disease, systemic lupus erythematosus) or patients with high titer autoantibodies at screening who are suspected of having high risk for developing autoimmune disease at the discretion of the Investigator or the Sponsor.

E 23. Patient with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

E 24. At any time: Patients with positive (or indeterminate) test for hepatitis B surface antigen (HBs-Ag); positive Immunoglobulin M (IgM) hepatitis B core antibody; positive total hepatitis B core antibody (HBc-Ab) confirmed by positive hepatitis B virus DNA (HBV

DNA); positive hepatitis C virus antibody (HCV-Ab) confirmed by positive hepatitis C virus RNA (HVC RNA).

E 25. Liver injury related criteria:

- Clinically significant/active hepatobiliary disease or
- Elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) >3 Upper Limit of Normal (ULN).

E 26. Abnormal lab values at Screening:

- Creatine phosphokinase (CPK) >3 ULN or
- Platelets <100 000 cells/mm^3 or
- Eosinophils >1500 cells/mm^3 or

E 27. Patients receiving live (attenuated) vaccines within 4 weeks before the baseline visit.

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

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

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

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Dupilumab

Dupilumab for children ≤30 kg bw at randomization: 150 mg/mL in pre-filled syringe to deliver a once q2w dose of 100 mg in a 0.67 mL subcutaneous injection.

Dupilumab for children >30 kg bw at randomization: 175 mg/mL in pre-filled syringe to deliver a once q2w dose of 200 mg in a 1.14 mL subcutaneous injection.

8.1.2 Placebo

Matching placebo in a prefilled syringe to deliver a once q2w dose of placebo in a 0.67 mL or 1.14 mL subcutaneous injection for children with ≤30 or >30 kg bw at randomization, respectively.

8.1.3 Preparation of investigational product

Dupilumab or matching placebo in glass pre-filled syringes will be dispensed to the patients. Additional information will be provided in the Pharmacy manual.

8.1.4 Dosing schedule

The IMP is administered every 14±3 days q2w. The doses of investigational product must be separated by ≥11 days to avoid overdose.

The IMP administrations will be performed by the Investigator or designee at scheduled study site visits following clinic procedures and blood collection (see Section 1.2). Patients will be monitored for a minimum of 30 minutes after each study-site administrated injection of IMP, to assess any injection site reactions (eg, for any signs or symptoms of a hypersensitivity reaction).

For all visits scheduled only for IMP administration, parent(s)/caregiver(s)/legal guardian(s) may decide to do the injection of IMP at home (ie, home administration of IMP). These parent(s)/caregiver(s)/legal guardian(s) will be trained by the Investigator or designee to administer IMP, by demonstration at Visit 2, Visit 3, and Visit 4 (injections performed by Investigator). After parent(s)/caregiver(s)/legal guardian(s) have successfully administered IMP under close supervision of the Investigator at Visit 5-Visit 8 (Weeks 6, 8, 10, and 12), the Investigator may approve them to perform home administration of IMP at all further visits that do not require a scheduled clinic visit (ie, at Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50). Patients should be monitored for 30 minutes after home administration of IMP. It is possible to start home administration at any visit following Visit 9, provided parent(s)/caregiver(s)/legal guardian(s) have been trained by the investigator or designee to administer IMP by demonstration

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

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

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

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

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

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

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

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Inhaled Corticosteroids and Second Controller Medication

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

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

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

Screening Period

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

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

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

Randomized Treatment Period

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

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

Post-treatment Period

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

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 of the patients' asthma control status.

8.2.2 Reliever Medication(s)

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.

Criterion for Loss of Asthma Control (LOAC) – Based on Increased Nebulizer Use (in e-CRF):

The criterion for LOAC based on a patients increased nebulizer use and the nebulizer-to-puff conversion factor (see tables below), is determined as follows:

Study personnel will convert salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use as shown on the following tables:

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 or 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 or 12 puffs.

After conversion of nebulizer-to-puff, and for every instance that the number of puffs is ≥6 additional puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to Baseline) on 2 consecutive days in any week, a LOAC event should be documented.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched pre-filled syringes. To protect the blind, each treatment kit of 0.67 or 1.14 mL (dupilumab/placebo) glass pre-filled syringes will be prepared such that the treatments (dupilumab and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Patients and Investigators will be blinded to assigned treatment. Patients and Investigators will not be blinded to dose regimen as the volumes are different.

Patient(s)/parent(s)/caregiver(s)/legal guardian(s), Investigators, and study site personnel will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.

8.3.2 Randomization code breaking during the study

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

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

Patient withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the subject will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the subject will not be withdrawn from treatment.

At the facilities where the systemic drug concentration measurements, ADAs and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

Patient(s)/parent(s)/caregiver(s)/legal guardian(s), Investigators, and site personnel will not have access to assay results for immunoglobulins (immunoglobulin G (IgG), IgG subclasses, Immunoglobulin A (IgA), IgM and IgE) after randomization and first administration of study medication, because these values have the potential for unblinding. Furthermore, neither patient(s)/parent(s)/caregiver(s)/legal guardian(s), Investigators nor site personnel will have access to total IgE, antigen-specific IgE, antigen-specific IgG4, Thymus and Activation-Regulated Chemokine (TARC) while the study is ongoing, as the related data are not essential for patient care and have the potential for unblinding.

The DMC will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

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

The Sanofi Clinical Supplies team will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system (IVRS/IWRS). This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the treatments to the patients.

Patients who meet the entry criteria will be randomized to receive either dupilumab or placebo. Rescreening is not permitted if the patient fails to meet inclusion criteria. Patients who meet exclusion criteria may be rescreened once during the open Screening Period of the study. There is no requirement for a waiting period between the screen-failure date and the rescreening date. The IVRS/IWRS report will flag rescreened patients. Patients that are rescreened must have parent(s)/caregiver(s)/legal guardian(s) resign a new ICF and sign a new IAF, and all Screening Visit 1 procedures must be repeated.

The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via an IVRS/IWRS that will be available 24 hours a day.

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

Randomization will be stratified by ICS dose (medium-dose versus high-dose) and eosinophil count (<300 cells/µL versus ≥300 cells/µL) at Screening, and by region.

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

8.5 PACKAGING AND LABELING

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

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

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

8.7 RESPONSIBILITIES

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

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

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

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

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

8.7.1 Treatment Accountability and Compliance

The Investigator or pharmacist will also keep accurate records of the quantities of the IMP dispensed, used and unused. The IMP tracking log and inventory form is to be updated each time investigational product is dispensed. The study monitor will periodically check the supplies of the IMP held by the Investigator or pharmacist to assess accountability.

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

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

An electronic diary is used by the parent(s)/caregiver(s)/legal guardian(s) for the daily recording of albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication use, daily use of background therapy (ie, medium-dose ICS with a second controller medication [ie, LABA, LTRA, LAMA, or methylxanthines] or high-dose ICS alone or high-dose ICS with second controller), and in case of an exacerbation event, recording of increased ICS dose and/or step up of second controller medication. Site personnel will review and download the electronic diary data at each clinic visit and will follow up with the parent(s)/caregiver(s)/legal guardian(s) accordingly.

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

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

8.7.2 Return and/or Destruction of Treatments

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

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

8.8 CONCOMITANT MEDICATION

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

8.8.1 Prohibited Concomitant Medication

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

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

  In Brazil, for patients in the yellow fever outbreak affected area (see Appendix N).
- Asthma relievers other than salbutamol/albuterol or levosalbutamol/levalbuterol: their use is not recommended unless in exceptional circumstances during the study period (eg, prescribed by a physician not participating in the study).
- Exposure to another antibody within a time period prior to Visit 1 that is less than 5 half-lives of the antibody. In case the half-life is not known, then the minimum interval since exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 1.
- Any investigational treatment or procedure.

8.8.2 Permitted Concomitant Medication

- Antihistamines
- Dermatological, ocular or intranasal corticosteroids (except for high-potency dermatological corticosteroids)

- Cytochrome P450 (CYP) enzyme substrates:

  The impact of dupilumab on CYP enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized. However, IL-4 was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (5, 6). Human peripheral blood mononuclear cells (PBMC) incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (5). Since the clinical significance of the limited in vitro findings for IL-4 and IL-13 involvement in CYP regulation and the impact of dupilumab on CYP enzymes is not fully understood, during the study treatment and at least up to the end of follow-up, caution should be used for drugs which are metabolized via these CYP isoforms and which have a narrow therapeutic index. This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal if needed (6, 7). Some examples of CYP450 substrates with narrow therapeutic index are provided in Appendix D.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

Two types of asthma exacerbation are defined in this study, as outlined below:

1) 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

2) A LOAC event 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;
   - Increase in ICS dose ≥4 times than the dose at Visit 2;
   - 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 peak expiratory flow obtained over the last 7 days prior to randomization (Day1);
   - Severe exacerbation event

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

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

9.1 PRIMARY ENDPOINT

The primary endpoint for this study is:

- Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period.

9.2 SECONDARY ENDPOINTS

9.2.1 Key Secondary Efficacy Endpoint

- Change from Baseline in pre-bronchodilator % predicted FEV1 at Week 12.

9.2.2 Secondary Efficacy Endpoints

- 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.

9.2.2.1 Disease-specific Efficacy Measures

9.2.2.1.1 Spirometry

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

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

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

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

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable and/or acceptable maneuvers, an explanation should be recorded.

The largest FEV1 and largest FVC should be recorded after the data are examined from all of the acceptable curves, even if they do not come from the same curve. The FEF 25-75% should be obtained from the single curve that meets the acceptability criteria and gives the largest sum of FVC plus FEV1 (best test).

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

The spirometer must be calibrated following the principles of the ATS/ERS guidelines every day that a study subject is seen and spirometry is carried out. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (ie, 3-liter syringe) that is used to calibrate the spirometer be subjected to a validated calibration according to the manufacturer's specifications.

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

9.2.2.1.2 Reversibility/Post-bronchodilator FEV1

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

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

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

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

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

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

9.2.2.2 Disease-specific, Daily Efficacy Assessments

9.2.2.2.1 Electronic Diary/PEF meter

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

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

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

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

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

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

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

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

9.2.2.2.2 Asthma Symptom Numerical Rating Scale (NRS) Score

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

9.2.2.2.3 Use of Reliever Medicine

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

9.2.2.3 Health Care Resource Utilization

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

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

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

9.2.2.4.1 Asthma Control Questionnaire–Interviewer Administered

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9.2.3 Safety and Tolerability Endpoints

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

Safety observations

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

9.2.3.1 Adverse Events

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

- SAEs
- AEs that are ongoing at database lock.

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

9.2.3.2 Vital Signs

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

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

9.2.3.3 ECG Variables

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

9.2.3.4 Physical Examination

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

9.2.3.5 Clinical Laboratory Safety Variables

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

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

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

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

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

Table 1 - Eligibility interpretation for hepatitis serology

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

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

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

9.2.3.6 Other Safety Laboratory Tests

9.2.3.6.1 Serum Immunoglobulins and Subtypes

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

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

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

9.2.3.7 Pregnancy Test

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

9.3 OTHER SECONDARY ENDPOINTS

9.3.1 Systemic Drug Concentration, Anti-drug Antibodies, and IgG responses to vaccination during drug treatment

- Serum functional dupilumab concentrations
- ADA
- IgG responses to vaccination with any vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza vaccine during dupilumab treatment (may be analyzed as exploratory endpoint if insufficient power).

9.3.1.1 Systemic Drug Concentration and Anti-drug Antibodies

9.3.1.1.1 Sampling Time

Predose blood samples will be collected for determination of functional dupilumab concentration in serum and anti-dupilumab antibodies (including neutralizing antibodies) on days designated in the Study Flow Chart (see Section 1.2 as well as Section 10.3.4, as needed for Brazil). The date of collection should be recorded in the patient e-CRF. The date and time also will be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

If an SAE or AESI occurs in a patient, blood samples should be collected for determination of functional dupilumab concentration, and anti-dupilumab antibody assessment at or near the onset and completion of the occurrence of the event, if possible. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled systemic drug concentration page in the e-CRF must be completed as well.

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

9.3.1.1.2 Handling Procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of systemic drug concentration and anti-drug antibodies is provided in Table 2.

Table 2 - Summary of handling procedures for dupilumab

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

9.3.1.1.3 Bioanalytic Method

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

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

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

ELISA: enzyme-linked immunosorbent assay

9.3.1.2 Humoral Immune Response to Vaccines

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

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

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

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

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

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

9.3.1.3 Biomarker endpoints

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

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

9.4 EXPLORATORY ENDPOINTS

9.4.1 Exploratory Endpoints

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

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

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

9.4.2 Pharmacodynamics and Phenotyping

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

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

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

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

9.4.2.1 Serum Biomarkers

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

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

TARC will be assayed with a validated immunoassay.

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

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

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

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

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

9.4.2.4.1 Paediatric Asthma Caregiver's Quality of Life Questionnaire

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

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

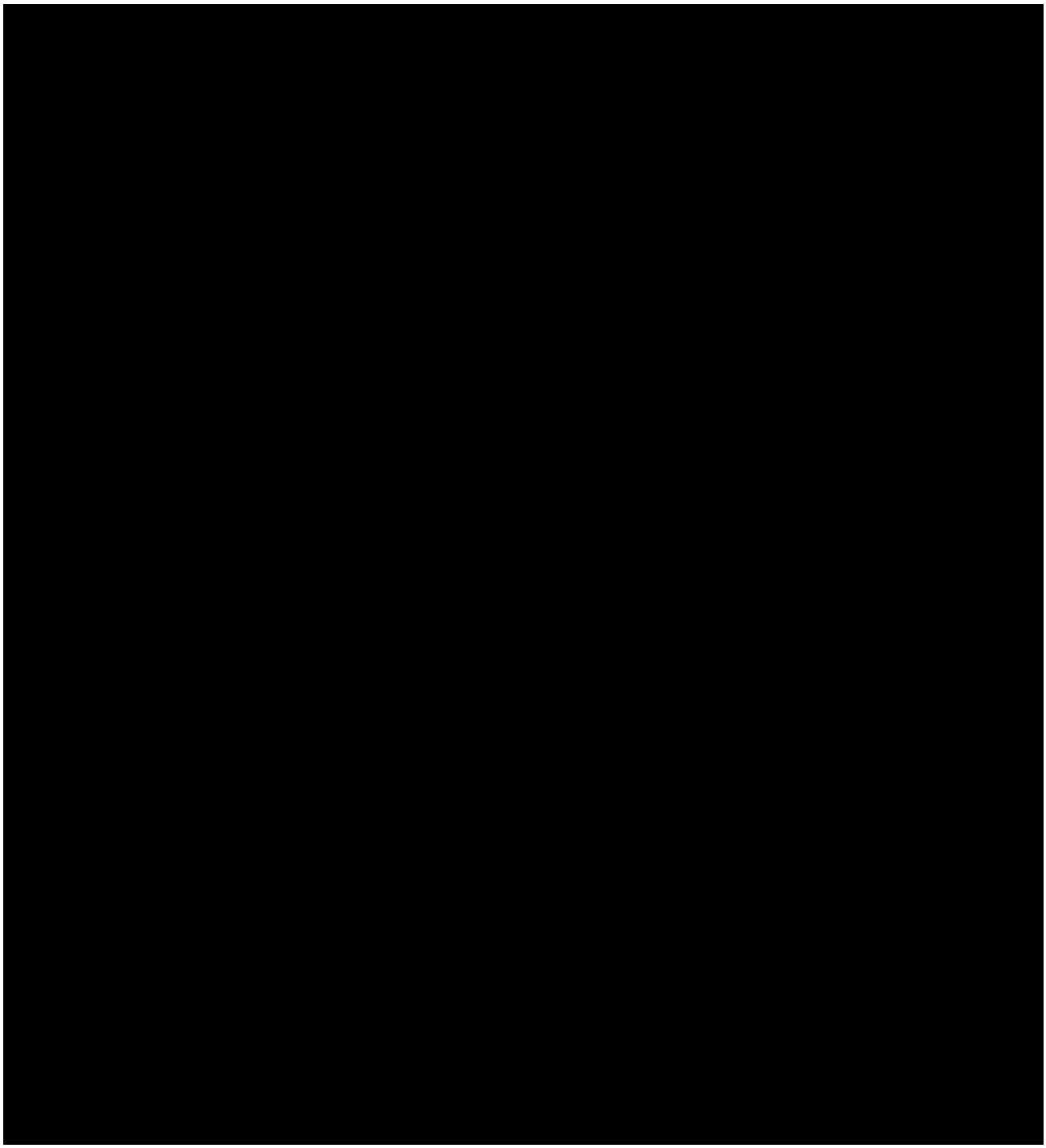
9.4.2.4.2 Pediatric Rhinoconjunctivitis Quality Of Life Questionnaire–Interviewer Administered in patients with comorbid allergic rhinitis.

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

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

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

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



9.6 APPROPRIATENESS OF MEASUREMENTS

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

10 STUDY PROCEDURES

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

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

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

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

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

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

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

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

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

1. PROs including HRQoL
2. Procedures:

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

3. Safety and laboratory assessments
4. IMP administration

10.1 VISIT SCHEDULE

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

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

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

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

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

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

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

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

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

The following procedures will then be performed:

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

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

- Perform spirometry.

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

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

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

- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS alone or in combination with a second controller as used during the Screening Period and instruct them to record daily usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit within a maximum of 35 days (Visit 2, Week 0) and request patient and their parent(s)/caregiver(s)/legal guardian(s) to come at approximately the same time of this visit.

10.1.3 Randomization Visit 2 (Week 0, Day 1)

- Reconfirm eligibility based on review of Inclusion/Exclusion Criteria.
- Record all medication use with start date and dose in e-CRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Assess menstruation status and perform urine dipstick pregnancy test for female patients who commenced menstruating, ie, are of childbearing potential
- Administer ACQ-IA (ACQ-7) and assess if ACQ-5 score is ≥1.5
- Administer all additional PROs:
  PAQLQ(S)-IA, PRQLQ-IA, EQ-5D-Y for children, PACQLQ.
- Administer HCRU
- Compliance with use of the mandatory background therapy, ICS in combination with one controller product as used just prior to screening, as defined as:
  - ≥80% of total number of prescribed doses of background medication taken during the Screening Period. Compliance is verified based on background medication use recorded on the patient electronic diary during the Screening Period.
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height)
- Perform spirometry

Entry criteria at Visit 2 include the requirement of a specific FEV1 and demonstration of reversibility as specified in Section 7.1 See below for additional directions.

- Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding

the last dose of LAMA for at least 24 hours prior to administration of investigational product. This will be verified before performing the PEF measurements.

- Pre-bronchodilator FEV1 must be ≤95% of predicted normal or pre-bronchodilator FEV1/FVC ratio <0.85.
- Post-bronchodilator FEV1 should be determined.
  Note: for patients that will have an additional and last attempt of reversibility testing (for eligibility) at the Baseline Visit 2, the post-bronchodilator FEV1 will come from the result of this reversibility test.
- Patients must meet the inclusion criteria for spirometry at Visit 2 prior to randomization. If a patient's FEV1 does not qualify, then the patient will not be randomized.
- Treatment Period stability limits will be established for FEV1 and PEF (The Treatment Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1).

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

- Call IVRS/IWRS to register visit: Randomize the patient and receive the first assignment for 1 treatment kit number.
  - Note: If entry criteria are not met: Call IVRS/IWRS to register visit and Screen-fail the patient.
- Perform blood sampling (prior to administration of IMP) for the following tests:
- Clinical laboratory testing: hematology/biochemistry (refer to Section 9.2.3.5)
  - Systemic drug concentration and ADA (refer to Section 9.3.1)
  - Obtain blood samples for total IgG, IgG subclasses1-4, IgM and IgA.
  - Biomarker set, total IgE, and antigen-specific IgE, and antigen-specific IgG4 panel (refer to Section 9.4.2.1)
  - [redacted]
- Download electronic diary/PEF meter and remind patient/parent(s)/caregiver(s)/legal guardian(s) to bring the device to the next visit.
- Dispense and administer IMP
  - For those parent(s)/caregiver(s)/legal guardian(s) who wish to learn and train to home-administer the IMP injection (see Section 8.1.3 for details):
    They will be trained by the Investigator or designee to administer IMP, by demonstration at V2, V3, and V4 (injections performed by Investigator). The training of parent(s)/caregiver(s)/legal guardian(s) for IMP injection is to be documented in the patient's study file.

  - Patients should be monitored for at least 30 minutes after study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.

- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient and their parent(s)/caregiver(s)/legal guardian(s) to record usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and instruct them to record daily usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit 2 weeks later (Week 2 ± 3 days) at approximately the same time of this visit.

10.1.4 Visit 3 (Week 2 [± 3 days])

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height)
- Assess menstruation status
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, or withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
  - Post-bronchodilator FEV1 should be determined
- Download electronic diary/PEF meter and remind patient/parent(s)/caregiver(s)/legal guardian(s) to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain next treatment kit number

- Dispense and administer IMP.
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those parent(s)/caregiver(s)/legal guardian(s) who wish to learn and train to home-administer the IMP injection (see Section 8.1.3 for details):
    They will continue to be trained by the Investigator or designee to administer IMP, by demonstration at V2, V3, and V4 (injections performed by Investigator). The training should be documented in the patient's medical records.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct the parent(s)/caregiver(s)/legal guardian(s) to record usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and instruct them to record daily usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit 2 weeks later (Week 4 ± 3 days) and ask patient to come in at approximately the same time of this visit.

10.1.5 Visit 4 (Week 4 [± 3 days]) and Visit 6 (Week 8 [± 3 days])

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height)
- Note for Visit 6: Any planned vaccination for seasonal trivalent/quadrivalent influenza may be administered at this visit or between Visit 6 and Visit 18 (Week 32; see Study Flow Chart Section 1.2)
- Assess menstruation status and perform urine dipstick pregnancy test for female patients of childbearing potential (who have commenced menstruating)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.

- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
  - Post-bronchodilator FEV1 should be determined
- Download electronic diary/PEF meter and remind patient/parent(s)/caregiver(s)/legal guardian(s) to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those parent(s)/caregiver(s)/legal guardian(s) who wish to learn and train to home-administer the IMP injection (see Section 8.1.3 for details):
    They will continue to be trained by the Investigator or designee to administer IMP, by demonstration at V2, V3, and V4 (injections performed by Investigator). The training should be documented in the patient's medical records.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct the parent(s)/caregiver(s)/legal guardian(s) to record usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and instruct them to record daily usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit 2 weeks later (± 3 days) at approximately the same time of this visit.

10.1.6 Visit 5 (Week 6 [± 3 days])

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height)
- Assess menstruation status

- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Download electronic diary/PEF meter and remind patient/parent(s)/caregiver(s)/legal guardian(s) to bring the device to the next visit
- Perform sampling for the following tests:
  - Blood sample for systemic drug concentration assay

    [redacted]
  - Blood samples for pre-vaccination antibody titers for the patient(s) scheduled to receive seasonal trivalent/quadrivalent influenza during this study, and within the next 8 weeks from Visit 5 (Study Flow Chart Section 1.2; see Section 9.3.1.2 for details).
- Call IVRS/IWRS to register visit and obtain new treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those parent(s)/caregiver(s)/legal guardian(s) willing and trained to perform home-administration of IMP-injection (see Section 8.1.3 for details):
    Under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will perform the injection, including feedback on technique by the Investigator or delegate. Assess that the training for IMP home administration is documented in the patient's study file.
- Remind patients and their parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct parent(s)/caregiver(s)/legal guardian(s) to record usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and instruct them to record daily usage in the electronic diary.

- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit 2 weeks later (Week 8 ± 3 days) and ask patient to come in at approximately the same time of this visit.

10.1.7 Visit 7 (Week 10 [± 3 days])

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height)
- Assess the menstruation status
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Download electronic diary/PEF meter and remind patient and their parent(s)/caregiver(s)/legal guardian(s) to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those parent(s)/caregiver(s)/legal guardian(s) willing and trained to perform home-administration of IMP-injection (see Section 8.1.3 for details):
    Under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will perform the injection, including feedback on technique by the Investigator or delegate. Assess that the training for IMP home administration is documented in the patient's study file.

- Remind parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct parent(s)/caregiver(s)/legal guardian(s) to record usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and instruct parent(s)/caregiver(s)/legal guardian(s) to record daily usage in the electronic diary
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit 2 weeks later (Week 12 ± 3 days) and ask patient to come in at approximately the same time of this visit.

10.1.8 Visit 8 (Week 12 [± 3 days])

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, height)
- Administer ACQ-7
- Administer all additional PROs:
  PAQLQ(S)-IA, PRQLQ-IA, PACQLQ.
- Administer HCRU
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
  - Post-bronchodilator FEV1 should be determined.
- Obtain urine for urinalysis (dipstick)
- Assess menstruation status and perform urine dipstick pregnancy test for female patients of childbearing potential (who have commenced menstruating)
- Perform blood sampling (prior to administration of IMP) for the following tests:

- Clinical laboratory testing (hematology/biochemistry)
- Systemic drug concentration,
- ADA
- Biomarker set (refer to Section 9.4.2)
- [redacted]
- Blood samples for pre-vaccination antibody titers for the patient(s) scheduled to receive vaccination (ie, any tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza) during this study, and within the next 8 weeks from Visit 8 (see Section 9.3.1.2 for details).
- Blood samples for post-vaccination antibody titers for the patient(s) who received vaccination (ie, any tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza) during this study, and within the previous 6 weeks prior to Visit 8 (see Section 9.3.1.2 for details).

- Call IVRS/IWRS to register visit and obtain treatment kit number.
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For parent(s)/caregiver(s)/legal guardian(s) willing and trained to perform home-administration of IMP-injection (see Section 8.1.3 for details):
    Under the close supervision of the Investigator or delegate, parent(s)/caregiver(s)/legal guardian(s) will perform the injection, including feedback on technique by the Investigator or delegate. Assess that the training for IMP home administration is documented in the patient's study file.
  - Dispense Home Dosing Diary parent(s)/caregiver(s)/legal guardian(s) willing and trained to perform home-administration of IMP-injection, and provide instructions on preparation, injection and dose.
  - For parent(s)/caregiver(s)/legal guardian(s) unable or unwilling to administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct them to record usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and instruct them to record daily usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the

last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.

- Schedule a site visit 4 weeks later (Week 16 ± 3 days) and ask patient to come in at approximately the same time of this visit

10.1.9 Visits 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 (Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50) – IMP Administration at Patient Home or Investigative Site

- Administer IMP
  - Patients should monitor themselves, or be monitored, for 30 minutes after home administration of IMP.
  - For parent(s)/caregiver(s)/legal guardian(s) willing and trained to perform home-administration of IMP-injection (see Section 8.1.3 for details): Parent(s)/caregiver(s)/legal guardian(s) will document in Home Dosing Diary.
  - For parent(s)/caregiver(s)/legal guardian(s) unable or unwilling to administer IMP, or if parent(s)/caregiver(s)/legal guardian(s) do not develop the comfort to inject the IMP at home, or the Investigator determines that injection by parent(s)/caregiver(s)/legal guardian(s) at home is not appropriate, alternative arrangements may be made: for example for qualified site personnel and/or healthcare professionals (eg, visiting nurse service) to administer IMP at these timepoints at the patient's home.
- **Applicable for Visit 27**: Blood samples for post-vaccination antibody titers for the patient(s) who received vaccination (ie, any tetanus, diphtheria and pertussis and/or seasonal trivalent/quadrivalent influenza) should be drawn 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) of the Randomized Treatment Period (Study Flow Chart Section 1.2; see Section 9.3.1.2 for details).

10.1.10 Visits 10, 12, 16, 18, 22, 24, 26 (Weeks 16, 20, 28, 32, 40, 44, 48)

- Check compliance with IMP
- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height)
- Note for Visit 12: Any planned vaccination for tetanus, diphtheria, pertussis may be administered at this visit or between Visit 12 and Visit 18 (Week 32; see Study Flow Chart Section 1.2)
- Administer ACQ-7
- Administer HCRU, only at Visit 26 (Week 46)
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.

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

10.1.11 Visit 14 (Week 24 [± 3 days])

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

trivalent/quadrivalent influenza) during this study, and within the next 8 weeks from Visit 14 (see Section 9.3.1.2 for details).

- Blood samples for post-vaccination antibody titers for the patient(s) who received vaccination (ie, any tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza) during this study, and within the previous 6 weeks prior to Visit 14 (see Section 9.3.1.2 for details).

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

10.1.12 Visit 20 (Week 36 [± 3 days])

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height)
- Obtain urine for urinalysis (dipstick)

- Assess menstruation status and perform urine dipstick pregnancy test for female patients of childbearing potential (who have commenced menstruating)
- Administer ACQ-7
- Administer all additional PROs:
  PAQLQ(S)-IA, PRQLQ-IA, and PACQLQ
- Administer HCRU
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
  - Post-bronchodilator FEV1 should be determined.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Perform blood sampling for the following tests:
  - Clinical laboratory testing (hematology/biochemistry)
  - [redacted]
  - Blood samples for post-vaccination antibody titers for the patient(s) who received vaccination (ie, any tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza) during this study, and within the previous 6 weeks prior to Visit 20 (see Section 9.3.1.2 for details).
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - Dispense Home Dosing Diary parent(s)/caregiver(s)/legal guardian(s) willing and trained to perform home-administration of IMP-injection, and provide instructions on preparation, injection and dose. And review the diary for home dosing. Re-check the instructions on home-administration and dosing and dispense Home Dosing Diary, as applicable.
  - For parent(s)/caregiver(s)/legal guardian(s) unable or unwilling to administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site

as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.

- Remind parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct them to record usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and them patient to record daily usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit 4 weeks (± 3 days) and ask patient to come at approximately the same time of this visit

10.1.13 Visit 28 (Week 52 [± 3 days], End of Treatment, and Early Treatment Discontinuation)

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Review patient Home Dosing Diary for content and completeness
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height)
- Perform physical examination
- Obtain urine for urinalysis (dipstick)
- Assess menstruation status and perform urine dipstick pregnancy test for female patients of childbearing potential (who have commenced menstruating)
- Administer ACQ-7
- Administer all additional PROs:
  PAQLQ(S)-IA, PRQLQ-IA, and PACQLQ:
  EQ-5D-Y for children
- Administer HCRU
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at

least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.

- Post-bronchodilator FEV1 should be determined

- Perform 12-lead ECG
- Assess menstruation status and perform urine dipstick pregnancy test for female patients of childbearing potential (who have commenced menstruating)
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Perform blood sampling for the following tests:
  - Clinical laboratory testing (hematology/biochemistry)
  - Serum immunoglobulins (total IgG, IgG subclasses, IgM and IgA)
  - Systemic drug concentration,
  - ADAs
  - Biomarker set, total IgE, and antigen-specific IgE, and antigen-specific IgG4 panel.
  - [redacted]
- Remind parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct them to record usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to continue their stable dose of ICS in combination with a second controller as used during the Screening Period and them patient to record daily usage in the electronic diary.
- Remind patient and their parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Call IVRS/IWRS to register EOT visit

At Visit 28 (EOT visit), for patients who will not continue with the 1-year long-term extension study, the controller medication regimen and dose used during the randomized period could be adjusted based on medical judgment of the patients' asthma control status.

10.1.14 Visit 29 and Visit 30 (Weeks 56 and 60 ± 5 days), Post-Treatment Period)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height)

- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Remind parent(s)/caregiver(s)/legal guardian(s) to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct them to record usage in the electronic diary.
- Remind parent(s)/caregiver(s)/legal guardian(s) to continue the stable dose of ICS in combination with a second controller which was maintained over the randomized treatment period (unless treatment modified based on medical judgment) and record daily usage in the electronic diary.
- Remind parent(s)/caregiver(s)/legal guardian(s) to withhold bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
- Schedule a site visit 4 weeks later (± 5 days) and ask patient to come in at approximately the same time of this visit

10.1.15 Visit 31 (Week 64, End of Study Visit)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight and height)
- Perform physical examination
- Obtain urine for urinalysis (dipstick)
- Assess menstruation status and perform urine dipstick pregnancy test for female patients of childbearing potential (who have commenced menstruating)
- Administer ACQ-7
- Administer all additional PROs:
  PAQLQ(S)-IA, PRQLQ-IA, EQ-5D-Y for children, PACQLQ

- Administer HCRU
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours, and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the PEF measurements.
  - Post-bronchodilator FEV1 should be determined.
- Perform 12-lead ECG
- Perform blood sampling for the following tests:
  - Clinical laboratories,
  - Systemic drug concentration,
  - ADAs
- Download electronic diary/PEF meter and take back the device
- Call IVRS/IWRS to register the EOS date

10.2 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

All the data collected in the e-CRF should be transcribed directly from source documents. Data downloaded from the study-associated central laboratories, spirometry, nitric oxide measurement, ECG, and patient electronic diary/PEF meter will be considered source data.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the e-CRF. In any case, all efforts should be made to maintain the patient for the 12 weeks follow up.

10.3.1 Temporary Treatment Discontinuation With Investigational Medicinal Product(s)

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

In addition, the following conditions(s) will be cause for temporary treatment discontinuation:

- Infections or infestations that do not respond to medical treatment
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix K on Guidelines for management of specific laboratory abnormalities

10.3.2 Permanent Treatment Discontinuation With Investigational Medicinal Product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of Criteria for Permanent Treatment Discontinuation

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

Patients must be withdrawn from the study (ie, from any further investigational product or study procedure) for the following reasons:

- At their own request or at the request of their legally authorized representative (Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- At the specific request of the Sponsor
  - Including some specific circumstances like the Yellow Fever outbreak in Brazil, where patients from affected areas who are not previously vaccinated with yellow-fever vaccine, are to be permanently discontinued from study drug (Section 8.8.1).
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor
- Any code breaking requested by the Investigator will lead to permanent treatment discontinuation.
- Pregnancy

- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Diagnosis of a malignancy during study.
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (See Appendix M).
- Serum ALT >3 ULN and Total Bilirubin >2 ULN (See Appendix K).
- Serum ALT >5 ULN if baseline ALT <2 ULN or ALT >8 ULN if baseline ALT >2 ULN (Appendix K).

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

10.3.4 Handling of Patients After Permanent Treatment Discontinuation

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

For patients in Brazil, see Appendix N.

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

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

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

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

10.3.5 Procedure and Consequence for Patient Withdrawal From Study

The patients may be withdrawn from the study at any time during the course of study if their parent(s)/caregiver(s)/legal guardian(s) decide to do so, and irrespective of the reason.

Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records checks.

For patients who withdraw, the patient and their parent(s)/caregiver(s)/legal guardian(s) should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

Patient(s)/parent(s)/caregiver(s)/legal guardian(s) may withdraw consent verbally or in writing and, if verbal, then the site needs to document in source records that patient withdrew consent verbally.

If possible, the patients who withdraw consent will be assessed using the procedures normally planned for the EOT visit and have EOS assessments completed at the same visit or at the last planned visit.

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

A subject should only be designated as lost to follow-up, if the site is unable to establish contact with the patient/parent(s)/caregiver(s)/legal guardian(s) after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered. Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of Adverse Events

10.4.1.1 Adverse Event

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

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

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

10.4.1.2 Serious Adverse Event

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

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

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

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

10.4.1.3 Adverse Event of Special Interest

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

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

  Note: antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents.
- Significant elevation of ALT (Appendix K)
  - ALT >5 × ULN in patients with baseline ALT ≤2 × ULN; or
  - ALT >8 × ULN if baseline ALT >2 × ULN
- Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial (It is an unlikely event to happen but for safety concerns, it is imperative to query pregnancy involving a male patient entered in the trial).
  - It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Section 10.4.1.2).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

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

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

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

Not applicable.

10.4.3 General Guidelines for Reporting Adverse Events

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

- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion, and/or
- Defined as an AESI

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

Table 4 - Summary of Adverse Event Reporting Instructions

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

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

10.4.4 Instructions for Reporting Serious Adverse Events

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

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

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

10.4.5 Guidelines for Reporting Adverse Events of Special Interest

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

10.4.6 Guidelines for Management of Specific Laboratory Abnormalities

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

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

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

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

10.5 OBLIGATIONS OF THE SPONSOR

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

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

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

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

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

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

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

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

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

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

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

10.6.2 Severe Injection Site Reactions

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

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

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

10.6.3 Infections

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

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

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

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

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

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

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

potentially contaminated food, close contact with carriers and vectors). Subsequent medical assessments (eg, stool exam, blood tests) must be performed in order to rule out parasitic infection/infestation (see also Section 10.4.1.3).

10.6.4 Elevated Liver Function Tests

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

Hepatitis virus tests and liver function tests (LFT), will be performed at Screening Visit 1, prior to randomization to exclude those patients with high risk of hepatitis infection or severe liver injury from this study (see Section 7.2.3).

In order to closely follow potential liver abnormalities, assessment of total protein, albumin, total bilirubin, ALT, AST, and ALP are measured as part of the clinical laboratory testing.

Clinical laboratory testing at Screening Visit 1 adds hepatitis screen (HBs-Ag, HBs-Ab, IgM and total-HBc-Ab, and HVC-Ab).

Guidance for the investigation of elevated LFTs is provided in Appendix K.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

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

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

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

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

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

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

11.2 DISPOSITION OF PATIENTS

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

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

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

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy Populations

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

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

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

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

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

The sponsor will implement two testing hierarchies based on the two different indication labels for the US and US reference countries and the EU and EU reference countries. Accordingly, for the US and US reference countries, the testing hierarchy will start with baseline blood eosinophils ≥300 cells/μL population; For EU and EU reference countries, the testing hierarchy will start with type 2 inflammatory phenotype population (patients with baseline blood eosinophils ≥150 cells/μL or baseline FeNO ≥20 ppb). For more details about multiplicity consideration, refer to Section 11.4.2.3.

The efficacy analyses will be conducted according to the treatment to which they are randomized.

Selected efficacy endpoints will also be analyzed based on the full ITT population. More details will be specified in the SAP.

11.3.2 Safety Population

The analysis population for the safety endpoints will be safety population defined as all patients exposed to study medication, regardless of the amount of treatment administered and regardless of whether they are randomized. The safety analyses will be conducted according to the treatment patients actually received.

Treatment emergent period for safety population is defined as the time between the first administration of study medication to the end of the Post-treatment Period or till the rollover to the 1-year long-term extension study.

In addition:

- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

11.3.3 Systemic Drug Concentration Population

The systemic drug concentration population will consist of all patients in the safety population with at least one evaluable functional dupilumab concentration result. Patients will be analyzed according to the treatment actually received.

11.3.4 Anti-drug Antibody (ADA) Population

The ADA population will consist of all patients in the safety population with at least one qualified ADA result in the ADA assay following the first dose of the study medication. Patients will be analyzed according to the treatment actually received.

11.4 STATISTICAL METHODS

11.4.1 Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of Investigational Medicinal Product Exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

An administration is considered compliant if an injection is performed with the planned dose as required by the protocol. No imputation will be made for patients with missing or incomplete data. When an administration is given with a dose above the planned dose, the corresponding administration is defined as above-planned dose noncompliance. When an administration is given with a dose below the planned dose, the corresponding administration is defined as below-planned dose noncompliance. Percentage of treatment compliance, above-planned dose and below-planned dose non-compliance will be summarized descriptively (N, Mean, standard deviation [SD], Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized.

11.4.2 Analyses of Efficacy Endpoints

Annualized rate of severe asthma exacerbation events during the 52 weeks is the primary efficacy endpoint of this study. Key secondary endpoints include change from baseline in pre-bronchodilator % predicted FEV1 at Weeks 12. Other secondary endpoints include change from baseline in pre-bronchodilator % predicted FEV1 at Weeks 2, 4, 8, 24, 36 and 52 and other time points in between; time to first severe exacerbation event; time to first LOAC event; change from baseline in other lung function measurements (absolute and relative FEV1, AM/PM PEF, FVC, FEF 25-75%, post-bronchodilator % predicted FEV1 at Weeks 2, 4, 8, 12, 24, 36, 52, and other time-points in between; change from baseline at Weeks 2, 4, 8, 12, 24, 36, 52, and other time-points for morning/evening asthma symptom score and nocturnal awakenings (electronic diary), use of reliever medication, and ACQ score. Change from baseline for PAQLQ(S)-IA score, PACQLQ score, PRQLQ-IA score (in those with history of allergic rhinitis) and health care resource utilization, will be assessed at Weeks 12, 24, 36, 52, 64; and percentage of patients requiring increase in dose or addition of background medication.

In addition to the primary approach to analyze change from baseline in ACQ-IA and PAQLQ(S)-IA total score, supportive responder analyses will also be performed for these endpoints at Week 12, 24, 36, 52 and 64. Details of these analyses will be provided in the statistical analysis plan.

11.4.2.1 Analysis of Primary Efficacy Endpoint(s)

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

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

11.4.2.1.1 Sensitivity Analysis

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

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

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

11.4.2.1.2 Subgroup Analysis

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

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

11.4.2.2 Analyses of Secondary Efficacy Endpoints

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

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

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

11.4.2.2.2 Analysis of Time-to-event Variables

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

11.4.2.2.3 Analysis of Change from Baseline for Other Continuous Variables

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

11.4.2.2.4 Analysis of Change from Baseline for Other Categorical Variables

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

11.4.2.2.5 Sensitivity Analyses

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

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

11.4.2.2.6 Subgroup Analysis

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

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

11.4.2.3 Multiplicity Considerations

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

For US and US reference countries:

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

For EU and EU reference countries:

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

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

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

11.4.2.4 Handling of Missing Data

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

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

11.4.3 Analyses of Safety Data

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

The observation period will be divided into 4 epochs:

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

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

The 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 lost to follow-up or the resolution/stabilization of all SAE and AESI.

All safety analyses will be performed on the safety population using the following common rules:

- The baseline value is defined generally as the last available value before the first dose of study drug.
- The following definitions will be applied to laboratory parameters, vital signs and ECG.
  - 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 a review of the literature and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
  - The criteria for PCSA will determine which patients had at least 1 PCSA during the treatment-emergent period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.3.1 Adverse Events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT), and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. 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.

The proportion of patients with at least 1 TEAE, serious TEAE, and TEAE leading to discontinuation of the study will be tabulated by treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the study drug. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

11.4.3.1.1 Adverse Events of Special Interest

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group.
- An overview summary of the number (%) of patients with
  - any AESI
  - any serious AESI (regardless of treatment-emergent status)
  - any treatment-emergent serious AESI
  - any AESI leading to death

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

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

11.4.3.1.2 Death

The following deaths summaries will be generated:

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

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

11.4.3.2 Clinical Laboratory Evaluation, Vital Signs and Electrocardiogram Data

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

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

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

11.4.3.3 Humoral Immune Response to Vaccines

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

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

11.4.4.1 Drug Concentration Analysis

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

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

11.4.4.2 Anti-drug Antibodies Analysis

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

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

Anti-drug antibodies at baseline will be summarized by:

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

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

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

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

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

11.4.4.3 Pharmacodynamics and Phenotyping

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

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

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

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

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

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

11.5 INTERIM ANALYSIS

There is no interim analysis planned for this study.

11.6 PLANNED DATABASE LOCK

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

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

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

12.2 INFORMED CONSENT

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

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

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

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

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

The ICF and the assent form used by the Investigator for obtaining the pediatric patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC)] for approval/favorable opinion.

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

Prior to and on the same date as the Screening Visit 1, and a patients registration in IVRS/IWRS, the Investigator or designee must have collected the signed and completed ICF/IAF.

[redacted]

[redacted]

The main study informed consent form, the assent form for girls who have started menstruating, [redacted] to be used by the Investigator for obtaining the patient's/parent(s)/legal guardian(s) informed consent/assent as applicable per national requirements must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

In addition, for Brazil, a country-specific ICF will be issued for the collection of additional blood samples for the assessment of pre and post Yellow Fever vaccination titers, dupilumab PK, and ADA levels. Refusal to sign the additional ICF will not impact the patient's ability to receive Yellow Fever vaccination (Appendix N).

If the race/ethnic origin of the patients will be collected in the clinical trial, the scientific justification should be specified in Section 14.5.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

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

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

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded in the e-CRF. The ICF will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (eg, patient's medical file, appointment

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

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

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

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

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

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

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

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

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

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

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

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

14.3 CONFIDENTIALITY

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

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities (eg, on African American population for FDA).

Analyses of subject genetic data will be conducted as described in the protocol as this is needed for pharmacogenetics analyses required for the purposes of the study or by regulatory authorities.

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

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements.

The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

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

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

14.8.1 By the Sponsor

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

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

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s). The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

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

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised ICF prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

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17 APPENDICES

Appendix A Low, Medium, and High-dose Inhaled Corticosteroids – Children (6 to <12 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 B Examples of Commonly Used Asthma Controller Therapies

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

Controller Group	Medications
Methylxanthines	Aminophylline
	Theophylline
	Dyphylline
	Oxtryphylline
	Diprophylline
	Acebrophylline
	Bamifylline
	Doxofylline

Note: This list is indicative and not exhaustive.

Appendix C List of Prohibited Live Attenuated Vaccines

Bacillus Calmette-Guérin (BCG) antituberculosis vaccine

Chickenpox (Varicella)

Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted

Measles (Rubeola)

Measles-mumps-rubella (MMR) combination

Measles-mumps-rubella-varicella (MMRV) combination

Mumps

Oral polio (Sabin)

Oral typhoid

Rotavirus

Rubella

Smallpox (Vaccinia)

Varicella Zoster (shingles)

Yellow fever

This list is indicative and not exhaustive.

Appendix D Examples of CYP substrates with narrow therapeutic range

CYP ENZYMES	SUBSTRATES WITH NARROW THERAPEUTIC RANGE[1]
CYP1A2	THEOPHYLLINE, TIZANIDINE
CYP2C8	PACLITAXEL
CYP2C9	WARFARIN, PHENYTOIN
CYP2C19	S-MEPHENYTOIN
CYP3A[2]	ALFENTANIL, ASTEMIZOLE[3], CISAPRIDE[3], CYCLOSPORINE[4], DIHYDROERGOTAMINE, ERGOTAMINE, FENTANYL, PIMOZIDE, QUINIDINE, SIROLIMUS, TACROLIMUS[4], TERFENADINE[3]
CYP2D6	THIORIDAZINE

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

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

Appendix E Asthma Symptom Score Numerical Rating Scale (NRS)

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

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

[redacted]

JULY 2011

ACQ-IA – North American /English- revised July 2011
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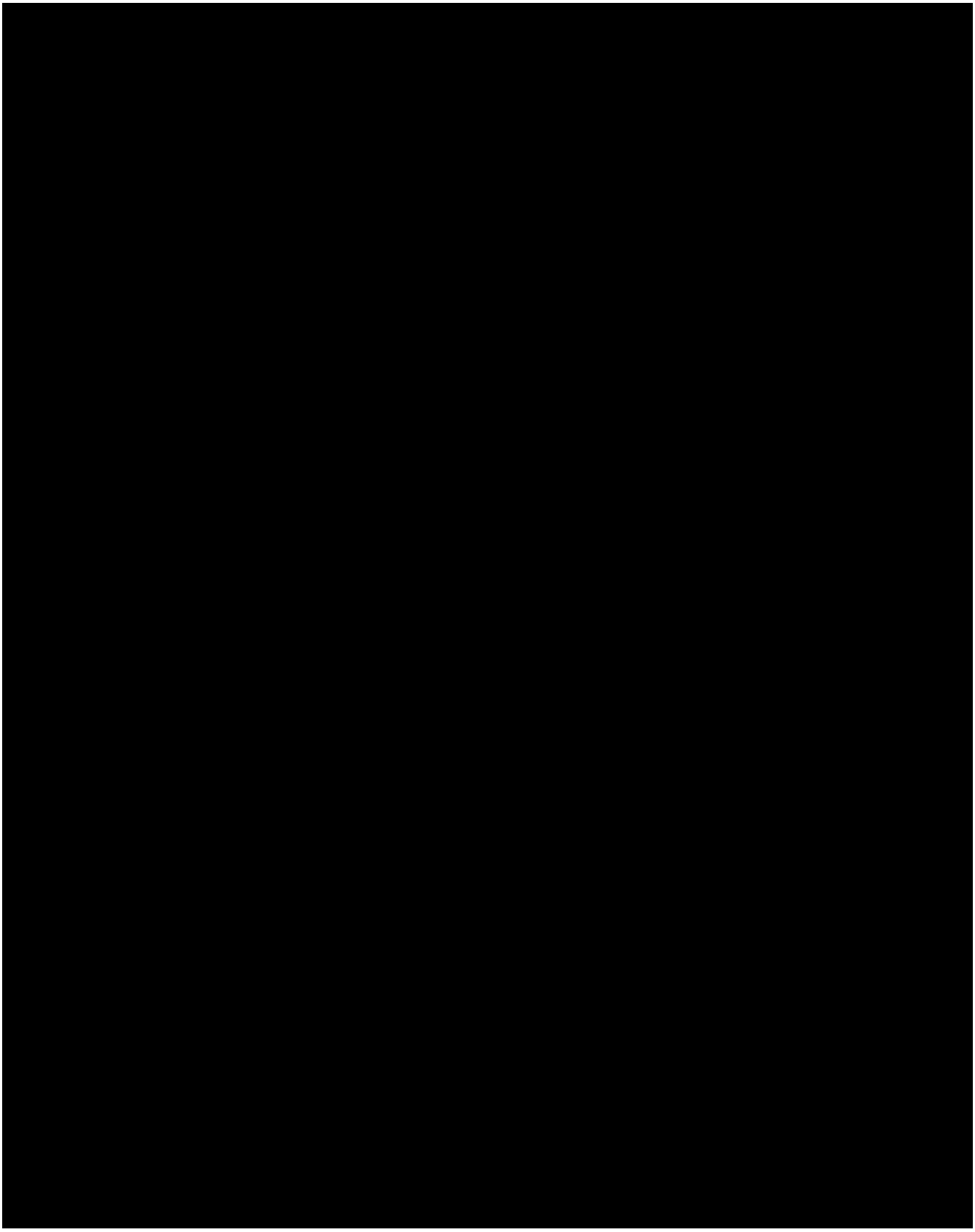

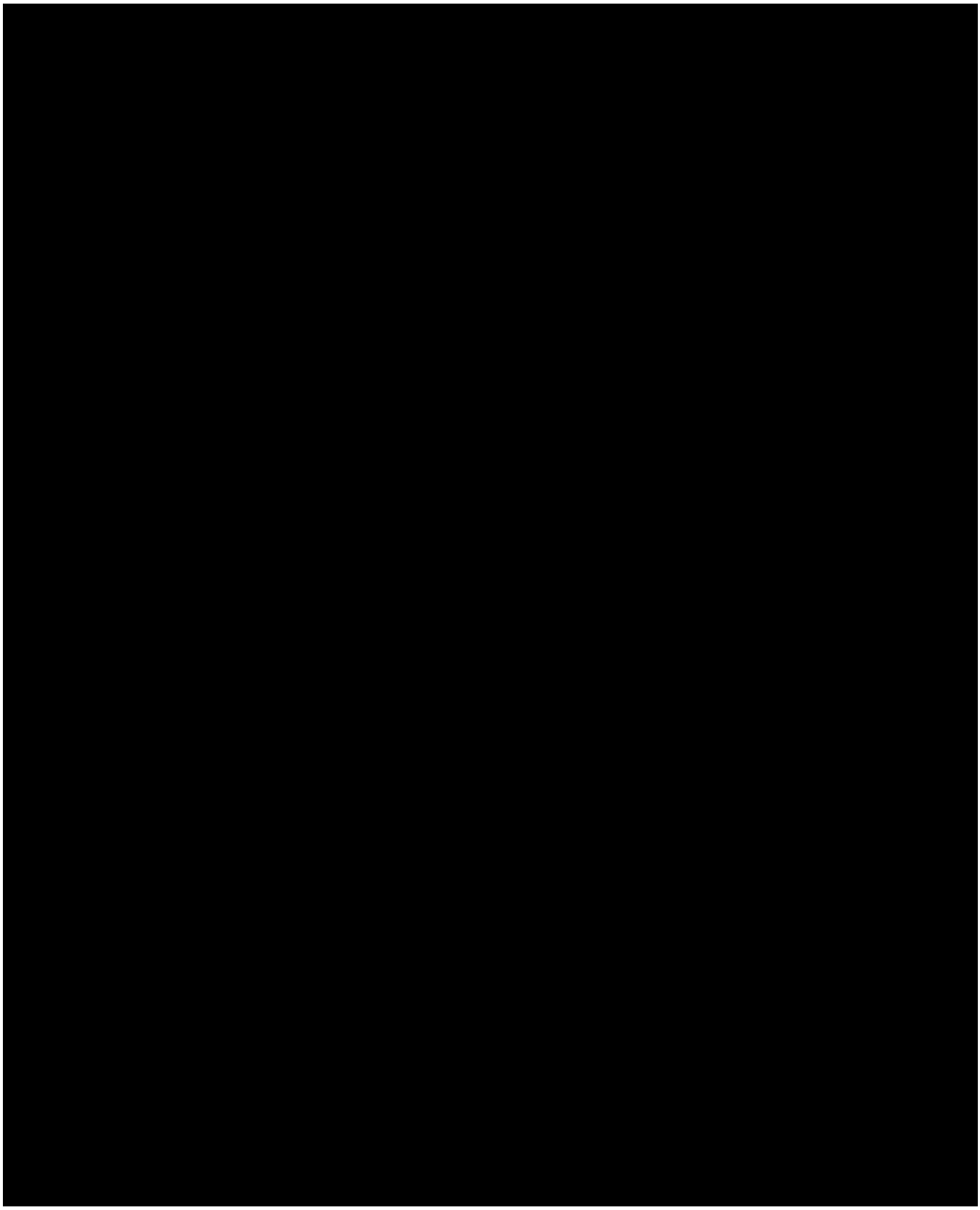

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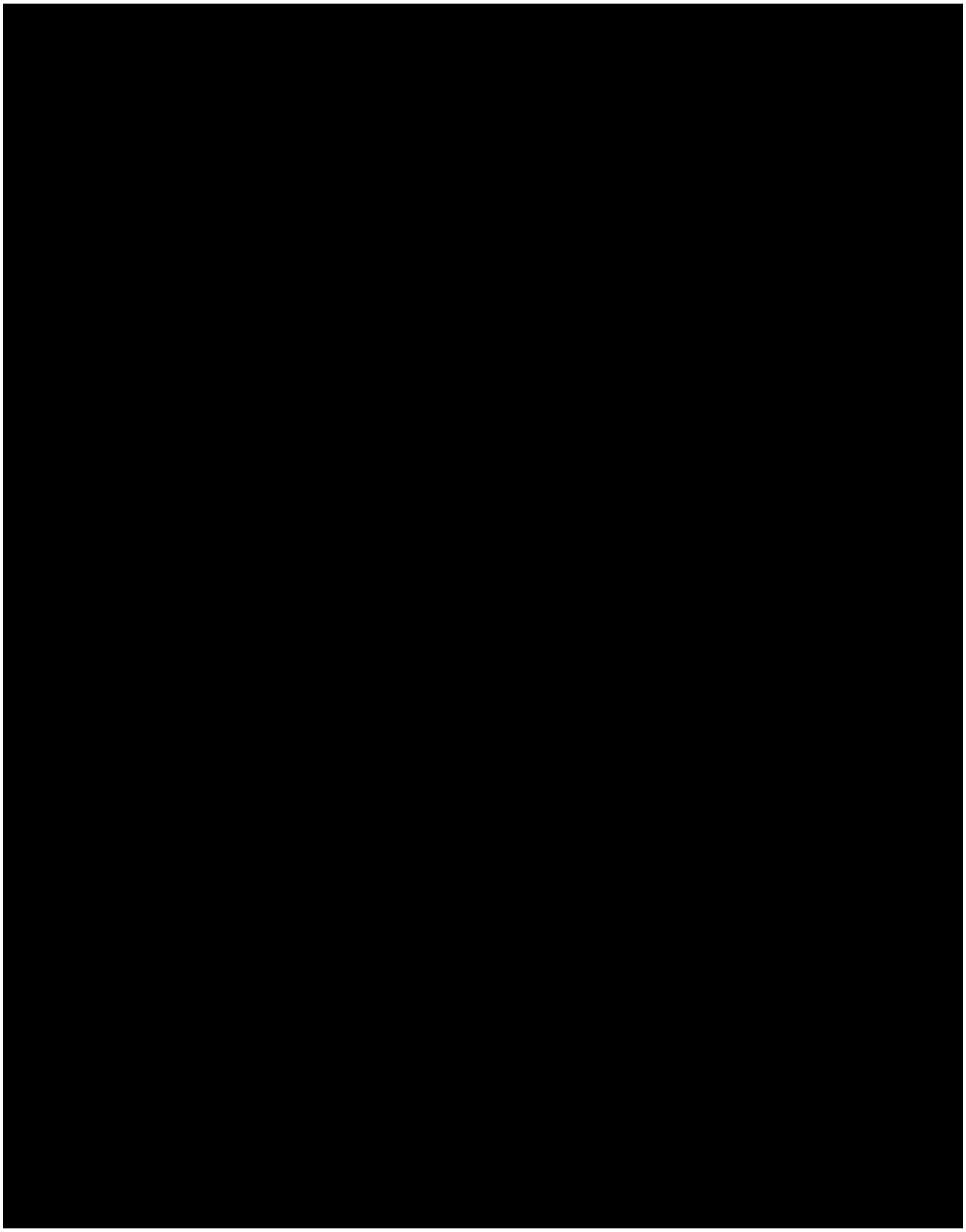
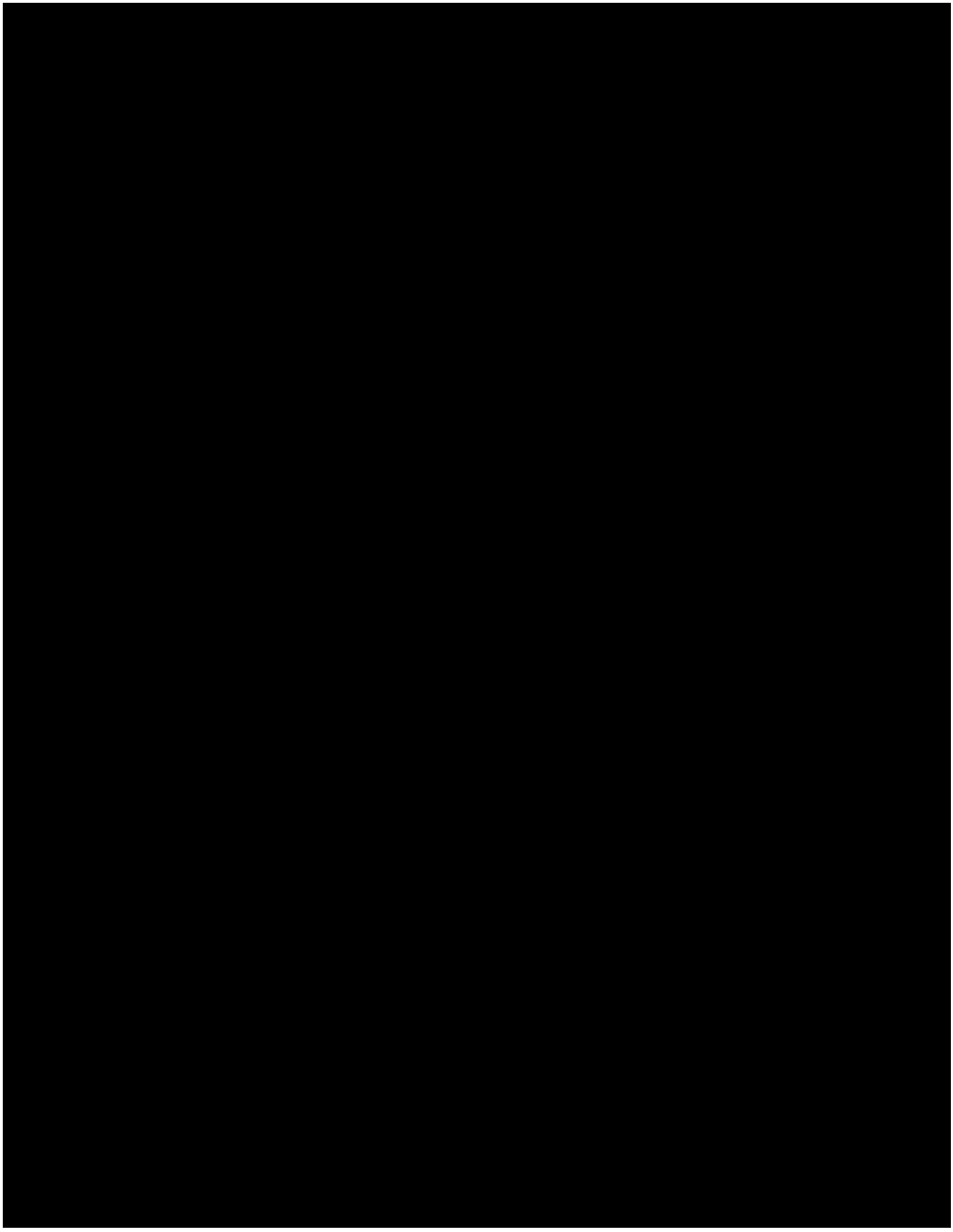


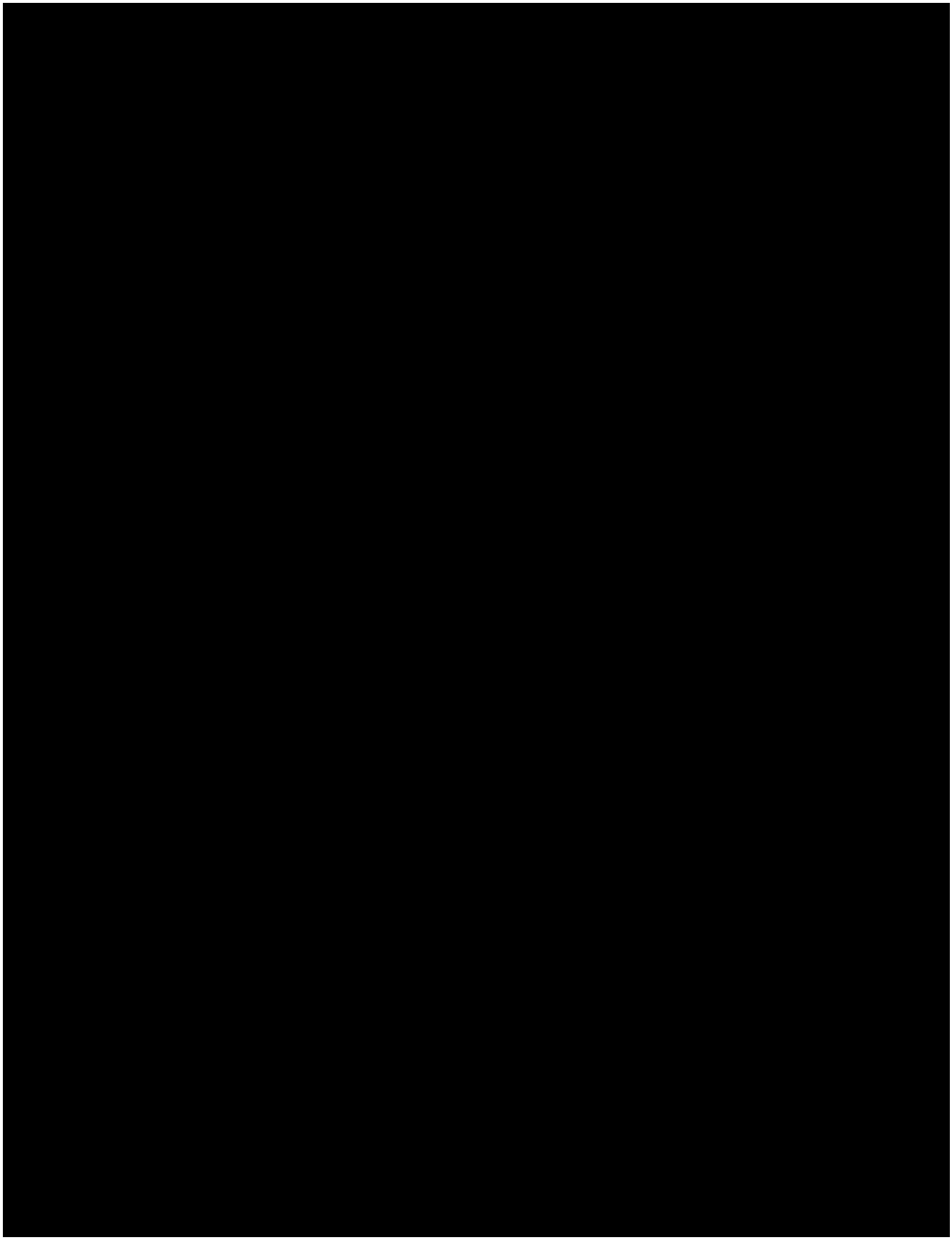
Appendix G Paediatric Asthma Quality of Life Questionnaire With Standardised Activities–Interviewer Administered (PAQLQ[S]-IA)

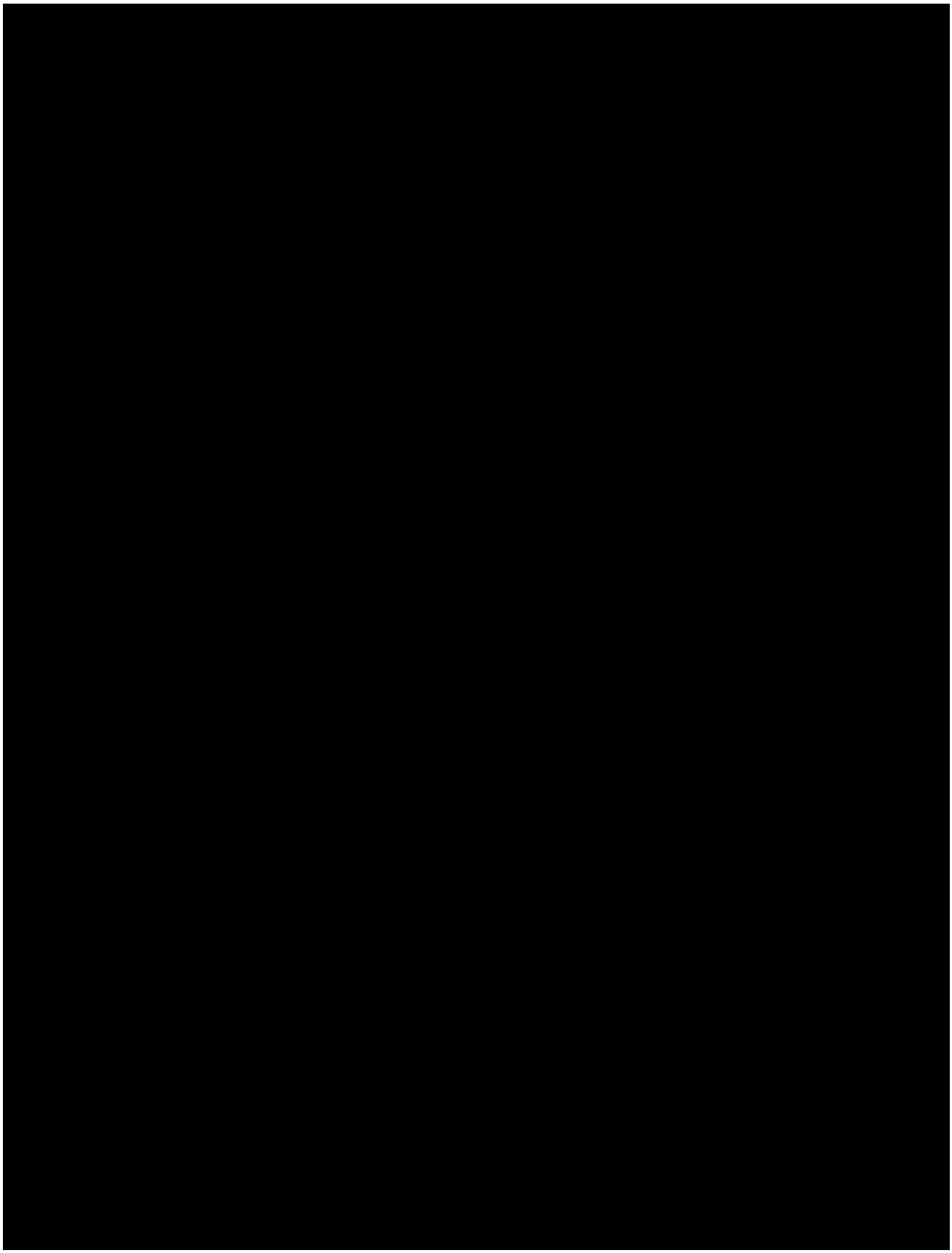
[redacted]

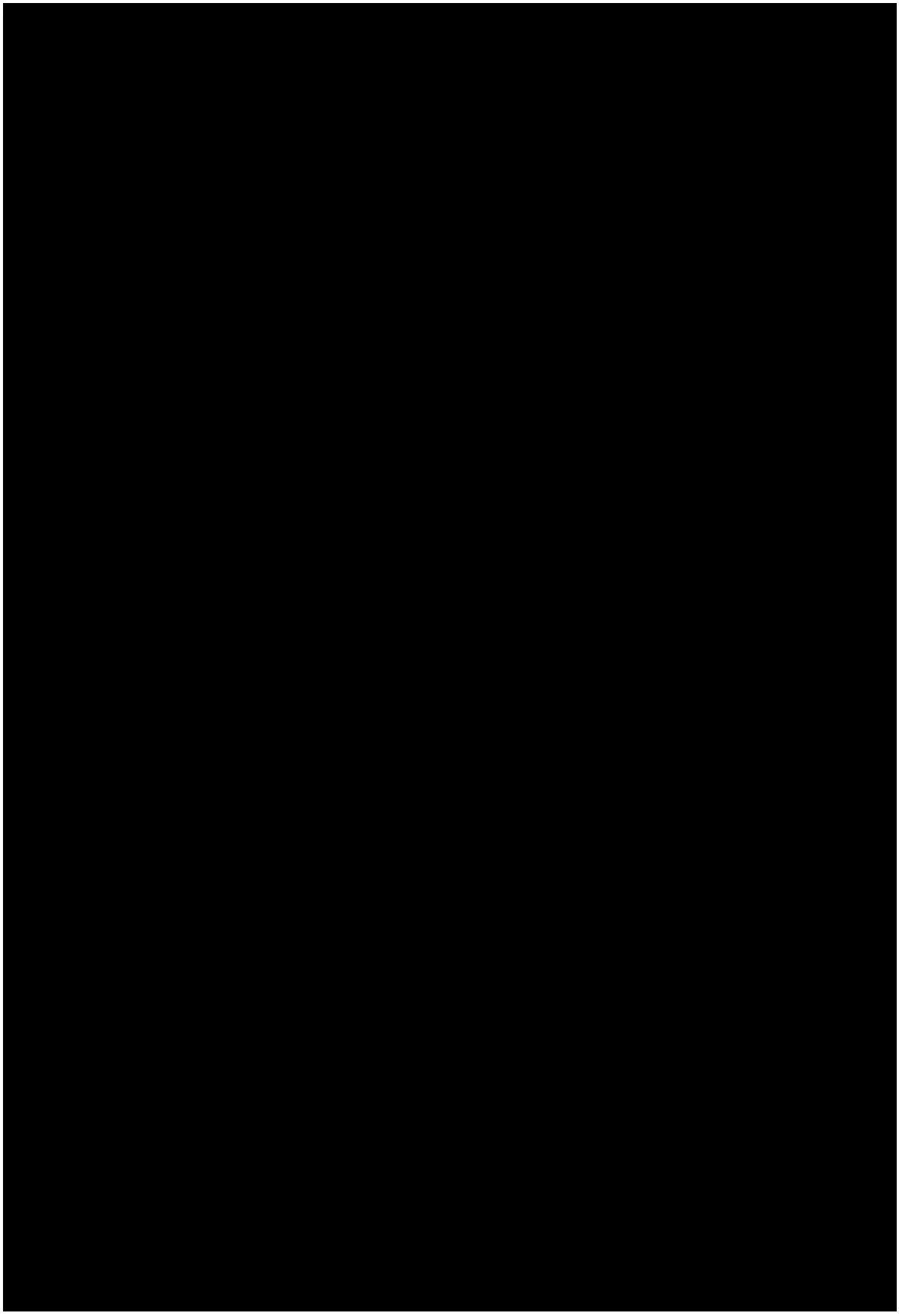
JANUARY 2001

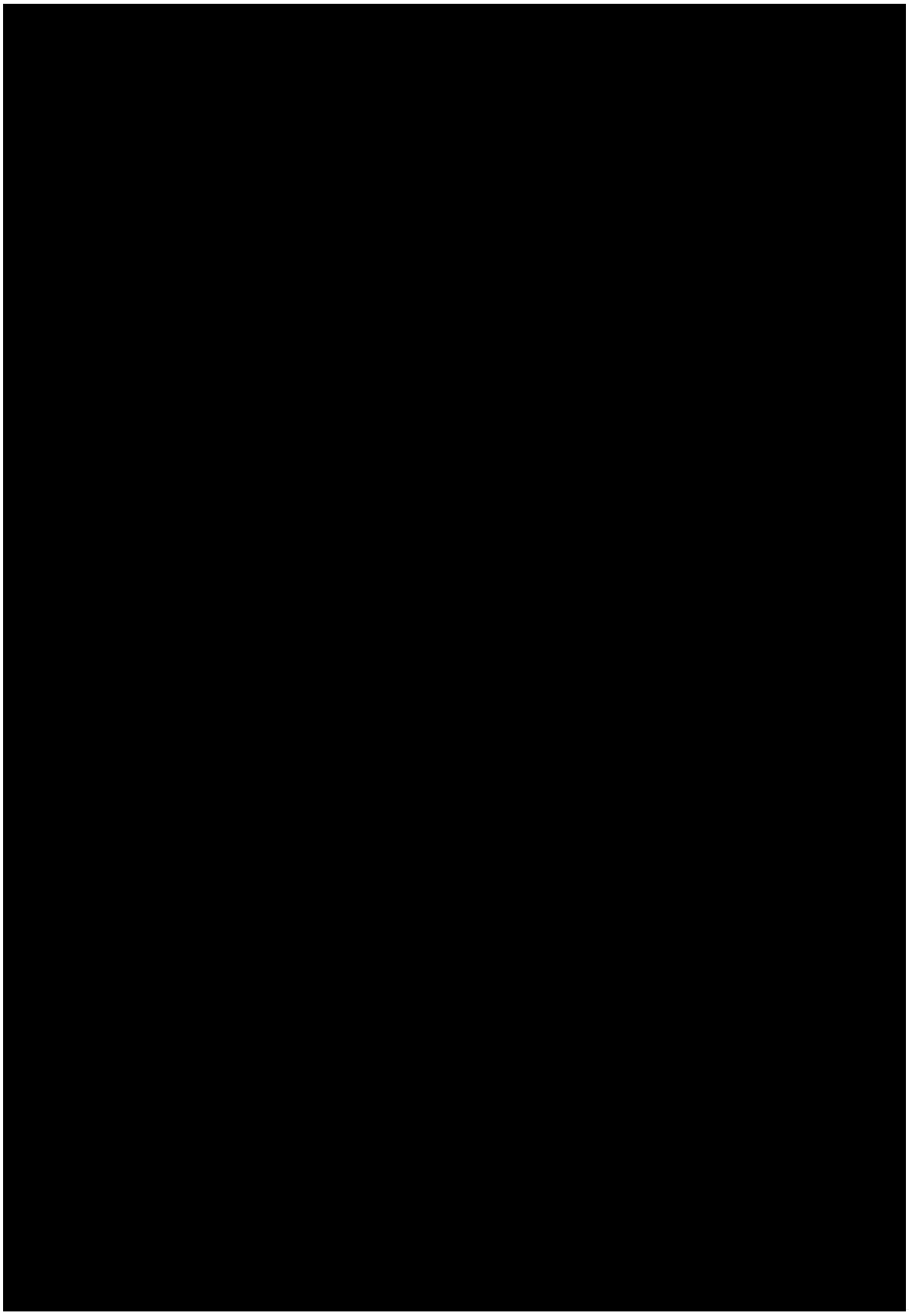
Revised 08 December 2010
PAQLQ(S)-IA - North American English Version











Appendix H Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ)

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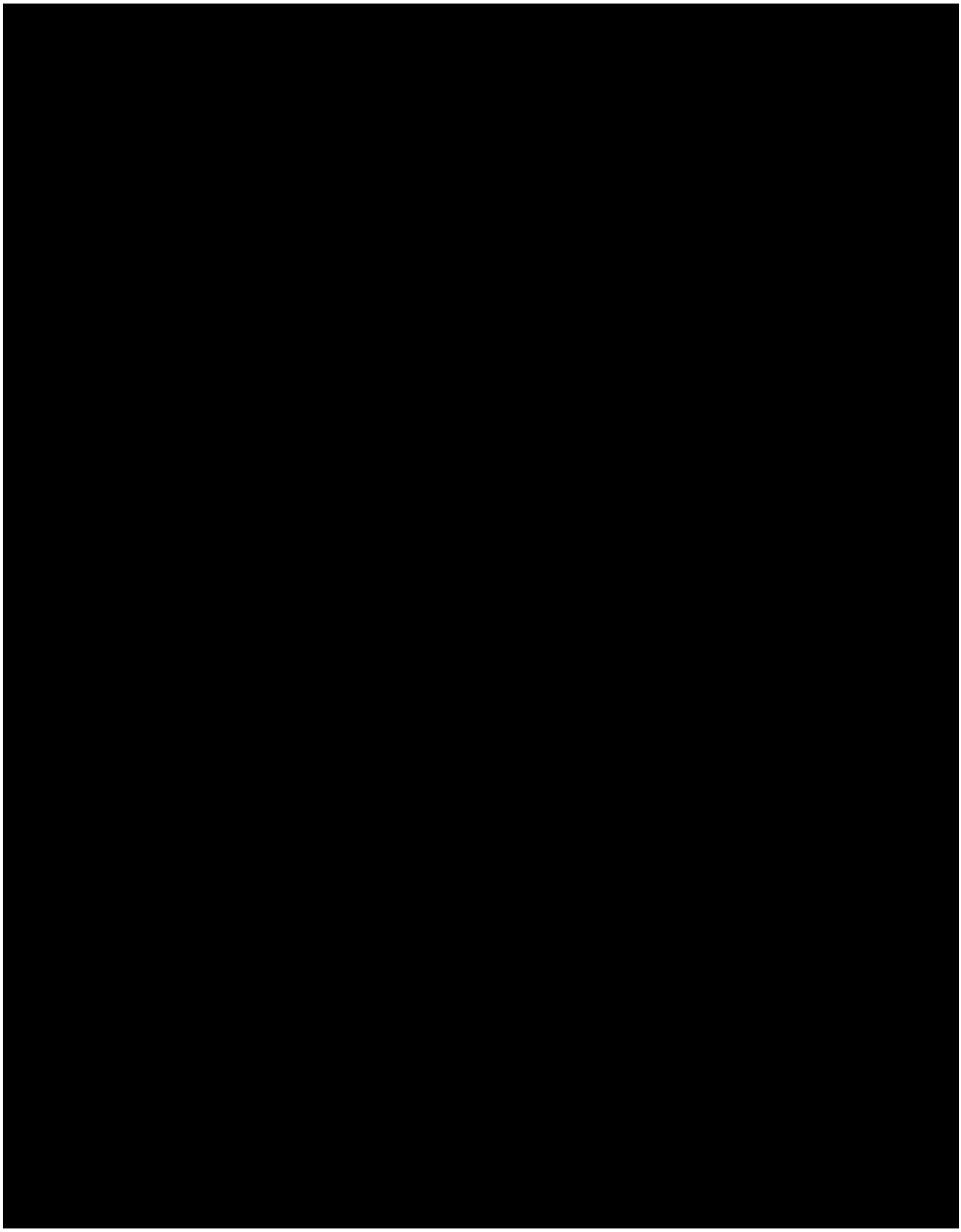
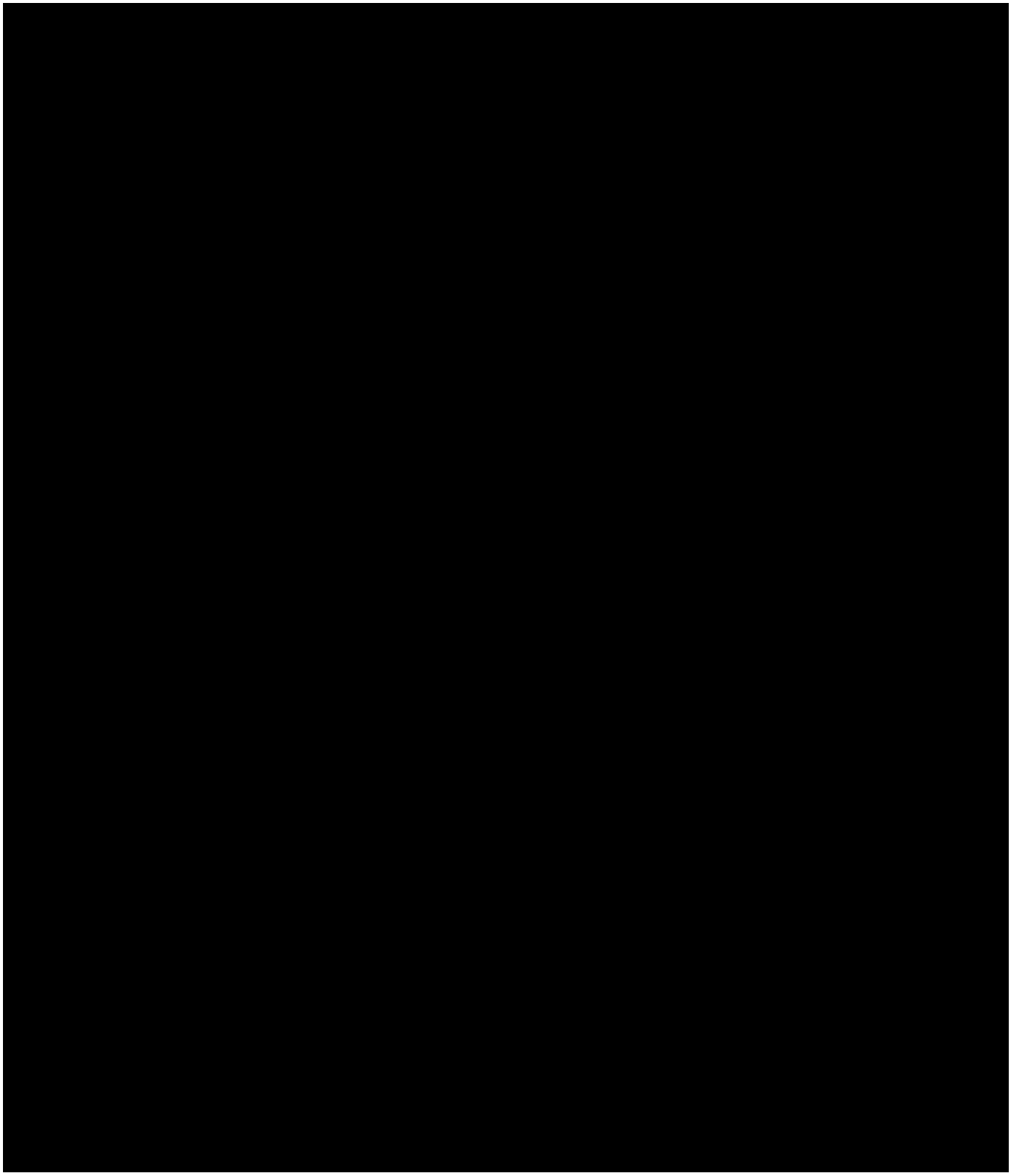
JANUARY 2001





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

[redacted]

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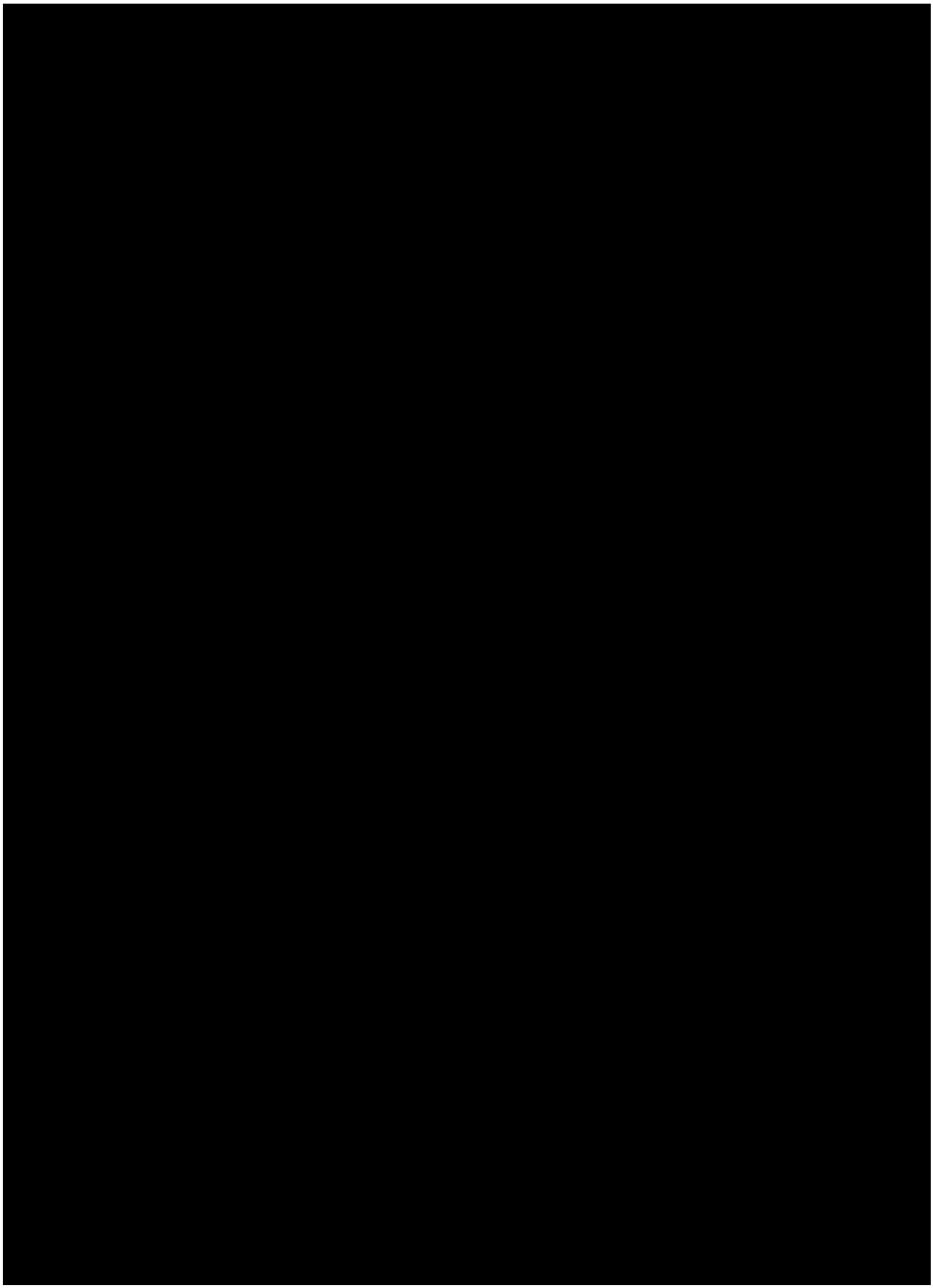
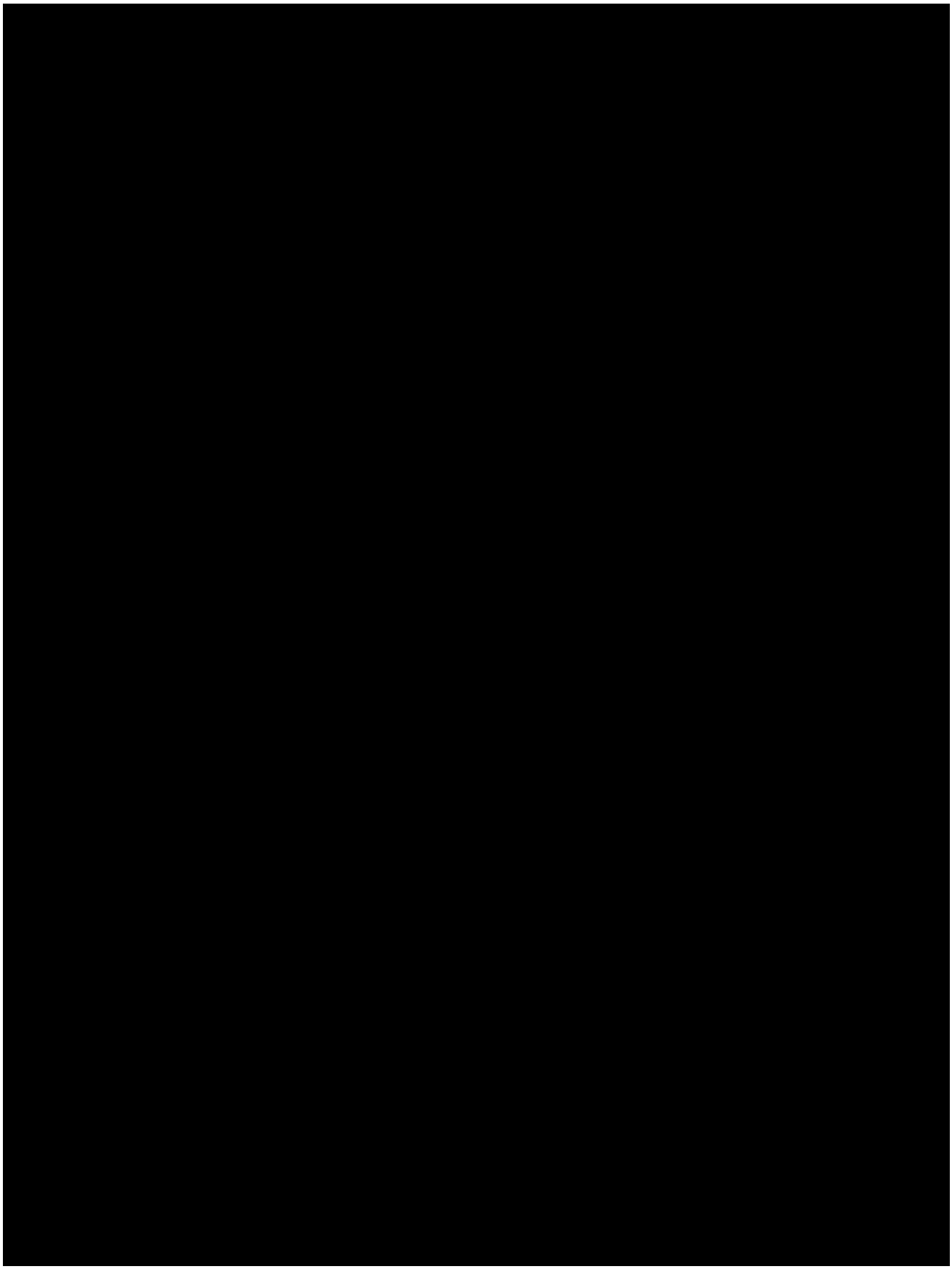
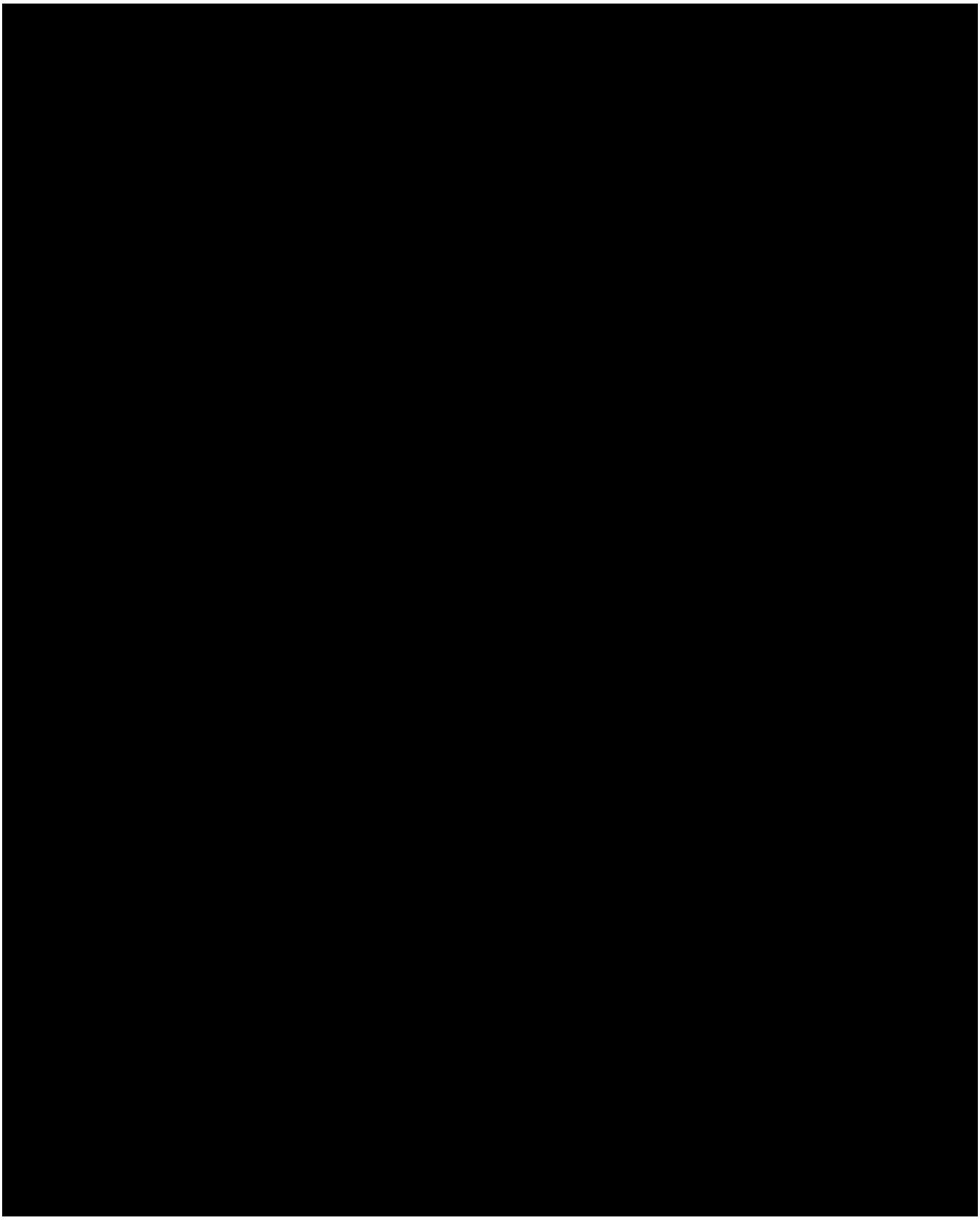
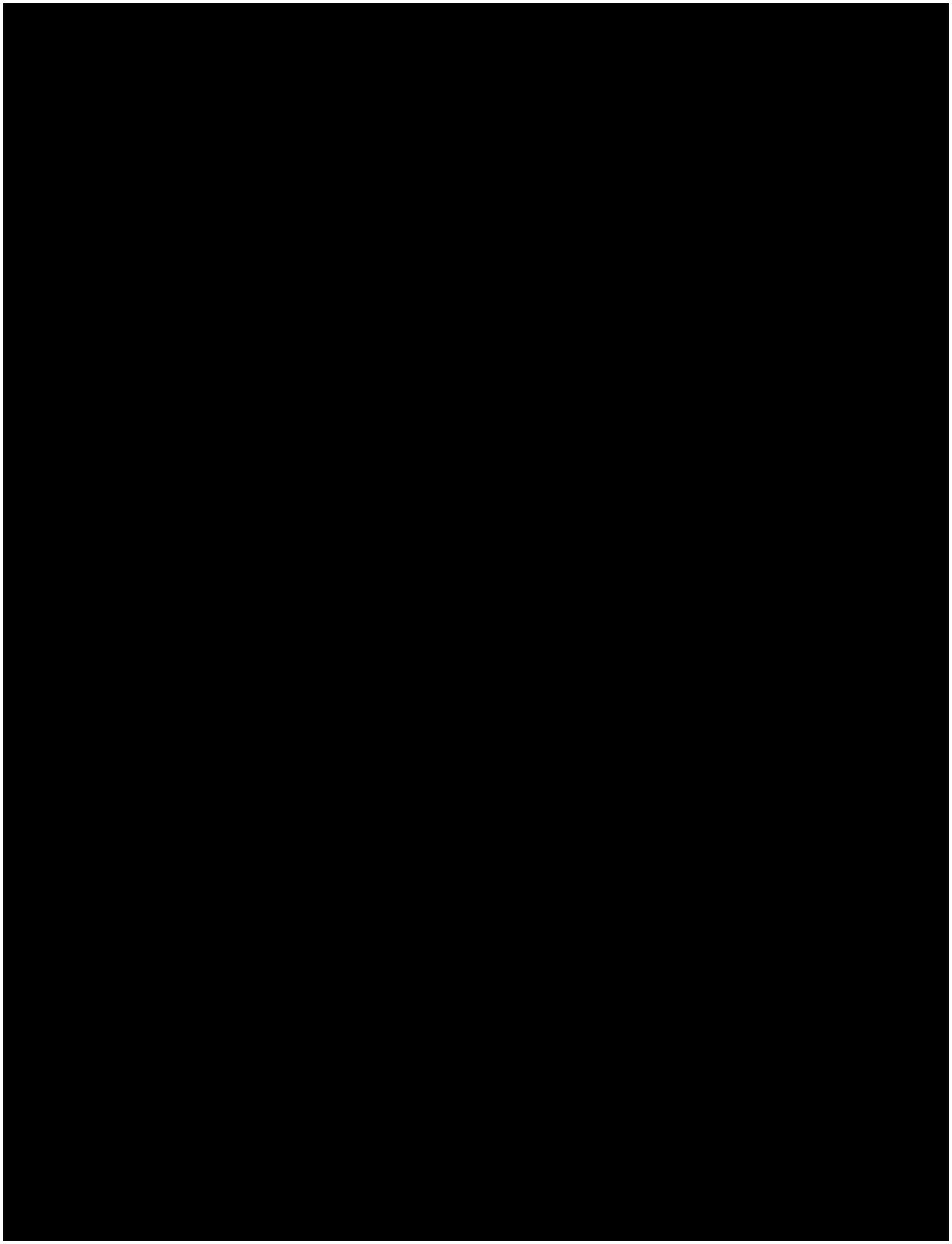
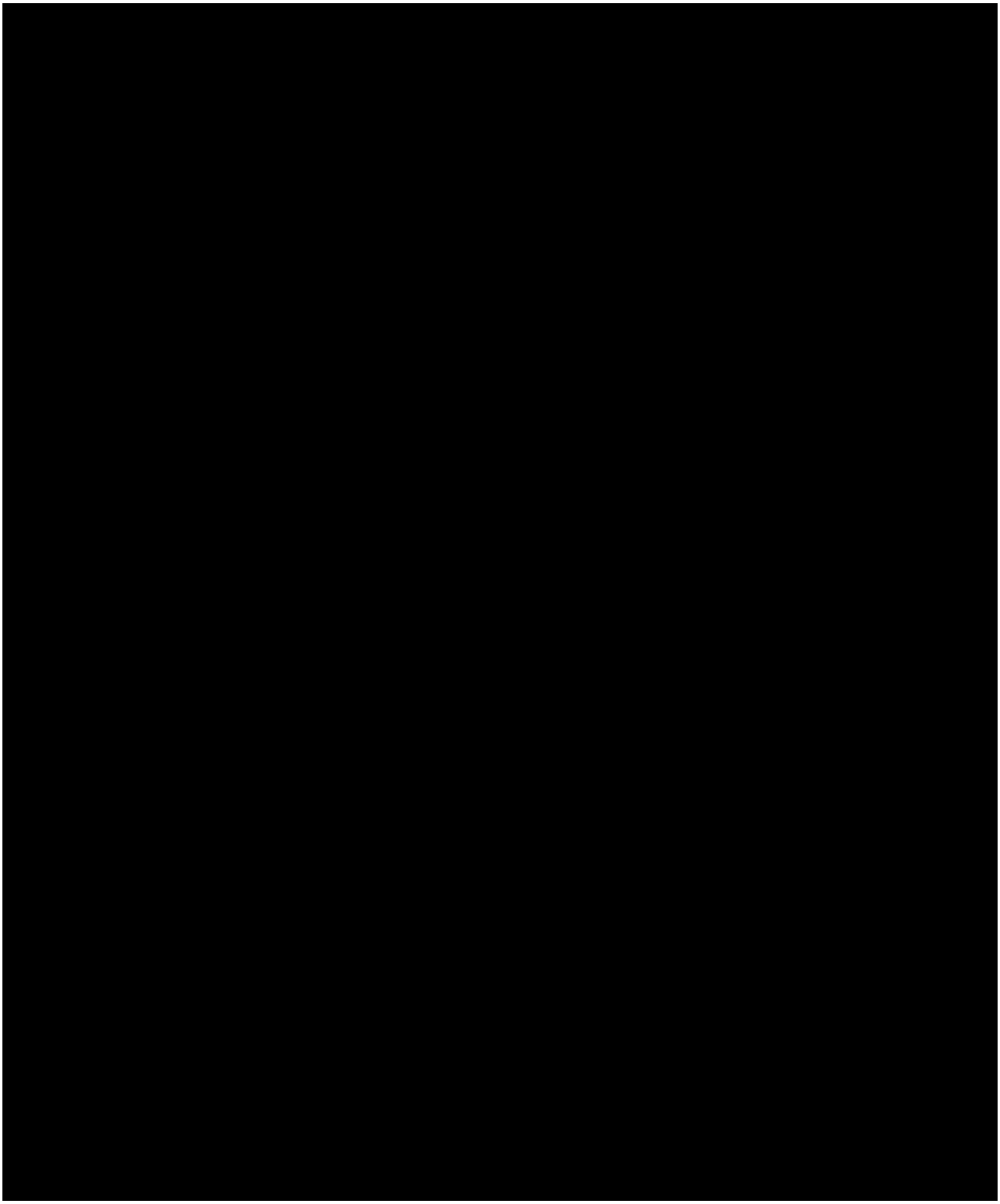




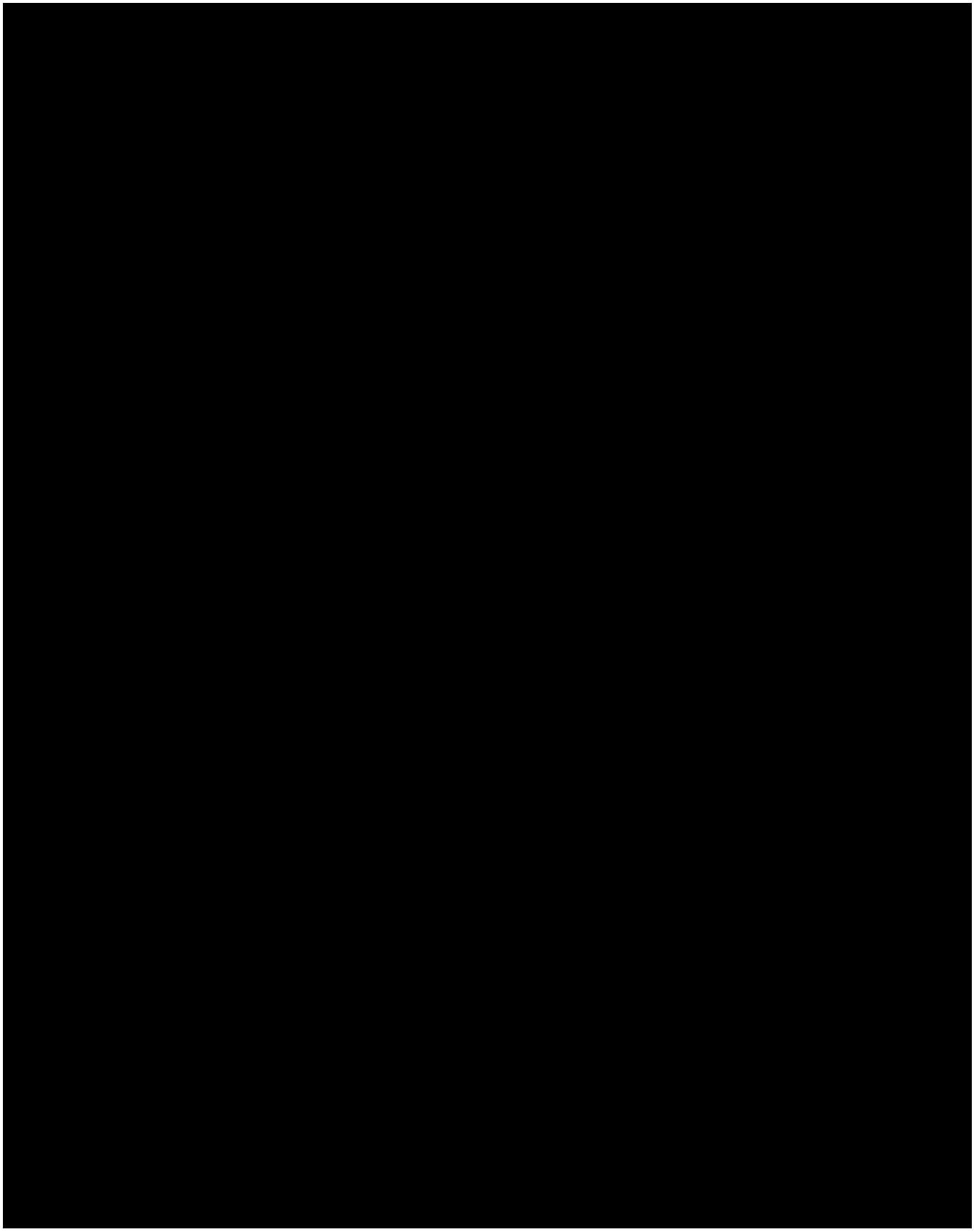


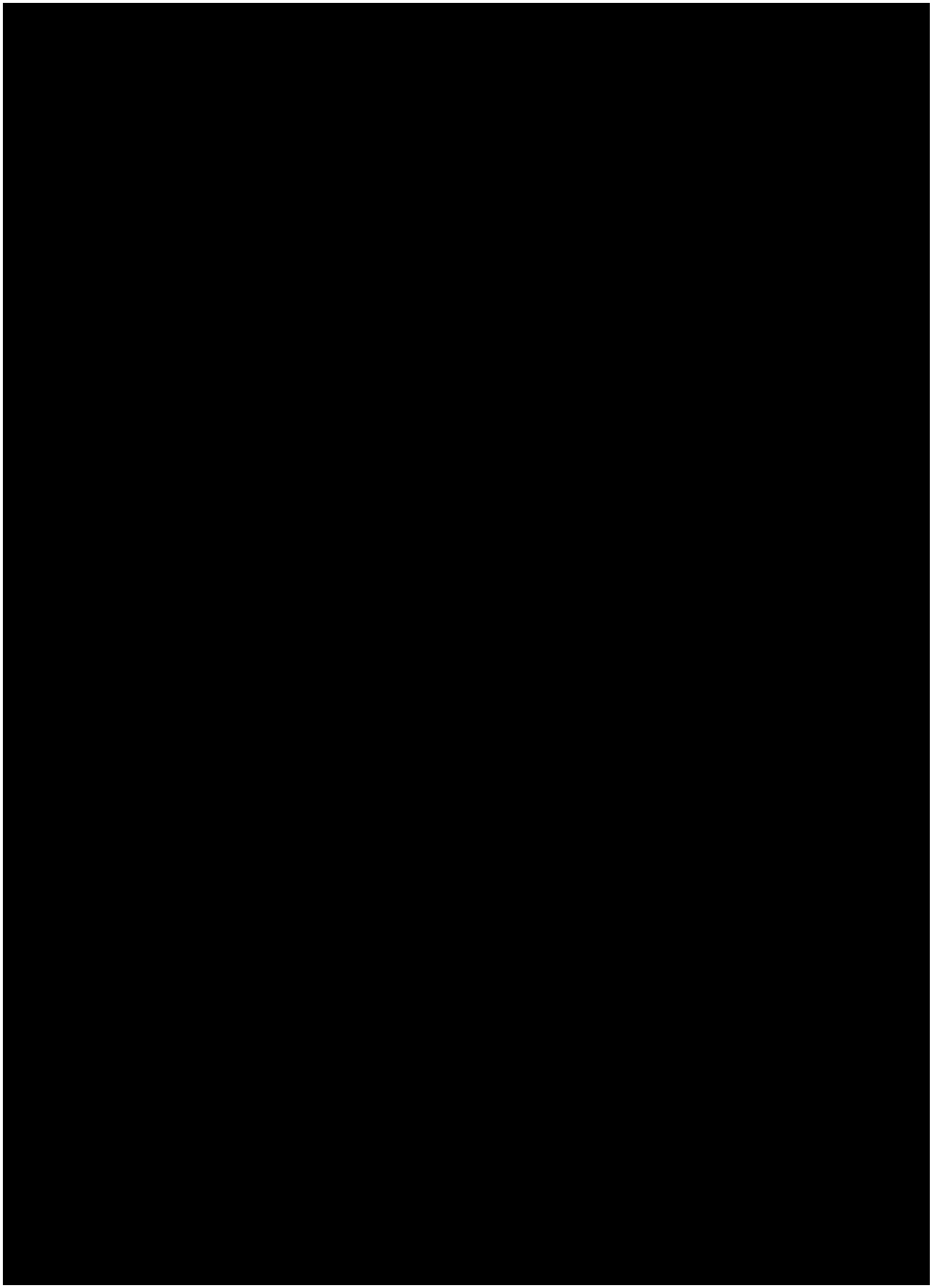


Appendix J Euro Qol (EQ-5D-Y) – for Children



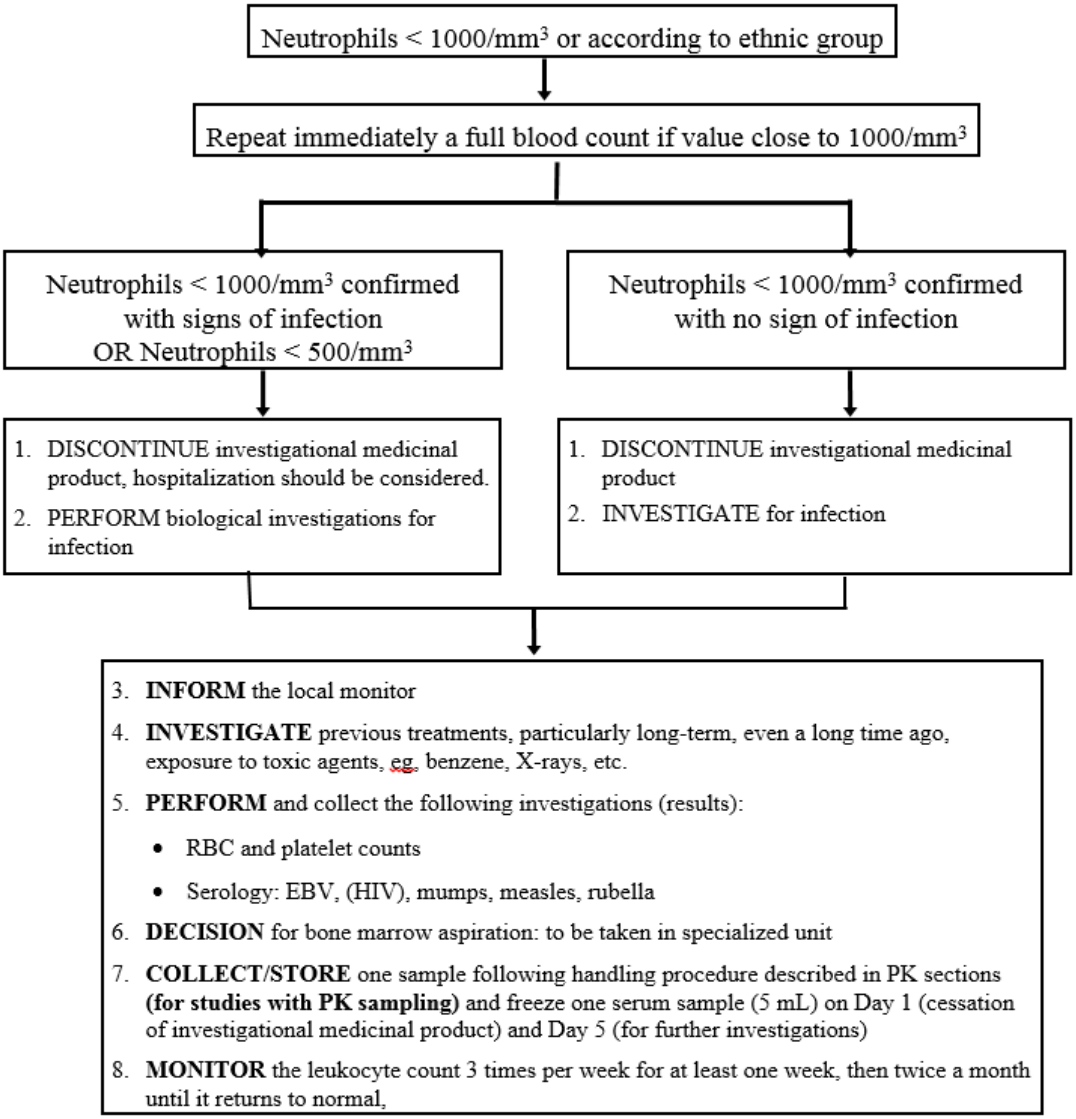
EQ-5D-Y





Appendix K General Guidance for the Follow-up of Laboratory Abnormalities by Sanofi

Neutropenia



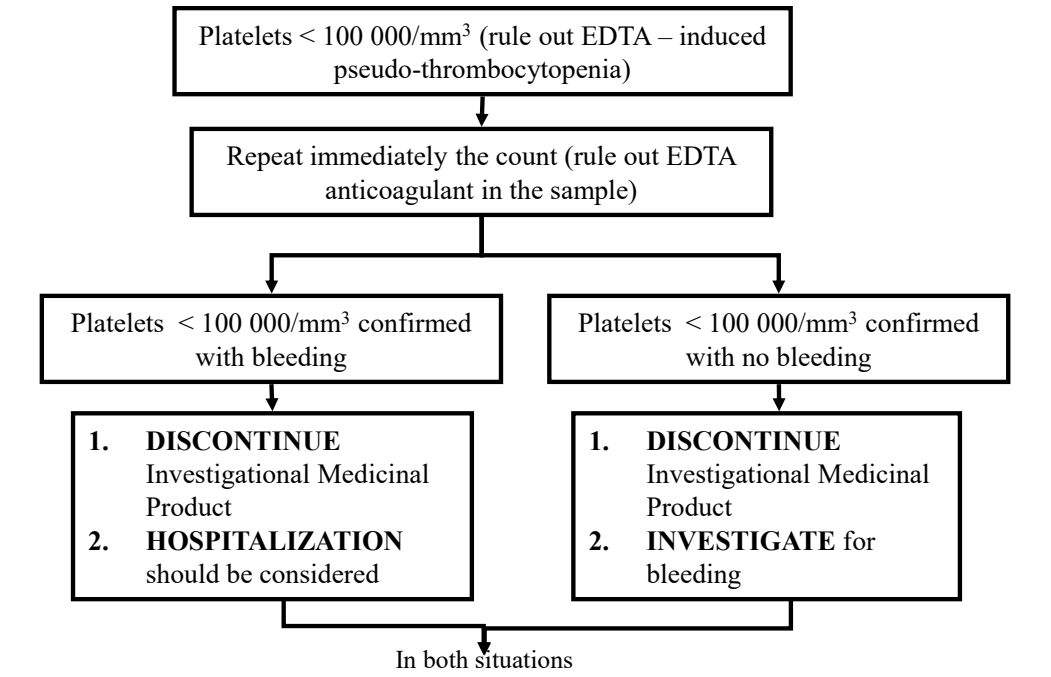
Note:

- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local authorities), an additional consent (eg, for HIV testing) will only be obtained in the case of event actually occurs.
- For individuals of African descent, the relevant value of concern is <1000/mm3

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

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

THROMBOCYTOPENIA

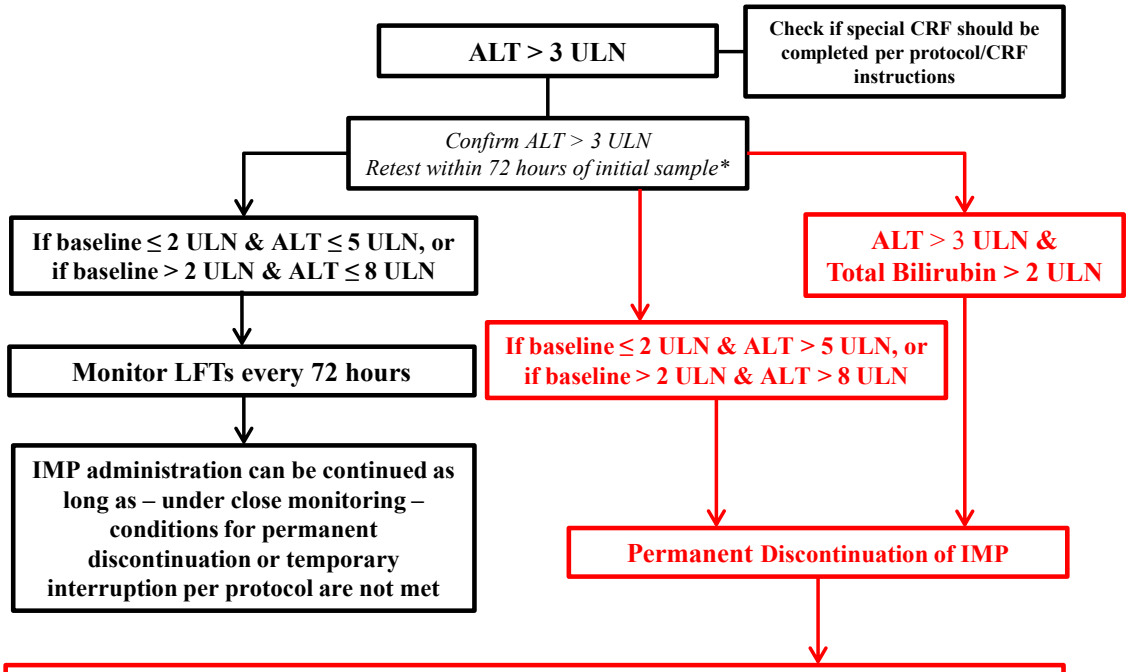


Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

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

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

ALT Increase

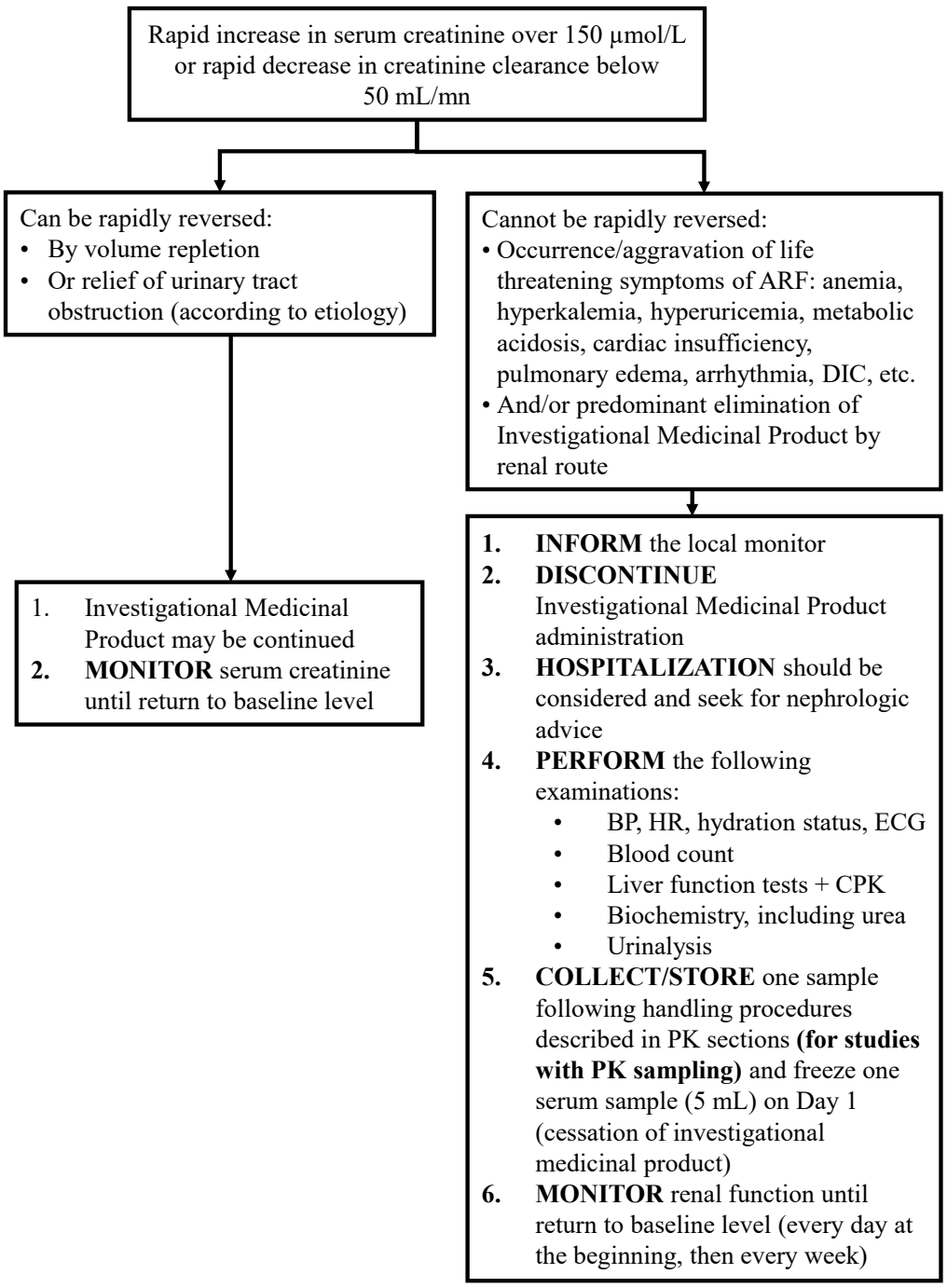


In ANY CASE, FOLLOW the instructions listed in the box below:

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

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

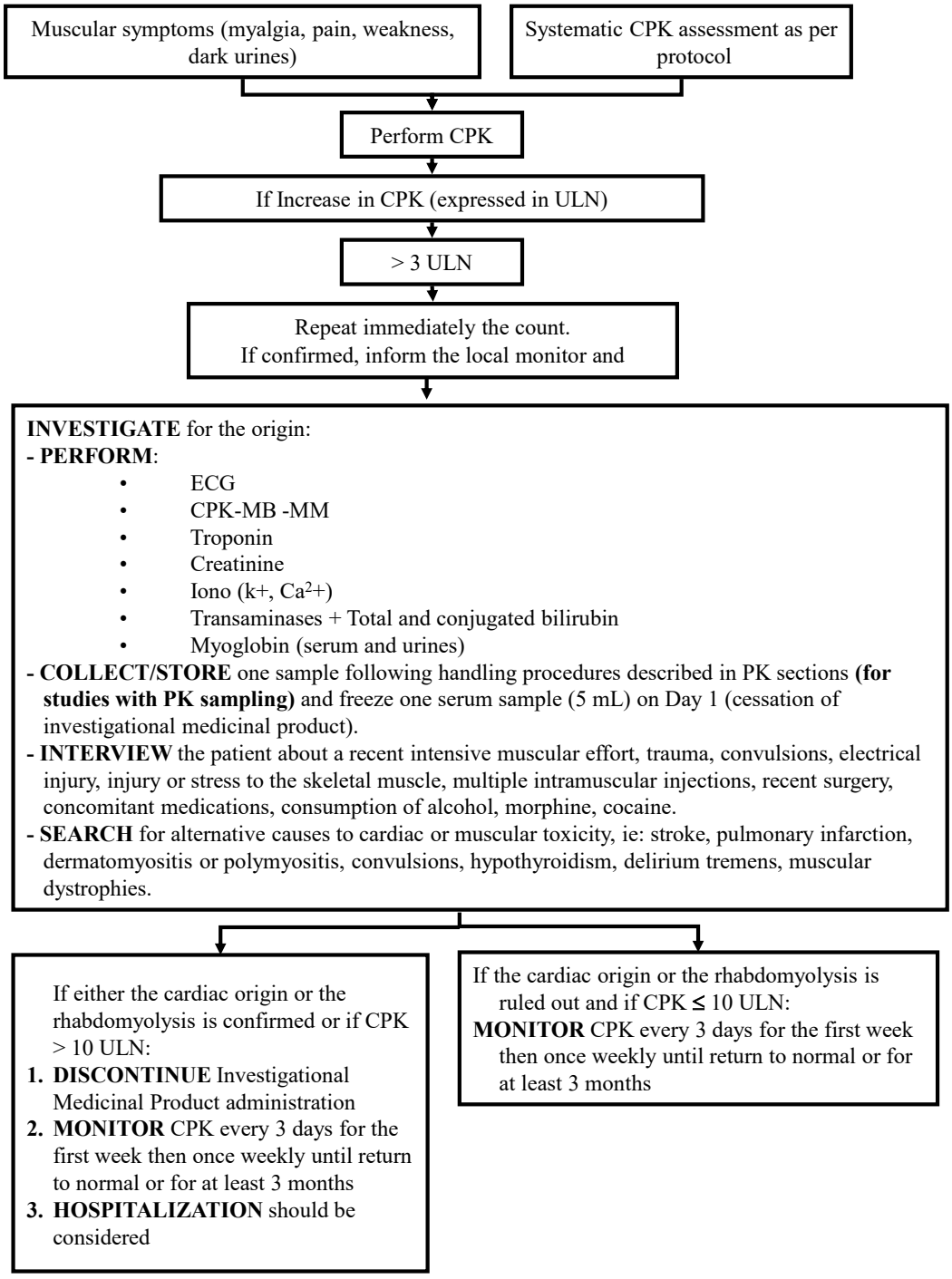
ACUTE RENAL FAILURE



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

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

SUSPICION OF RHABDOMYOLYSIS



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

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

Appendix L Definition of Anaphylaxis

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

Adapted from:
Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA , Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-397

Clinical criteria for diagnosing anaphylaxis

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

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

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

Appendix M List of Opportunistic Infections

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

NOTE: This list is indicative and not exhaustive.

Appendix N Country specific requirements

Amendment for Brazil dated 02-Feb-2018

Section 8.8.1 Prohibited medication (Section 8.8.1)

In Brazil, due to the Yellow Fever outbreak, any patient who is not previously vaccinated with the yellow-fever vaccine (in the outbreak affected area) should be unblinded and should be permanently discontinued from treatment with study drug (Section 10.3.3). Patients who discontinue IMP must continue to be followed in the study until EOS (Section 10.3.4).

Section 9.3.1.1.1 Sampling time (Section 9.3.1.1.1)

Predose blood samples will be collected for determination of functional dupilumab concentration in serum and anti-dupilumab antibodies (including neutralizing antibodies) on days designated in the Study Flow Chart (see Section 1.2 as well as Section 10.3.4, as needed for Brazil).

Section 10.3.3 List of criteria for permanent discontinuation (Section 10.3.3)

- At the specific request of the Sponsor
  - Including some specific circumstances like the Yellow Fever outbreak in Brazil, where patients from affected areas who are not previously vaccinated with yellow-fever vaccine, are to be permanently discontinued from study drug (see below).

Section 10.3.4 Handling of patients after permanent treatment discontinuation (Section 10.3.4)

In Brazil, any patient who is permanently discontinued from treatment with study drug due to the Yellow Fever outbreak must complete all EOT procedures. These patients should continue to be followed in the study until EOS. Specific blood samples for ADA, dupilumab PK, and pre-vaccination Yellow Fever antibody titer should be performed, when possible, prior to vaccination in patients who received dupilumab. Post-vaccine blood samples for ADA, PK, and Yellow Fever antibody titers will also be collected following the appropriate interval (4-6 weeks after vaccination and may be extended up to 8 weeks). A specific ICF must be signed prior to collection of these samples (See below).

Brazilian patients who are discontinued early from treatment due to the Yellow Fever outbreak will remain eligible for the 1 year long term extension study.

Section 12.2 Informed consent (Section 12.2)

For Brazil, a country-specific ICF will be issued for the collection of additional blood samples for the assessment of pre and post Yellow Fever vaccination titers, dupilumab PK, and ADA levels. Refusal to sign the additional ICF will not impact the patient's ability to receive Yellow Fever vaccination.

Appendix O Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amended protocol03 is located directly before the Table of Contents (TOC).

Amended protocol 02 dated 18-Jun-2018:

Table 5 - Summary of changes: amended protocol 02

Sections	Initial wording	Amended or new wording	Reason/Justification for change	Reasons for substantial amendment
Sections: Clinical Trial Summary and Section 11 Statistical considerations	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. Patients will be randomized (2:1 ratio) to receive dupilumab or matching placebo. After a patient is randomly assigned to dupilumab or matching placebo, the dosage of dupilumab or matching placebo for the patient, 200 or 100 mg SC once q2w, will be determined based on bw >30 kg or ≤30 kg, respectively. Randomization will be stratified by ICS dose (medium-dose versus high dose) and eosinophil count (<300 cells/μL versus ≥300 cells/μL) at Screening, and by region.	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. Patients will be randomized (2:1 ratio) to receive dupilumab or matching placebo. After a patient is randomly assigned to dupilumab or matching placebo, the dosage of dupilumab or matching placebo for the patient, 200 or 100 mg SC once q2w, will be determined based on bw >30 kg or ≤30 kg, respectively. Randomization will be stratified by ICS dose (medium-dose versus high-dose) and eosinophil count (<300 cells/μL versus ≥300 cells/μL) at Screening, and by region.	**Change:** Increase in study sample size. **Reason for change**: Due to an update on the assumptions used to perform the sample size calculation. The original effective size assumption was based on the observed risk reduction in the dupilumab Phase 2b study in adult patients with uncontrolled persistent asthma. This assumption is being updated based on the effect size observed in the recently concluded Phase 3 dupilumab clinical trial in adult and adolescent patients with uncontrolled persistent asthma. The sample size is adjusted to maintain 90% power based on a more accurate estimation of treatment effect from a larger clinical study.	Change in sample size

Sections	Initial wording	Amended or new wording	Reason/Justification for change	Reasons for substantial amendment
	To ensure scientific validity, alerts will be built into the interactive voice response system (IVRS) system to limit enrolling patients in the following stratification subgroups: 1. Background therapy with medium-dose ICS not to exceed 50%, or 146 patients, 2. Eosinophil <150 cells/µL not to exceed 20%, or 58 patients	To ensure scientific validity, alerts will be built into the interactive voice response system (IVRS) system to limit enrolling patients in the following stratification subgroups: 1. Background therapy with medium-dose ICS not to exceed 50%[redacted] 2. Eosinophil <150 cells/µL not to exceed 20%[redacted]		
Sections: Clinical Trial Summary and Section 7.1 Inclusion criteria	Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puff inhalations with metered-dose inhaler [MDI]) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levoalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication if tolerated by the patient). Documented reversibility or positive airway hyperresponsiveness to methacholine within 12 months prior to Screening V1 is considered acceptable	Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puff inhalations with metered-dose inhaler [MDI]) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levoalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication if tolerated by the patient). Note: A maximum of 3 visits to meet the qualifying criterion of reversibility may be made during the screening period and prior to the patient's randomization. Note: Documented reversibility or positive airway hyperresponsiveness to methacholine within 12 months prior to Screening V1 is considered acceptable	**Change:** Reversibility attempts definition during the screening period **Reason for change:** To clarify that for patients that will have an additional and last attempt of reversibility testing (for eligibility) at the Baseline Visit 2 before patient's randomization using the IRT (Interactive Response Technology), the post-bronchodilator FEV1 will come from the result of this reversibility test.	Clarification of an inclusion criterion
Section 11.1 Determination of sample size	Randomization will be stratified by ICS dose (medium-dose versus high-dose) and eosinophil count (<300 cells/µL versus ≥300 cells/µL) at Screening, and by region (Latin America: Argentina,	Randomization will be stratified by ICS dose (medium-dose versus high-dose) and eosinophil count (<300 cells/µL versus ≥300 cells/µL) at Screening, and by	**Change:** To include Russia and Ukraine among Eastern Europe region	Inclusion of new

Sections	Initial wording	Amended or new wording	Reason/Justification for change	Reasons for substantial amendment
	Brazil, Colombia, Chile and Mexico; Eastern Europe: Poland, Hungary, Romania, Lithuania and Turkey; Western Countries: Australia, Canada, Italy, South Africa, Spain, and USA). The final definition of region may be updated in the SAP, if additional countries are included in the study. If during the study, additional countries are included, necessary changes will be made to the randomization algorithm. These changes will be documented in the SAP.	region (Latin America: Argentina, Brazil, Colombia, Chile and Mexico; Eastern Europe: Poland, Hungary, Romania, Lithuania, Turkey, Russia and Ukraine; Western Countries: Australia, Canada, Italy, South Africa, Spain, and USA). The final definition of region may be updated in the SAP, if additional countries are included in the study. If during the study, additional countries are included, necessary changes will be made to the randomization algorithm. These changes will be documented in the SAP.	**Reason for change**: to add new countries in the study	countries/sites in the trial
Sections: Flowchart and 9.3.1.2 Humoral Immune Response to Vaccines	Scheduled blood sample collection for pre- and post-vaccine antibody titers (ie, for IgG response assessment), 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 48 (ie, Visit 5 and Visit 26, respectively).	Scheduled blood sample collection for pre- and post-vaccine antibody titers (ie, for IgG response assessment), 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).	**Change:** To change last possible date for post vaccination sample collection from W48 to W50 **Reason for change:** To correct last possible date for post vaccination sample collection to W50 considering it can be drawn up to 6 weeks after vaccination	Change in schedule of samples
Section 8.8.1 Prohibited Concomitant Medication and 8.8.2 Permitted Concomitant Medication	**8.8.1 Prohibited Concomitant Medication** The following concomitant treatments are not permitted during the Screening Period or during the Randomized Treatment Period: • SCS for diagnoses other than severe exacerbation of asthma and/or high-potency topical, ocular, or intra-nasal steroids within 30 days before Screening Visit 1, during the Screening Period, and/or during the Randomized Treatment Phase of this study.	**8.8.1 Prohibited Concomitant Medication** The following concomitant treatments are not permitted during the Screening Period or during the Randomized Treatment Period: • SCS for diagnoses other than severe exacerbation of asthma and/or high-potency topical steroids within 30 days before Screening Visit 1, during the Screening Period, and/or during the Randomized Treatment Phase of this study. Intra-articular	**Change:** Clarification on topical corticosteroids to be avoided during study **Reason for change:** To clarify that potent dermatological topical corticosteroids are to be avoided during the study. This definition of potency does not apply to ocular and intranasal corticosteroids	Clarification of prohibited concomitant medication

Sections	Initial wording	Amended or new wording	Reason/Justification for change	Reasons for substantial amendment
	Intra-articular steroids are not allowed to be used in the above mentioned period. 8.8.2 Permitted Concomitant Medication • Antihistamines • Topical, ocular or intranasal corticosteroids (except for high-potency)	steroids are not allowed to be used in the above mentioned period. 8.8.2 Permitted Concomitant Medication • Dermatological, ocular or intranasal corticosteroids (except for high-potency dermatological corticosteroids)		
Section 10.1.1 Screening Period (Week -5 to Week 0, maximum 35 days prior Day 0)	Patients that fail the initial screening for exclusion criteria, eg, concomitant medications, may be re-screened for study eligibility one additional time (as described in *Section* 8.4). For patients re-screened a new ICF/IAF, as applicable, must be signed by patient/parent(s)/caregiver(s)/legal guardian(s), and a new patient number will be allocated. All of the Visit 1 procedures must be repeated (refer to *Section* 8.4 for further instructions related to re-screening) unless a prior assessment is performed within the time frame permitted prior to study entry.	Patients that fail the initial screening for exclusion criteria, eg, concomitant medications, may be re-screened for study eligibility one additional time (as described in *Section* 8.4). For patients re-screened a new ICF/IAF, as applicable, must be signed by patient/parent(s)/caregiver(s)/legal guardian(s), and a new patient number will be allocated. All of the Visit 1 procedures must be repeated (refer to *Section* 8.4 for further instructions related to re-screening).	**Change:** removal of using prior assessments for re-screening **Reasons for change:** Values from previous assessments cannot be re-used for the purpose of re-screening	Change in re-screening
Section 9.2.2.2.1 Electronic Diary/PEF meter		Baseline reliever use will be the mean number of reliever use recorded for the 7 days prior to the first dose of investigational product. Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day1. There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available for both measurements.	**Reason for change:** To include reliever medication baseline definition	

Sections	Initial wording	Amended or new wording	Reason/Justification for change	Reasons for substantial amendment
Appendix K **General Guidance for the follow up of laboratory abnormalities by Sanofi**	•Neutrophils value Neutrophils <1500/mm^3 or according to ethnic group	•Neutrophils value Neutrophils <1000/mm^3 according to ethnic group	**Change:** neutrophils value for Sanofi follow up of abnormalities **Reasons for change:** To adjust the neutrophil count defining neutropenia in the study population age group (pediatric trial)	Change of safety monitoring parameter

Amendment protocol 01 dated 10-Mar-2017

- **FeNO results**

In section: 9.4.2.2

Rationale:

- Blinding of FeNO results as described in Section 9.4.2.2 was determined to be operationally not feasible. Therefore, the FeNO value will not be blinded to investigators or site personnel, as well as patient(s)/parent(s)/caregiver(s)/legal guardian(s).

- **Live attenuated vaccines**

In section(s): Sections 7.2.3 and 8.8.1

Rationale:

- In order to clearly define the interval between live (attenuated) vaccines administration and IMP administration and be consistent with other dupilumab trials, an Exclusion Criterion E27 will be added to clarify that live (attenuated) vaccines are not allowed within 4 weeks before the baseline visit. Section 8.8.1 Prohibited Concomitant medication will be rewritten to clarify that live (attenuated) vaccines are allowed in the screening period if taken at least 4 weeks prior to baseline visit.

- **PAQLQ Domains**

In section: 9.2.2.4.2

Rationale:

- The number of domains was incorrectly described as 4, instead of 3.

- **PAQLQ (S)-IA Periodicity**

In section(s): Clinical Trial Summary (Secondary Endpoints Efficacy) and Section 11.4.2

Rationale:

- The periodicity of PAQLQ(S)-IA was incorrectly marked as Weeks 2, 4, 8, 12, 24, 36, 52. Its correct periodicity is at Weeks 12, 24, 36, 52, 64.

- **Inhaled Corticosteroids Doses**

In section: Appendix A

Rationale:

- Medium and high doses of beclometasone dipropionate (CFC and HFA) and budesonide (DPI) are inconsistent with GINA Guidelines 2015. Therefore, the table will be updated with the correct values for medium and high dose of beclometasone dipropionate (CFC and HFA) and budesonide (DPI).

- **PEF meter**

In Section: 9.2.2.2.1

Rationale:

- AM and PM time frames were extended by 2 hours, ie, to end at 11:59 AM and 11:59 PM, respectively.
- Albuterol/salbutamol or levoalbuterol/levosalbutamol reliever medication are the only medications to be withheld for at least 6 hours before PEF measurement, if possible.

- **IMP compliance check**

In section: 10.1.10

Rationale:

- IMP compliance must be verified at these visits. This information is missing in the protocol.

- **Informed Assent Form (IAF) for girls who started menstruating**

In section: 1.2 and 12.2

Rationale:

- Clarified that as soon as the investigator is notified that the first menses of a female patient have occurred (at any time during this study) a separate IAF must be obtained from such female patients at the earliest visit to the site. This information is missing in the protocol.

- **Patient monitoring**

In section: 8.1.4

Rationale:

- To avoid confusion and make it clear that patients should be monitored after home administration of IMP.

- **Country list/Region**

In section: 11.1

Rationale:

- New Zealand is not a part of the study and should be removed.

- **Template**

In section: Appendix K

Rationale:

- Instructions from the protocol template, which should be removed were left in the final version of the protocol in error.

- Added clarification of PK sample blood volume for pediatric study.

- **Vaccination Response**

In section: 10.1.2

Rationale:

- Vaccination information and vaccination plan during the treatment period should be collected for all patients at screening, because the vaccination response is not an optional assessment.

- **Adverse Event of Special Interest**

In section: 10.4.1.3

Rationale:

- An error was noted in the asthma pediatric study EFC14153 study where “suicidal behavior” was noted as AESI. Suicidal behavior was an AESI for atopic dermatitis (AD) trials; however, there was no signal of these events in patients treated with dupilumab. Therefore, suicidal behavior was removed from the AESI.

- **Term ‘Slum areas’**

In section: 10.6.3

Rationale:

- An alternative terminology, "heavily populated informal settlements" will be used for the term ‘slum areas’.

- **Typographical Errors**

In section: 1.1 (Overview of Study Design) schematic picture

Rationale:

- To correct a typographical error in subject number ‘195’ (correct number ‘196’) in the schematic picture of the overall study design in the original final protocol.
- To add footnote about background therapy with inhaled corticosteroids.

In section: 1.2 (Study flowchart) footnote U

Rationale:

- Although correctly found in the study flowchart at Week 6, in footnote ‘U’ it is written that DNA sampling collection is to be performed at Week 0.
- Blood DNA can be collected any time during the protocol, taking into consideration blood collection volume limitation, if any, at the time.

In section: 7.2.3

Rationale:

- Deleted E23 (about previous history of malignancy), because it is a duplicate of E6 (about history of malignancy).
- Clarified E25 Liver injury related criteria
- Corrected E26 Abnormal lab values at Screening

In addition, other minor changes were implemented.

Signature Page for VV-CLIN-0528583 v6.0
efc14153-16-1-1-amended-protocol03

Approve & eSign	[redacted]

Approve & eSign	[redacted]