NCT number: NCT02414854

AMENDED CLINICAL TRIAL PROTOCOL 04

COMPOUND: dupilumab (SAR231893)

A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma

STUDY NUMBER: EFC13579

VERSION DATE / STATUS: 26-May-2017 / Approved

CLINICAL STUDY DIRECTOR: [redacted]

STUDY NAME: LIBERTY ASTHMA QUEST

Protocol Amendment 08 – Global	Version number 1: (electronic 2.0)	Date: 26-May-2017
Protocol Amendment 07 - Global	Version number 1: (electronic 1.0)	Date: 9-Aug-2016
Amended Clinical Trial Protocol 03-France	Version number 1: (electronic 1.0)	Date: 15-Dec-2015
Protocol Amendment 06-France	Version number 1: (electronic 1.0)	Date: 15-Dec-2015
Amended Clinical Trial Protocol 05-Germany	Version number 1: (electronic 4.0)	Date:09-Nov-2015
Amended Clinical Trial Protocol 04-Germany	Version number 1: (electronic 2.0)	Date: 23-Oct-2015
Protocol Amendment05-Local for Germany	Version number 1: (electronic 1.0)	Date: 23-Oct-2015
Amended Clinical Trial Protocol 2	Version number 1: (electronic 1.0)	Date: 21-Sep-2015
Protocol Amendment 4 - Global	Version number: 1 (electronic 1.0)	Date: 21-Sep-2015
Amended Clinical Trial Protocol 1-Germany	Version number: 1 (electronic 1.0)	Date: 28-Jul-2015
Protocol Amendment 3 - Local for Germany	Version number: 1 (electronic 1.0)	Date: 28-Jul-2015
Amended Clinical Trial Protocol 1	Version number: 1 (electronic 1.0)	Date: 21-May-2015
Protocol Amendment 2 - Global	Version number: 1 (electronic 1.0)	Date: 21-May-2015
Amended Clinical Trial Protocol 1 - Japan	Version number: 1 (electronic 1.0)	Date: 10-Apr-2015
Protocol Amendment 1 - Local for Japan	Version number: 1 (electronic 1.0)	Date: 10-Apr-2015
Clinical Trial Protocol	Version number: 1 (electronic 1.0)	Date : 25-Feb-2015

Version Number: 1	EudraCT :	**2014-004940-36**
	IND Number:	**105379**
	WHO universal trial number:	U1111-1163-1293
Date: 26-May-2017	Total number of pages:	161

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		

CLINICAL TRIAL SUMMARY

COMPOUND: Dupilumab	**STUDY No: EFC13579**
TITLE	A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary Objective** • To evaluate the efficacy of dupilumab in patients with persistent asthma **Secondary Objective(s)** • To evaluate the safety and tolerability of dupilumab • To evaluate the effect of dupilumab on improving patient reported outcomes (PROs) including health related quality of life (HRQoL) • To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies (ADA) **Exploratory Objective(s)** • To explore the association of biomarkers with treatment response • To explore the association of genetic profiles with treatment response • To explore the association of vaccine response with treatment
STUDY DESIGN	**General design** Multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma. **Periods** The clinical trial consists of 3 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): 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 not participating in the long term extension study <u>Screening Period</u> Prior to screening, patients must be on a stable background therapy of a medium to high dose of inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], methylxanthines, etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are

	excluded). The Screening Period will be 4±1 weeks (21-35 days) in duration. <u>Randomized Treatment Period</u> Patients will be randomized to either dupilumab or matching placebo administered SC for a treatment duration of 52 weeks. During the Randomized Treatment Period, patients will continue the stable dose(s) of controller medication used during the Screening Period. Patients who permanently discontinue the study medication will be asked and encouraged to return to the site for study visits and participate in assessments according to the visit schedule until the end of the study with a +/-5 day window (See study flowchart for patients after permanent treatment discontinuation in Section 1.3). At the time of permanent treatment discontinuation, patients will perform early treatment discontinuation visit (ETD) with all the assessments defined for Visit 18 (EOT). Under exceptional circumstances when a patient cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs, concomitant medication and asthma exacerbation events should be collected. In addition, patients who discontinue early from treatment or patients who choose not to participate in the open label extension (OLE) study 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/or clinical presentation at the time of discontinuation or at the time of last study visit. <u>Post-treatment Period</u> After completing the treatment period, patients will be evaluated for 12 weeks in the post-treatment period. During this follow-up period, patients could 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. During the post-treatment period, patients will continue to collect diary information that can be used to determine asthma control. Eligible patients who complete the treatment period will be offered the opportunity to participate in the OLE study with dupilumab. Patients subsequently enrolled in the OLE study will not participate in the post-treatment period of this trial.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** Adults and adolescent patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines and the following criteria: A) Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1. - Note for Japan: for subjects aged 18 years and older, ICS must be on ≥200 mcg of fluticasone propionate twice daily or equivalent; for subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent.

	- Patients requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1. B) Pre-bronchodilator forced expiratory volume (FEV_1) ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents at Visits 1 and 2, prior to randomization. C) Asthma Control Questionnaire 5-question version (ACQ-5) score ≥1.5 at Visits 1 and 2, prior to randomization. D) Reversibility of at least 12% and 200 mL in FEV_1 after the administration of 200 to 400 mcg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) before randomization. E) Must have experienced, within 1 year prior to Visit 1, any of the following events: - Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once. - Hospitalization or emergency medical care visit for worsening asthma. **Exclusion Criteria:** • Patients <12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (For those countries where local regulations permit enrollment of adults only, subject recruitment will be restricted to those who are ≥18 years of age). • Weight is less than 30 kilograms. • Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc) which may impair lung function. • A subject who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to the Screening Visit up to and including the Baseline Visit). • Evidence of lung disease(s) other than asthma, either clinical evidence or imaging [eg, Chest X-ray, computed tomography (CT), Magnetic resonance imaging(MRI)] within 12 months of Visit 1 as per local standard of care. • Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis. • Current smoker or cessation of smoking within 6 months prior to Visit 1. • Previous smoker with a smoking history >10 pack-years. • Comorbid disease that might interfere with the evaluation of IMP.

Total expected number of patients	At least 1638 patients will be randomized to dupilumab or placebo with at least 690 patients with a baseline blood eosinophil count $\geqslant 300$ cells/L (0.3 giga/L) and with approximately 84 adolescent patients. In addition, recruitment for patients on medium dose of ICS will be stopped at approximately 819 to ensure at least 50% patients are on high dose of ICS. In addition, in order to have additional patients treated with drug manufactured using the intended commercial process, approximately 220 patients will be randomized in addition to the originally planned sample size (1638).
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	Dupilumab (SAR231893/REGN668) or matching placebo Dupilumab: 150 mg/mL in a prefilled syringe to deliver 300 mg in 2 mL; 175 mg/mL in pre-filled syringe to deliver 200 mg in 1.14 mL Placebo: Prefilled syringe to deliver 2 mL and 1.14 mL respectively.
Route(s) of administration	Subcutaneous
Dose regimen	Randomized 2:2:1:1 to the following regimens: • dupilumab 300 mg SC q2w with a 600 mg loading dose • dupilumab 200 mg SC q2w with a 400 mg loading dose • placebo SC q2w in pre-filled syringe to deliver 2 mL with placebo loading dose • placebo SC q2w in pre-filled syringe to deliver 1.14 mL with placebo loading dose
Noninvestigational medicinal product(s) (if applicable) **Formulation**	**Inhaled corticosteroid in combination with other controllers** Screening Period Prior to and during the Screening Period, patients must be on a stable dose of medium to high dose ICS in combination with a second controller medication (eg, LABA, LTRA, methylxanthines, etc). Patients needing a third controller are elligible for this study. Randomized Treatment Period During this period, patients will continue taking their controller medication(s) at stable dose used during screening period. Post-treatment Period Upon completing the Randomized Treatment Period, patients not continuing with the OLE study, will continue treatment with the controller medication regimen and dose used during the randomized period, which could be adjusted based on the medical judgement of the Investigator of the patients' asthma control status. **Reliever Medication** Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol metered dose inhaler (MDI) as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

Route(s) of administration	Oral inhalation, nebulizer: ICS, ICS combination, albuterol/salbutamol or levalbuterol/levosalbutamol; for other background controllers: according to label
Dose regimen	ICS: medium to high dose Albuterol/salbutamol or levalbuterol/levosalbutamol: as needed Other background controllers: referring to label
ENDPOINT(S)	**Primary Endpoints:** • Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 **Key Secondary Endpoint:** • Percent change from baseline in pre-bronchodilator FEV_1 at week 12 **Secondary Endpoint(s):** **Efficacy** • Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 giga/L • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L • Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L • Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients on high dose of ICS • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients on high dose of ICS • Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients on high dose of ICS • Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 giga/L • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L • Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L • Absolute change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 8, 24, 36, and 52 • Percent change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 8, 24, 36, and 52 • Change from baseline in other lung function measurements (% predicted FEV_1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%, post-bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52

	• Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period • Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period • Time to first severe exacerbation event • Time to first loss of asthma control event (LOAC) • Change from baseline in Asthma Control Questionnaire (ACQ)-5 score and ACQ-7 score at Weeks 2, 4, 8, 12, 24, 36, and 52 • Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in: - Morning/evening asthma symptom score and nocturnal awakenings (e-diary) - Use of daily puffs of rescue medication • Change from baseline in Health care resource utilization at Weeks 12, 24, 36, and 52 • Change from baseline in PROs at Week 12, 24, 36, and 52: - Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years) - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) - Hospital Anxiety and Depression Scale (HADS) - 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis and/or chronic rhinosinusitis - Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis **Safety and tolerability** • Adverse events (AEs) • Vital signs • Physical examination • Electrocardiogram (ECG) • Clinical laboratory tests **Systemic drug concentration and Anti-drug antibodies** • Serum functional dupilumab concentrations • ADA **Biomarkers and others** • Fractional exhaled nitric oxide (FENO) levels • Blood eosinophils • Total and antigen-specific IgE • Thymus and activation-regulated chemokine (TARC) • Periostin • Eosinophil cationic protein (ECP) • Eotaxin-3 • (Optional). Blood samples for exploratory genetic analysis of DNA and RNA to assess the relationship of DNA variants and/or RNA expression with asthma and response to dupilumab treatment. • (Optional). Blood samples for exploratory analysis of vaccine IgG response during treatment.

	Criteria for asthma exacerbations during the study Two types of asthma exacerbation events are defined: • 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 • A LOAC event during the study is defined as any of the following: - ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared with baseline) on 2 consecutive days; - ≥20% decrease in pre-bronchodilator FEV1 compared with baseline; - Increase in ICS dose ≥4 times than the dose at Visit 2; - A decrease in AM or PM PEF of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1(randomization). - 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, 21-35 days) • Randomized Treatment Period (52 weeks) • Post-treatment Period (12 weeks)
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size calculation of this study was based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary endpoints: annualized rate of severe exacerbations during the 52-week treatment period and absolute change from baseline in FEV_1 at Week 12. Assuming the number of severe exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline eosinophil count ≥300 cells/μL (0.3 giga/L), approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for the subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at Week 12 for the overall population, and 690 patients will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline eosinophil count ≥300 cells/□(0.3 giga/L). The overall study recruitment will continue until at least 1638 patients in total and 690 patients with eosinophils ≥300 cells/μL (0.3 giga/L) are randomized. The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized into the study. In addition, approximately 84

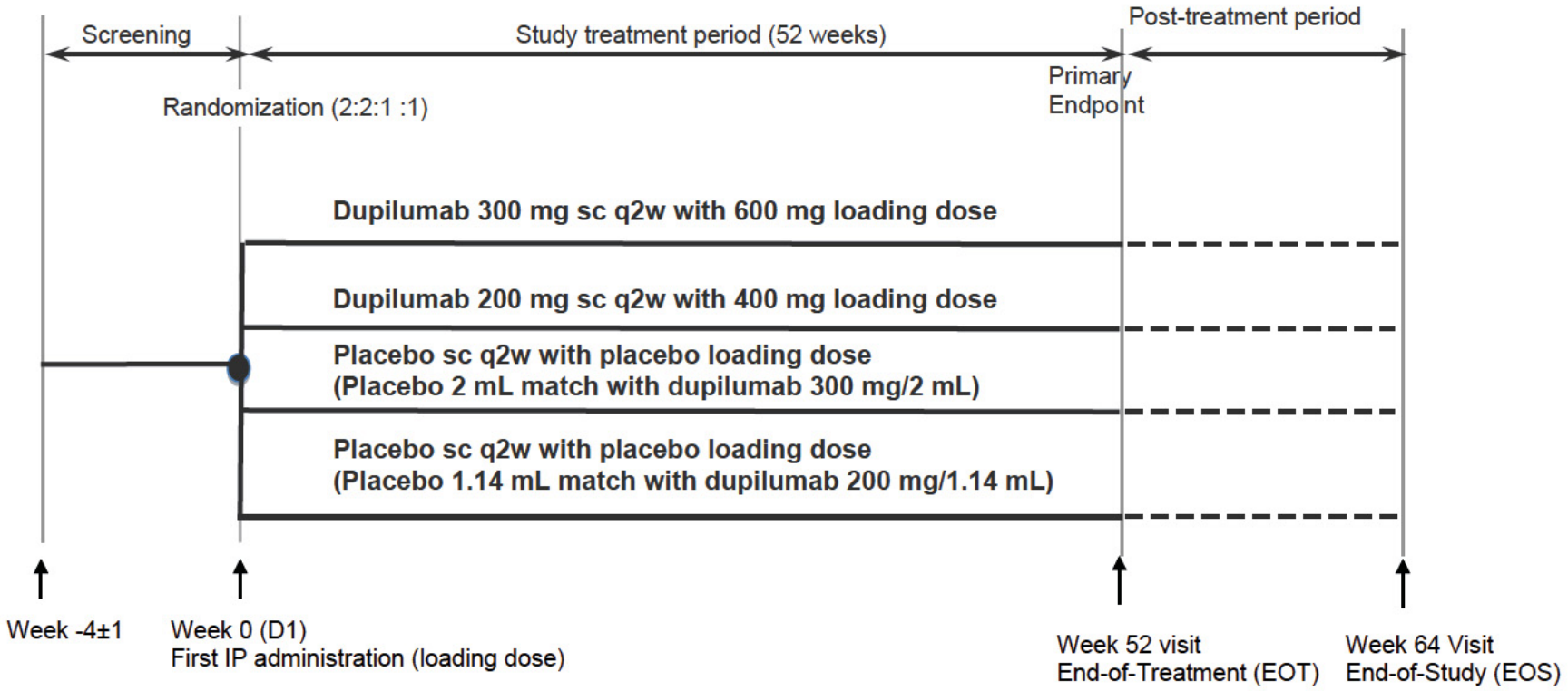
	adolescent patients will be randomized. Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w, dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL. Randomization will be stratified by age (<18 years, ≥18 years) at screening, central eosinophil count (<300 cells/µL, ≥300 cells/µL) at screening, ICS dose level (medium, high) and country. In addition, in order to have additional patients treated with drug manufactured using the intended commercial process, approximately 220 patients will be randomized in addition to the originally planned sample size (1638). **Analysis populations:** The primary analysis population for the efficacy endpoints will be intent-to-treat (ITT) population defined as all randomized patients. The efficacy analyses will be conducted according to the treatment to which they are randomized. The secondary analysis population for the efficacy endpoints will be HEos (High Eosinophils) ITT defined as all randomized patients with baseline eosinophil count ≥300 cells/µL 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. The safety analyses will be conducted according to the treatment that patients actually received. **Analysis of the primary endpoints:** The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed treatment duration will be the offset variable. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the additional off-treatment severe exacerbation events up to Week 52 will be included in the analysis and the last contact date at Week 52 will be used to calculate the offset variable. The change from baseline in FEV_1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline FEV_1 values up to Week 12 as response variables, and factors for treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV_1 value, and baseline-by-visit interaction as covariates. 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 in FEV_1 at Week 12 will be derived from the mixed-effect model. For patients discontinuing the treatment before Week 12,

	off study-treatment FEV_1 values measured up to Week 12 will be included in the primary analysis. Subgroup analyses will be performed for the two primary endpoints using the same methods by baseline eosinophil levels (≥300 cells /µL vs. <300 cells /µL and ≥150 cells /µL vs. <150 cells /µL). **Multiplicity considerations** To strongly control the type-I error rate for the primary family (2 primary endpoints and 2 doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300mg q2w versus placebo, 2) absolute change from baseline in FEV_1 at Week 12 for 300mg q2w versus placebo, 3) annualized severe exacerbation rate for 200mg q2w versus placebo and 4) absolute change from baseline in FEV_1 at Week 12 for 200mg q2w versus placebo. If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significant level. The first four tests will be 1) % change from baseline in FEV_1 at Week 12 for 300 mg q2w versus placebo 2) absolute change from baseline in AQLQ global score at Week 12 for 300 mg q2w versus placebo 3) % change from baseline in FEV_1 at Week 12 for 200 mg q2w versus placebo, 4) absolute change from baseline in AQLQ global score at Week 12 for 200 mg q2w versus placebo. The remaining list of secondary endpoints to be tested in the hierarchical order will be specified in SAP. The overall familywise error rate will be strongly controlled at a 2-sided 5% level for all tested endpoints across dose groups. **Handling of missing data** Sensitivity analyses excluding the additional off-treatment measurements will be performed to corroborate the primary analyses. The reason and pattern of missing data will be carefully examined and tipping point analyses and other sensitivity analyses may be performed. **Analysis of other secondary endpoints** The annualized rate of exacerbation events, including severe exacerbation events resulting in hospitalization or emergency room visit and LOAC events, will be analyzed using the same way as for severe exacerbation events. Time to severe exacerbation will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of asthma events prior to the study as covariates. The Kaplan-Meier method will be used to derive the proportion of patients with an asthma exacerbation event at Weeks 12, 24, 36, and 52, specific to each treatment group. The change from baseline for continuous endpoints will be analyzed using a MMRM in the same fashion as for the endpoint of FEV_1. Sex and height will be included as covariates only in the models for spirometry parameters. . The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics. **Interim Analysis** There is no interim analysis planned for this study.

	Planned database lock date: The database lock is planned based on the time when approximately 1638 patients (originally planned sample size) 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)	The total duration of the study (per patient) is expected to be up to 69 weeks: • 4±1 weeks for screening • 52 weeks of treatment • 12 weeks of post-treatment follow-up

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Background therapy: medium to high dose ICS plus second controller (LABA, LTRA, etc)
Third controller is allowed

1.2 STUDY FLOW CHART FOR PATIENTS WHO WILL COMPLETE TREATMENT

	SCR[a]	Randomized Treatment Period																											Post-treatment Period		
		RND[c]																										EOT[b]			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	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
Informed Consent	x																														
Incl/Excl Criteria	x	x																													
Patient Demography	x																														
Medical/Surgical History	x																														
Reversibility[d]	x																														
Post-bronchodilator FEV_1[d]		x	x	x		x		x						x						x								x			x
Spirometry[e]	x	x[f]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
CXR or MRI (if none within previous 12 months, MRI is only for Germany) [g]	x																									X					
Prior & concomitant medication[h]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
Physical Examination	x													x														x			x
Randomization		x																													
Call IVRS/IWRS	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x			x
Investigational Product Administration[i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	X	x				
Dispense or download e-diary/PEF meter[j]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x

	SCR[a]	Randomized Treatment Period																												Post-treatment Period		
		RND[c]																										EOT[b]			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	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
Dispense/Review Home Dosing Diary								x		x		x		x		x		x		x		x		x		X		x			
ACQ-7[k]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
AQLQ(S)		x						x						x						x								x			X
Health Care Resource Utilisation		x		x		x		x		x		x		x		x		x		x		x		x		X		x	x	x	x
Exhaled NO[l]	x	x	x	x				x		x		x		x						x						X		x	x	x	x
Vital Signs[m]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
ECG	x		x	x				x						x						x								x			x
Pregnancy test[n]	x	x		x		x		x		x		x		x		x		x		x		x		x		X		x			x
Clinical lab testing[o]	x	x		x		x		x		x		x		x		x		x		x		x		x		X		x	x	x	x
Hepatitis B viral load[p]		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
Urinalysis[q]	x							x						x						x								x			x
Serum immunoglobulins (IgG, IgM, IgA)	X							x						x						x								x			x
Systemic drug concentration (functional dupilumab) [r]		x	x	x		x		x		x				x						x								x	x	x	x
Anti-drug antibodies[r]		x						x						x														x			x
Biomarker set [s]		x						x						x						x								x			
Periostin		x		x				x																				x			
Antigen-specific IgE		x						x						x														x			

	SCR[a]	Randomized Treatment Period																											Post-treatment Period		
		RND[c]																										EOT[b]			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	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
Archival serum[t]		X						X						X						X								X			
Pharmacogenetics: blood samples for DNA and RNA[u]		X																													
EQ-5D-5L		X						X						X						X								X			X
HADS[v]		X						X						X						X								X			X
SNOT-22[w]		X						X						X						X								X			X
RQLQ(S) +12[x]		X						X						X						X								X			X
Vaccine IgG	X[y]				*z*	*z*	*z*	*z*		*z*		*z*		*z*		*z*		*z*		*z*		*z*		*z*		*z*		*z*			

a The Screening Period is 4±1 weeks (21-35 days) in duration to collect baseline data on asthma control and assure eligibility criteria.

b Patients who permanently discontinue treatment early will continue the remaining visits per protocol schedule with a +/-5 day window until end of study (See section 1.3). At the time of permanent treatment discontinuation the patients will perform early treatment discontinuation (ETD) visit with all the assessments defined for Visit 18 (EOT).

c Randomization Visit (Visit 2) is defined as Day 1. Visit windows for subsequent visits are +/- 3 days.

d Three attempts may be made during the Screening Period until the Baseline visit to meet the qualifying criteria for reversibility. During the treatment period, post-bronchodilator FEV_1 will be determined at the designated treatment visits. If other attempt for reversibility test was performed at Baseline visit, then the post-bronchodilator FEV_1 will come from the result of this reversibility test.

e Forced expiratory volume (FEV_1), 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of Long-Acting Muscarinic Antagonist (LAMA) for at least 24 hrs. This will be verified before performing the measurements.

f Treatment Period stability limits will be established for FEV_1 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.

g Perform chest X-ray or MRI (MRI is for Germany only) if no chest imaging (X-ray, CT, MRI) available within the previous 12 months as per local standard of care or if there is local requirement.. At Visit 17, it is only applicable for patients who plan to participate in the OLE study and available chest imaging is over 12 months from entry into the OLE study.

Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis.

h Prior to screening, patients must be on a stable background therapy of a medium to high dose of inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], methylxanthine , etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1 (patients requiring systemic steroids as controller medication or biologics are excluded).

i Every 2 week (q2w) investigational product administrations must be separated by at least 11 days. The randomized Treatment Period visits occur every 2 weeks up to Week 12 and then every 4 weeks, alternating with q2w home administration of IMP (patient, caregiver, or health care professional) without study visit up to the end of treatment period at Week 52. After Week 12, if the patient or Investigator decides not to administer IMP at home, the IMP injections can be performed at the site by way of unscheduled visits. Patients will be monitored at the study site for a minimum of 30 minutes after injections in the first 12 weeks.

j 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, 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.

k ACQ-7 is completed in the patient's electronic diary during clinic visits. ACQ-7 (Asthma Control Questionnaire 7-question version) score will be used to follow up evaluations in all patients. ACQ-5 (the first 5 items of the ACQ-7) score is used for eligibility evaluation at visit 1 and visit 2 for all patients and follow up evaluations in all patients.

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

m Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit. Height (cm) will be measured only at screening (Visit 1) for adults, and be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit for adolescents. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

n Serum pregnancy test at Visit 1 and urine dipstick pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 2 prior to randomization.

o Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with five-part differential count, 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. Clinical laboratory testing at Visit 1 and Visit 17 (only applicable for patients who plan to participate in the OLE study) include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab) including HBcAb IgM and total, hepatitis C virus antibodies (HCV Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). In case of results showing HBs Ag (negative), and HBc Ab total (positive), a hepatitis B virus DNA (HBV DNA) testing must be performed prior to randomization to determine eligibility. In case of results showing HCV Ab (positive), a HCV virus RNA (HCV RNA) testing must be performed prior to randomization to determine eligibility. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer). The blood sample for serum chemistry must be taken with the patient in fasting state which means no intake of any food or drink except for water for at least 8 hours (if the visit can only be done at a different time of the day and the patient is not fasting, then he/she should be advised to eat light food and the site should document that serum chemistry was not obtained under fasting conditions).

p This is only applicable for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at the screening visit.

q Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood protein, nitrite, leukocyte esterase, urobilinogen and bilirubin. If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis will be performed by central laboratory.

r Systemic drug concentration and ADA samples are to be collected prior to dosing. In the event of any SAE or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe injection site reaction lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes.. See Section 9.3.1 for more details.

s Biomarker set includes Eotaxin-3, eosinophil cationic protein (ECP), total IgE, Thymus and Activation-Regulated Chemokine (TARC). Blood eosinophil count will be measured as part of hematology test. Exhaled nitric oxide assessment is described separately in the flowchart.

t Archival serum in case needed for retrospective safety follow-up or additional biomarker analysis, and this is optional and a separate written consent form must be signed.

u This is optional and a separate written consent form must be signed before sampling. For those who consented, the sample should be drawn at Week 0, before IMP administration.

v HADS includes Hospital Anxiety and Depression Scale- Anxiety subscale (HADS-A) and Hospital Anxiety and Depression Scale- Depression subscale.

w For those patients with bilateral nasal polyposis and/or chronic rhinosinusitis.

x For those patients with comorbid allergic rhinitis.

y Patients will be encouraged to provide vaccination plans for the following vaccines, tetanus (alone or combined), any injectable influenza, any pneumococcal and any meningococcal, which are in line with the patients age and local medical practice (live attenuated vaccines are excluded) during the study. Subjects planning to receive any of the above listed vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccination.

z Optional collection of blood for assay of vaccine IgG in serum for each vaccine of interest: the first sample should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Pre-vaccine blood sample collection will not take place until patient is on treatment of IMP for at least 6 weeks. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits.

1.3 STUDY FLOW CHART FOR PATIENTS AFTER EARLY PERMANENT TREATMENT DISCONTINUATION

VISIT	ETD[a]																										EOS
Week[a]		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	64
Visit[a]		4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	21
Post-bronchodilator FEV_1	x	x		x		x						x						x								x	x
Spirometry[b]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x
Prior & concomitant medication	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x
Physical Examination	x											x														x	
Call IVRS/IWRS	x																										x
Dispense or download e-diary/PEF meter[c]	x																										
Dispense/Review Home Dosing Diary	x																										
ACQ-7[d]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x
AQLQ(S)	x					x						x						x								x	X
Health Care Resource Utilization	x																										
Exhaled NO[e]	x																										
Vital Signs[f]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x
ECG	x	x				x						x						x								x	
Urine Pregnancy dipstick test	x																										
Clinical lab testing[g]	x					x						x						x								X	
Hepatitis B viral load[h]	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

VISIT	ETD[a]																										EOS
Week[a]		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	64
Visit[a]		4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	21
Urinalysis[i]	x																										
Serum immunoglobulins (IgG, IgM, IgA)	x																										
Systemic drug concentration (functional dupilumab) [j]	x	x		x		x		x				x						x								x	x
Anti-drug antibodies[j]	x					x						x														x	x
Biomarker set [k]	x																										
Periostin	x																										
Antigen-specific IgE	x																										
Archival serum[l]	x																										
EQ-5D-5L	x																										
HADS[m]	x																										
SNOT-22[n]	x																										
RQLQ(S) +12[o]	x																										
Vaccine IgG [p]	x																										

a Patients who permanently discontinue treatment early will continue the remaining visits per protocol schedule with a +/-5 day window until end of study. At the time of permanent treatment discontinuation, patients will perform early treatment discontinuation (ETD) visit with all the assessments defined for Visit 18 (EOT). Visit 19 (Week 56) and Visit 20 (Week 60) will not be performed.

b Forced expiratory volume (FEV_1), 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of Long-Acting Muscarinic Antagonist (LAMA) for at least 24 hrs. This will be verified before performing the measurements.

c 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, 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.

d ACQ-7 is completed in the patient's electronic diary during clinic visits. ACQ-7 (Asthma Control Questionnaire 7-question version) score will be used to follow up evaluations in all patients. ACQ-5 (the first 5 items of the ACQ-7) score is used for eligibility evaluation at visit 1 and visit 2 for all patients and follow up evaluations in all patients.

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

f Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), body weight (kg) and height (cm). Height (cm) will be measured only for adolescents. Vital signs will be measured in the sitting position using the same arm at each visit.

g Only hematology and serum chemistry tests will be done, see Section 9.2.2.5 for details.

h This is only applicable for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at the screening visit.

i Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood protein, nitrite, leukocyte esterase, urobilinogen and bilirubin. If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis will be performed by central laboratory.

j In the event of any SAE, or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe injection site reaction lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes. See Section 9.3.1 for more details.

k Biomarker set includes Eotaxin-3, eosinophil cationic protein (ECP), total IgE, Thymus and Activation-Regulated Chemokine (TARC). Blood eosinophil count will be measured as part of hematology test. Exhaled nitric oxide assessment is described separately in the flowchart.

l Archival serum in case needed for retrospective safety follow-up or additional biomarker analysis, and this is optional and a separate written consent form must be signed.

m HADS includes Hospital Anxiety and Depression Scale- Anxiety subscale (HADS-A) and Hospital Anxiety and Depression Scale- Depression subscale.

n For those patients with bilateral nasal polyposis and/or chronic rhinosinusitis.

o For those patients with comorbid allergic rhinitis.

p It indicates the sampling of post vaccination and if it is within 6 weeks after vaccination as applicable.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

ACQ-5	Asthma Control Questionnaire 5-question version
ACQ-7	Asthma Control Questionnaire 7-question version
AD	Atopic dermatitis
ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANA	Anti-nuclear Antibodies
ATS	American Thoracic Society
AQLQ(S)	Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥ 12 years)
BCG	Bacillus Calmette-Guérin
CDMS	Clinical Data Management System
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRFs	Case Report Forms
CPK	Creatine phosphokinase
CSR	Clinical Study Report
CV	Curriculum Vitae
CV%	Coefficient of Variation
CYP	Cytochrome P450
CT	Computed Tomography
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DRF	Discrepancy Resolution Form
ECG	Electrocardiography
ECP	Eosinophil Cationic Protein
e-CRF	Electronic Case Report Form
ERS	European Respiratory Society
EQ-5D-5L	EuroQoL Working Group Health Status Measure 5 Dimensions, 5 Levels

EOS	End-of-Study
EOT	End-of-Treatment
ETD	Early Treatment Discontinuation
FEF	Forced expiratory flow
FENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GSO	Global Safety Officer
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale- Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale- Depression subscale
HBc Ab	Hepatitis B Core Antibody
HBs Ab	Hepatitis B Surface Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C Virus Antibody
HEos	High Eosinophils
HLGT	High-Level Group Term
HLT	High Level Term
HIV	Human Immunodeficiency Virus
HRQoL	Health related quality of life
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
ID	De-identification Code
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL-4	Interleukin 4
IL-4Rα	Interleukin 4 Receptor Alpha Subunit
IL-13	Interleukin 13

IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board / Institutional Ethics Committee
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
IUD	Intrauterine Device
IUS	Intrauterine System
ITT	Intent-To-Treat
K-M	Kaplan-Meier
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LFT	Liver Function Test
LOAC	Loss Of Asthma Control
LTRA	Leukotriene receptor antagonist
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
MID	Minimal Important Difference
MMR	Measles, Mumps, Rubella
MMRM	Mixed-effect Model with Repeated Measures
MMRV	Measles, Mumps, Rubella, Varicella
MRI	Magnetic Resonance Imaging
NIMP	Noninvestigational Medicinal Product
NRS	Numerical Rating Scale
OLE	Open label extension
PCSA	Potentially Clinically Significant Abnormalities
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
Pop	Population
PROs	Patient-Reported Outcomes
PT	Preferred Term
RNA	Ribonucleic Acid
RQLQ(S)+12	Standardized Rhinoconjunctivitis Quality Of Life Questionnaire , ages 12+
SAP	Statistical Analysis Plan

SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SC	Subcutaneously
SD	Standard Deviation
SNOT-22	Sinonasal Outcomes Test 22-item scale
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARC	Thymus and Activation-Regulated Chemokine
TEAE	Treatment-Emergent Adverse Event
Th2	Type 2 T-helper cell
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

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. However, it is estimated that 5% to 10% of asthma patients have symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs. These patients account for up to 50% of the total health cost through hospital admissions, use of emergency services, and unscheduled physician visits (1).

The long term adverse effects of systemic and inhaled corticosteroids on bone metabolism, adrenal function, and growth in children lead to attempts to minimize the amount of corticosteroid usage. Additionally, the consequences of unresponsiveness to therapy or lack of compliance with therapy is loss of asthma control and ultimately, asthma exacerbation. 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 (2). Recent therapeutic approaches in asthma have been focused on trying to control the type 2 T-helper cell (Th2) response. Up-regulation of interleukin-4 (IL-4) and interleukin-13 (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 receptors Type I and Type II, as well as the IL-13 receptor. 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.

4.2 RATIONALE

This is a phase 3, randomized, placebo-controlled efficacy and safety study to be conducted in patients with persistent asthma while on a medium to high dose ICS, in combination with a second controller. This study is designed to investigate the efficacy and safety profile of dupilumab over one year in a patients with asthma who are in need for an additional of another treatment added to their current 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 confirm the efficacy of dupilumab on multiple asthma domains including lung function, prevention of severe exacerbations and

symptom control. The effect on lung function and symptom control will be evaluated over short term and long terms.

4.2.1 Population rationale

In this study, dupilumab will be added-on to an inhaled corticosteroid in combination with one or two other controller medications in patients with persistent asthma. The population is comprised of patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines (3) and entry criteria described in Section 7. As described above, in addition to suffering the symptoms associated with a lack of asthma control, such patients utilize a disproportionate level of health care services, may suffer the long term adverse effects of systemic and inhaled corticosteroids, and ultimately, are at increased risk of a severe asthma exacerbation.

4.2.2 Design rationale

This study is a randomized, double blind, placebo-controlled, parallel group study. The clinical trial consists of three periods, using an add-on therapy approach to inhaled corticosteroid in combination with one or two other controller medicines:

- Screening Period (4±1 weeks)
- Randomized Treatment Period (52 weeks)
- Post-treatment Period (12 weeks)

This study has two arms of placebo with different volume, which is to match the different dose regimens of dupilumab 300 mg q2w and 200 mg q2w respectively. Both the patient and investigator will be blinded to assigned active drug or placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

4.2.3 Endpoint rationale

There are two primary endpoints for this study. One primary endpoint is the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period, as this is one of the most clinically relevant endpoints to evaluate an asthma controller medication. The treatment period of 52 weeks is sufficient for assessing this type of event and avoiding the potential impact of seasonality. The other primary endpoint is the absolute change from baseline in pre-bronchodilator FEV_1 at Week 12, as this is a well-accepted parameter to determine the effect of a drug on lung function. Safety endpoints are typical for investigational drugs at the current stage of clinical development.

Other endpoints including systemic drug concentration/ADA and biomarkers of drug action have been used previously to evaluate the exposure/effect relationship of dupilumab in asthma patients.

4.2.4 Rationale for dose and regimen selection

The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg every 2 weeks (q2w) or 200 mg q2w. Patients randomized to 300 mg q2w will get an initial loading dose of 600 mg on Day 1 while patients randomized to 200 mg q2w will get an initial loading dose of 400 mg on Day 1, and q2w dosing will commence 2 weeks after the loading dose. The administration of the loading dose of dupilumab will allow systemic concentrations to reach target saturation, potentially reducing the time to onset of clinical effect.

Proof of concept has been established in the ACT11457 study at 300 mg weekly. One hundred and four patients with persistent, moderate-to-severe asthma and a blood eosinophil count of at least 300 cells per microliter or a sputum eosinophil level of at least 3%, partially controlled or uncontrolled by medium-to-high doses of ICS plus LABA (fluticasone/salmeterol, budesonide/formoterol, or mometasone/formoterol) were randomized to the study. The study showed significant efficacy in a population of mostly severe asthmatics with poor asthma control and decreased lung function with mostly high doses of ICS in combination with a LABA.

In the dose ranging study (DRI12544 study), 776 patients with asthma uncontrolled by medium-to-high dose ICS plus LABA were randomized in the study. Four dose regimens (300 mg q2w with 600mg loading dose, 200 mg q2w with 400mg loading dose, 300mg q4w with 600 mg loading dose and 200mg q4w with 400 mg loading dose) were tested in the study. The results showed that 300 mg q2w and 200 mg q2w treatment with dupilumab provided a significant improvement on FEV_1 at week 12 and a statistically significant reduction in the annualized rate of severe exacerbations when compared to placebo. Both dose regimens provided comparable efficacy on most of the efficacy endpoints regardless of the eosinophil count at baseline. Both doses were safe and well tolerated with a profile comparable to that seen with placebo except for an increased number of injection site reactions. To further characterize the optimal regimen for patients, both regimens will be assessed in the current trial.

The Pop PK model predictions demonstrated that exposure in adolescents at the highest proposed adult Phase 3 dose (300 mg q2w) is not expected to exceed the observed adult exposure at the dupilumab dose regimen of 300 mg once weekly, which was observed to be generally well tolerated in adults. Therefore, adolescent dosing at 300 mg q2w or 200 mg q2w regimen is expected to yield dupilumab exposure that is expected to result in efficacious exposures and unlikely to be associated with a heightened safety risk in this age population.

Dupilumab has been safe and well-tolerated in all clinical trials completed to date in healthy volunteers and patients with Atopic dermatitis (AD) or asthma who were dosed for up to 16 weeks with a maximum dose of 300 mg administered every week. The phase 3 study will utilize less frequent dosing. No important identified risks have been established during the dupilumab clinical program. A low discontinuation rate has been observed across the completed clinical trials in dupilumab treated patients. The reported rate of suspected unexpected serious adverse reaction (SUSAR) has also been low. In addition, no imbalance in the frequency of TEAEs between patients treated with dupilumab versus placebo has been observed, with the exception of injection site reactions, nasopharyngitis and headache. In summary, the safety data observed so far in completed and currently ongoing studies in AD and asthma patients (at the same or even higher

doses than that proposed for this study) have demonstrated a positive benefit-risk profile for dupilumab in comparison to placebo.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate the efficacy of dupilumab in patients with persistent asthma

5.2 SECONDARY

To evaluate the safety and tolerability of dupilumab

To evaluate the effect of dupilumab on improving PROs including HRQoL

To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies

5.3 EXPLORATORY

To explore the association of biomarkers with treatment response

To explore the association of genetic profiles with treatment response

To explore the association of vaccine response with treatment

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This study is a multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma with a medium to high dose of ICS in combination with a second controller medication (a third controller is allowed).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

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): 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 not participating in the long term extension study.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur at last patient who has completed 52 weeks treatment and elect to enter the long term extension study or at the end of a 12-week safety follow-up period for those patients who complete the treatment and elect not to enter extension study as well as for those who permanently discontinue medication and continue for all the remaining visits.

6.3 INTERIM ANALYSIS

Not applicable.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

A data monitoring committee (DMC) is independent from sponsor 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 primary responsibilities of the DMC are to review and evaluate the safety data during the course

of the trial and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

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

6.4.2 Executive advisory committee

An executive advisory committee is commissioned for the dupilumab clinical development program. The executive advisory committee is made up of 5-7 key academic clinicians, with selection criteria including a key opinion leader in strategic regions including Japan, US, Europe and Latin America. These clinicians have been selected based on their publications, experience in conducting clinical asthma/nasal polyps studies, and their ability to both challenge and provide input during the protocol review process, speak to heath authority/ethics committee for operational issues/challenges/unexpected safety issues. Furthermore, they can speak with credibility to feasibility issues and impact the recruitment. These clinicians will provide invaluable insight and direction to ensure a successful clinical program.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Adults and adolescent patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines and the following criteria:

A) Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1.

- Note for Japan: for subjects aged 18 years and older, ICS must be on ≥200 mcg of fluticasone propionate twice daily or equivalent; for subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent.
- Patients requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1.

B) Pre-bronchodilator forced expiratory volume (FEV_1) ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents at Visits 1 and 2, prior to randomization.

C) Asthma Control Questionnaire 5-question version (ACQ-5) score ≥1.5 at Visits 1 and 2, prior to randomization.

D) Reversibility of at least 12% and 200 mL in FEV_1 after the administration of 200 to 400 mcg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) before randomization.

E) Must have experienced, within 1 year prior to Visit 1, any of the following events:

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

I 02. Signed written informed consent.

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 4 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Patients <12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (For those countries where local regulations permit enrollment of adults only, subject recruitment will be restricted to those who are ≥18 years of age).

E 02. Weight is less than 30 kilograms.

E 03. Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc) which may impair lung function.

E 04. A subject who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to the Screening Visit up to and including the Baseline Visit).

E 05. Evidence of lung disease(s) other than asthma, either clinical evidence or imaging (Chest X-ray, CT, MRI) within 12 months of Visit 1 or at the screening visit, as per local standard of care.

Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis.

E 06. A subject who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to Visit 1 or during the screening period.

E 07. Current smoker or cessation of smoking within 6 months prior to Visit 1.

E 08. Previous smoker with a smoking history >10 pack-years.

E 09. Comorbid disease that might interfere with the evaluation of IMP.

E 10. Known or suspected alcohol and/or drug abuse.

E 11. Inability to follow the procedures of the study (eg, due to language problems or psychological disorders).

E 12. Patients requiring non-selective beta-1 adrenergic receptor blockers for any reason, or initiation or change in dose of a selective beta-1 adrenergic receptor blocker within 1 month prior to Visit 1 or plan to initiate or change in dose of a selective beta-1 adrenergic receptor blocker during the screening period or the randomized treatment period.

E 13. 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, primary biliary

cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.) as well as other diseases within 2 months or 5 half-lives prior to Visit 1, whichever is longer.

E 14. 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 15. Patients on or initiation of Bronchial thermoplasty within 3 years prior to Visit 1 or plan to begin therapy during the Screening Period or the Randomized Treatment Period.

E 16. 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 17. Patients receiving medications or therapy that are prohibited as concomitant medications (See Section 8.8).

E 18. Patients who have previously been treated in any clinical trial of dupilumab.

E 19. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative 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 20. Non-compliance with use of the mandatory background therapy, eg, ICS/LABA combination, 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 21. A subject with a 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, uncontrolled hypertension, bronchiectasis. Active tuberculosis or non-tuberculous mycobacterial infection, 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 would be performed on a country by country basis according to local guidelines if required by regulatory authorities 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 22. Pregnant or breast-feeding women.

E 23. Women of childbearing potential (pre-menopausal female biologically capable of becoming pregnant) who:

- Do not have a confirmed negative serum beta-hCG test at Visit 1.
- Who are not protected by one of the following acceptable forms of effective contraception during the study:
  - Established use of oral, injected, implanted or inserted hormonal contraceptive.
  - Intrauterine device (IUD) with copper or intrauterine system (IUS) with progestogen
  - Barrier contraceptive (condom, diaphragm or cervical/vault caps) used with spermicide (foam, gel, film, cream or suppository), if allowed by local regulation
  - Female sterilization (eg tubal occlusion, hysterectomy or bilateral salpingectomy),
  - Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients the study, the vasectomized male partner should be the sole partner for that patient
  - True abstinence in keeping with the preferred and usual lifestyle and if allowed by local regulation; periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) is not an acceptable method of contraception
  - Postmenopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception

E 24. Deleted.

E 25. Diagnosed 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 26. History of HIV infection or positive HIV serology at Visit 1.

E 27. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, penumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per investigator's judgment.

E 28. 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 29. Live attenuated vaccinations within 4 weeks prior to Visit 1 or planned live attenuated vaccinations during the study; see Appendix A for list of prohibited live attenuated vaccines.

E 30. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.) 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 31. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

E 32. Patients with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

E 33. Patients with any of the following result at screening:

- Positive (or indeterminate) HBs Ag or,
- Positive IgM HBc Ab or
- Positive total HBc Ab confirmed by positive HBV DNA or
- Positive HCV Ab confirmed by positive HCV RNA

E 34. Liver injury related criteria:

- Clinically significant/active hepatobiliary disease or
- Alanine Aminotransferase (ALT) >3 Upper Limit of Normal (ULN)

E 35. Abnormal lab values at Screening:

- Creatine phosphokinase (CPK) >10 ULN or
- Platelets <100,000 cells/mm3 or
- Eosinophils >1500 cells/mm3

7.2.4 Additional exclusion criteria during or at the end of screening

E 36. Patient who has withdrawn consent before enrollment/randomization.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Dupilumab

Sterile dupilumab of various concentrations will be provided in 150 mg/mL in glass pre-filled syringe to deliver 300 mg in 2 mL and 175 mg/mL in glass pre-filled syringe to deliver 200 mg in 1.14 mL.

8.1.2 Placebo

Sterile placebo for dupilumab will be provided in identically matched glass pre-filled syringe to deliver 2 mL or 1.14 mL, which will match dupilumab 300 mg (2 mL) and 200 mg (1.14 mL) respectively.

8.1.3 Preparation of investigational product

Dupilumab or matching placebo in glass pre-filled syringes will be dispensed to the patients.

8.1.4 Dosing schedule

Two injections of IMP will be administered on Day 1 at Visit 2 as a loading dose. Subsequently one injection of IMP will be given every 14 ± 3 days (q2w). The doses of investigational product must be separated by ≥11 days to avoid an overdose.

The Investigator or delegate will train the patient (or caregiver(s)) how to prepare and inject IMP at Visit 2 and will inject the first of the 2 injections. The patient (or caregiver(s)) will perform the second injection under the supervision of the Investigator or delegate. This training must be documented in the patient's study file. At subsequent study visits, patients are trained to self-inject IMP, and the patients are allowed to self-inject IMP at home after 6 injections at investigational site, counting from Visit 3.

Patients should be instructed to avoid missing any doses of medication during the study. Any patient who misses one dose should be reminded to be diligent, in order to avoid further missing doses thereafter. In case of missed dose(s) no loading dose of 2 injections will be administered when restarting the treatment, whatever the number of missed doses. The patients should continue on their scheduled IMP treatment and visit, even if more than 2 consecutive doses are missed.

When the patient has a study visit, the IMP will be administered following clinic procedures and blood collection. Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.

For doses not given at the study site, diaries will be provided to record information related to the injections. The diary will be kept as source data in the patient's study file.

If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site.

If the study visit is not performed at the site as scheduled, the dose will be administered by the patient and/or their caregiver/health care professional, or arrangements must be made for an unscheduled visit at the site to administer the IMP. When IMP is administered at home, the patients must be advised by the site staff to self-monitor for potential signs and symptoms that may suggest a hypersensitivity reaction for at least 30 minutes after administration.

If the patient, or caregiver(s) do not develop the comfort to inject the investigational drug at home, or the Investigator determines that patient (or caregiver) injection at home is not appropriate, injections can be performed at the site by way of unscheduled visits.

Subcutaneous 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. Injection in the upper arms could be done only by a trained person (Parent/ caregiver trained by Investigator or Delegate) or health care professional but not the patient themselves. This instruction pertains to the day that the loading dose is injected as well as the administration of q2w injections. For each injection, the anatomic site of administration will be recorded in the electronic case report form (e-CRF) and, as applicable, the home diary.

Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the patient. Patients will complete a dosing diary to document compliance with self-injection (or caregiver) injection of IMP.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Inhaled corticosteroid in combination with one or two other controllers

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor.

The recognized asthma controllers for the study will include the following 5 classes: ICS, LABA, LAMA, Anti-leukotrienes and methylxanthines. Please refer to Appendix O for a list of commonly used asthma controller medication.

8.2.1.1 Screening period

Prior to screening, patients must be on a stable background therapy of a medium to high dose of ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects

aged 18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller medication (Refer to Appendix O on the recognized controller medication class) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are excluded). If patients take two different ICS, the total daily dose of ICS should be calculated to evaluate the eligibility criteria on daily dose of ICS which will be still considered as one controller. Please refer to medium and high dose of ICS in Appendix B. The minimum daily dose of flucticasone propionate is 500 mcg (≥250 mcg of fluticasone propionate twice daily), which is equal to the upper limit of medium daily dose for fluticasone propionate as instructed in Appendix B. For ICS other than fluticasone propionate, please refer to the table in Appendix B which indicates the upper limit of the medium daily dose for each ICS which is equivalent to 500 mcg/day of fluticasone propionate.

If the Study Investigator based on his/her medical judgment, decides to optimize use of asthma medications prior to Visit 1 irrespective of potential participation in the study, note that changes in ongoing asthma medications must occur at least 1 month prior to Visit 1. The introduction of new controller medications must occur at least 3 months prior to Visit 1 with a stable dose for at least 1 month prior to Visit 1.

8.2.1.2 Randomized treatment period

During this period, patients will continue to take their controller medication(s) used during the screening period. The dose and regimen should not be changed. Only a transient increase in dose of ICS in addition to other rescue medication will be allowed to treat acute symptoms of asthma as per investigator's guidance. This will be recorded in the eDiary.

8.2.1.3 Post-treatment period

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

8.2.2 Reliever medication

The reliever medication will not be dispensed or supplied by the sponsor.

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

The description of the criterion for qualifying an asthma exacerbation event based on nebulizer using, will use the nebulizer-to-puff conversion factor for application to loss of asthma control (LOAC) definition.

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

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
2.5	4
5.0	8
7.5	12
10	16
*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs	

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

Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
1.25	4
2.5	8
3.75	12
5	16
*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs	

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

Criterion used to specify an asthma exacerbation event in eCRF based on nebulizer use:

After conversion of nebulizer-to-puff, in 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, tick the "Qualifying criteria box" on the asthma exacerbation event.

All other reliever medications rather than albuterol/salbutamol or levalbuterol/levosalbutamol should be avoided.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched 2 mL or 1.14 mL pre-filled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab / placebo) or 1.14 mL (dupilumab / placebo) glass pre-filled syringes will be prepared such that the treatments (dupilumab and its matching placebo according to its dose) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Both the patient and investigator will be blinded to assigned active drug or placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

Study patients, 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 adverse event (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.

Subject 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, anti-drug antibodies 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.

Patients, investigators and site personnel will not have access to assay results for immunoglobulins (IgG, IgG subclasses, IgA and IgM) after the first administration of study medication because these values have the potential for unblinding. Furthermore, neither patients, investigators nor site personnel will have access to eotaxin-3, antigen-specific IgE, total IgE, Eosinophil Cationic Protein (ECP), TARC or periostin while the study is ongoing, as the related data are not essential for patient care and have the potential for unblinding.

The Data Monitoring Committee will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled [redacted] 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. 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.

Patients who meet exclusion criteria may be re-screened once during the open screening period of the study; a different patient identification will be issued. Re-screening is not permitted if the patient fails to meet inclusion criteria. There is no requirement for a waiting period between the screen-failure date and the re-screening date. The IVRS/IWRS report will flag re-screened patients. Patients that are re-screened must sign a new consent form and all Visit 1 procedures must be repeated.

The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) that will be available 24 hours a day.

Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w, dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL. Randomization will be stratified by age (<18 years, ≥18 years) at screening, central eosinophil count (<300 cells/μL, ≥300 cells/μL) at screening, ICS dose level (medium, high) and country.

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 and placebo will be supplied as one glass pre-filled syringe packed in a patient kit box. Both glass pre-filled syringe and box will be labeled.

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

Control of investigational product 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 IMPs 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 IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, to 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

Measures taken to ensure and document treatment compliance and IMP accountability include:

- Proper recording of treatment kit number as required on appropriate e-CRF page for accounting purposes;
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned.
  - The completed patient injection diary (returned to the site at each visit), returned treatment kit boxes and any unused prefilled syringes will be used for drug accountability purposes.
- The Investigator or designee tracks treatment accountability/compliance, either by diary, or by counting the number of used treatment kits and fills in the appropriate page of the patient treatment log.

The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log form.

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 patients and be returned to sites for destroy. The Investigator will not destroy any unused IMP 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. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

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

8.8 CONCOMITANT MEDICATION

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

8.8.1 Prohibited Concomitant Medication

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

- Systemic steroids (systemic steroids can only be used to treat an asthma exacerbation, and are not allowed to be used for other conditions from 1 month or at least 5 half-lives prior to Visit 1, whichever is longer, or during the screening period or the randomized treatment period. Intra-articular steroids are considered as systemic steroids and are not allowed to be used in the above mentioned period.)
- Anti-immunoglobulin E (IgE) therapy (eg, omalizumab, is not allowed to be used from 130 days prior to Visit 1, or during the screening period or the randomized treatment period)
- Biologic therapy (Biologic therapy is not allowed to be used from 2 months or at least 5 half-lives prior to Visit 1, whichever is longer, or during the screening period or the randomized treatment period).
- Systemic immunosuppressant (immunosuppressants are not allowed to be used from 2 months or at least 5 half-lives prior to Visit 1, whichever is longer, or during the screening period or the randomized treatment period)
- Allergen immunotherapy (except if initiated more than 3 months prior to Visit 1 and dose stabled 1 month prior to Visit 1)
- Bronchial thermoplasty

- Intravenous immunoglobulin (IVIG) therapy
- Live Attenuated Vaccines: refer to Appendix A
- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with dose stabled 1 month prior to Visit 1)
- Asthma relievers other than salbutamol/albuterol or levosalbutamol/levalbuterol: their use is not recommended during the study period. In case of use in exceptional circumstances (eg, prescribed by a physician not participating in the study), their use will be documented in the patient's file and reported in the eCRF.
- Other investigational drugs

8.8.2 Permitted concomitant medication

- Antihistamines are permitted as concomitant medication.
- Topical, ocular or intranasal corticosteroids are permitted during the study.

CYP substrates:

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized. However, interleukin-4 (IL-4) was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (4), (5). Human peripheral blood mononuclear cells (PBMC) incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (6). 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 (4), (5), (6). Some examples of CYP450 substrates with narrow therapeutic index are provided in Appendix C.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary endpoints

There are two primary endpoints for this study, the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period and the absolute change from baseline in pre-bronchodilator FEV_1 at week 12.

9.1.1.1 *Asthma exacerbation events*

Two types of asthma exacerbation events are defined:

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

A loss of asthma control (LOAC) event during the study is defined as any of the following:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days;
- ≥20% decrease in pre-bronchodilator FEV1 compared with baseline;
- 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 PEF 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 (ex, infections including viral and bacterial, allergen exposure, exercise and others) of the exacerbation events will be collected in eCRF**.**

9.2 SECONDARY ENDPOINT(S)

Key secondary Endpoints:

- Percent change from baseline in pre-bronchodilator FEV_1 at Week 12

9.2.1 Efficacy endpoints

- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 giga/L
- Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients on high dose of ICS
- Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients on high dose of ICS
- Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients on high dose of ICS
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 8, 24, 36, and 52
- Percent change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 8, 24, 36, and 52
- Change from baseline in other lung function measurements (% predicted FEV_1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF]25-75%, post-bronchodilator FEV_1 at Weeks 2, 4, 8, 12, 24, 36, and 52
- Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period
- Time to first severe exacerbation event
- Time to first loss of asthma control event (LOAC)
- Change from baseline in Asthma Control Questionnaire (ACQ)-5 score and ACQ-7 score at Weeks 2, 4, 8, 12, 24, 36, and 52
- Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in:
  - Morning/evening asthma symptom score and nocturnal awakenings (e-diary)
  - Use of daily puffs of rescue medication
- Change from baseline in Health care resource utilization at Weeks 12, 24, 36, and 52.
- Change from baseline in PROs at Week 12, 24, 36, and 52:

- Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)
- European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L)
- Hospital Anxiety and Depression Scale (HADS)
- 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis and/or chronic rhinosinusitis
- Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis

9.2.1.1 Disease-specific efficacy measures

9.2.1.1.1 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 (7). For pre-bronchodilator measured parameters, including FEV_1, 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.

For post-bronchodilator FEV_1, the measure should follow the steps as that at screening test for reversibility validation.

At all visits, spirometry 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. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements.

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

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

The largest FEV_1 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 FEV_1 (best test).

Automated best efforts, which combine FEV_1 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.

Spirometry will be performed centrally and all recordings will be centrally read by independent experts. Further details on spirometry will be available in a separate operational manual provided to the sites.

9.2.1.1.2 Reversibility/Post-bronchodilator FEV_1

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Subjects will receive two to up to four puffs of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed MDI. Alternatively and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. Reversibility, which is defined as an increase in absolute FEV_1 of 12% over the baseline value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of bronchodilator administration. If the subject does not meet the reversibility at Visit 1, up to 3 assessments can be performed at any time during the screening period until the Baseline Visit (Visit 2).Whenever the reversibility was repeated, the pre-bronchodilator FEV_1 should again meet the inclusion criteria of ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents.

For post-bronchodilator FEV_1, the measure should follow the steps as that at screening test for reversibility validation. If other attempt for reversibility test was performed at Baseline visit, then the post-bronchodilator FEV_1 will come from the result of this reversibility test.

9.2.1.1.3 ACQ (Asthma Control Questionnaire)

The ACQ 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.

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

The ACQ-7 has 7 questions- the first 5 items assess 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, plus 6. short-acting bronchodilator use and 7. FEV_1 (pre-bronchodilator use, %

and % predicted use). Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment) (see Appendix D).

Clinic staff scores the FEV_1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

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

Measurement properties such as reliability and ability to detect change have been documented in the literature (8).

The ACQ-7 questionnaire will be put into eDiary to be completed by all patients regardless of adults or adolescents. Patients should complete ACQ-7 before spirometry test.

9.2.1.1.3.2 ACQ-5 (Asthma Control Questionnaire, 5-question version)

The ACQ-5 is short version of ACQ-7, and ACQ-5 score is the mean of the first 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Measurement properties such as reliability and ability to detect change have been documented in the literature (9).

9.2.1.2 Disease-specific, daily efficacy assessments

9.2.1.2.1 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
- Record oral steroids use for exacerbation event

At screening (Visit 1), patients will be issued an electronic diary/PEF. Patients 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 patients. In addition, the investigator will instruct the patients 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 12:00 PM) prior to taking any albuterol/salbutamol or levalbuterol/levosalbutamol
- PM PEF performed in the evening (between 5:30 PM and 12 AM) prior to taking any albuterol/salbutamol or levalbuterol/levosalbutamol
- Patients should try to withhold albuterol/salbutamol or levalbuterol/levosalbutamol for at least 6 hours prior to measuring their PEF
- 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.

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

9.2.1.2.2 Asthma Symptom Score Numerical Rating Scale (NRS)

Patients 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. An MCID of 0.35 is being used (10) (see Appendix E).

9.2.1.2.3 Use of rescue medicine

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the patients 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.

9.2.1.3 Health care resource utilization

A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, school days' loss, etc) will be administered at Visit 2 and every 4 weeks thereafter.

9.2.1.4 Patient-reported outcomes

Patients should complete the following PROs before spirometry test.

9.2.1.4.1 Asthma Quality of Life Questionnaire (AQLQ (S)

The AQLQ (S) was designed as a self-administered patient reported outcome to measure the functional impairments that are most troublesome to patients as a result of their asthma (see Appendix F). The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items)
- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental Stimuli (4 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 AQLQ(S) is 0.5 (11).

9.2.1.4.2 22-item Sinonasal Outcome Test in those patients comorbid with bilateral nasal polyposis and/or chronic rhinosinusitis

SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on health-related quality of life (see Appendix G). The SNOT-22 has 22 items, 5 domains and a global score. The 5 domains include Nasal (range 0-30) with MID of -2.5, Ear (range 0-15) with MID of -1.25, Sleep (0-20) with MID of -1.67, General and Practical (0-30) with MID of -2.50, and Emotional (0-15) with MID of -1.25. The range of the global score is 0-110 and an MID (the smallest difference between clinical trial arms mean change from baseline [point estimates] that will be interpreted as important) of 8.9 (12). Lower scores indicate less impact and the recall period is past 2 weeks.

9.2.1.4.3 Hospital Anxiety and Depression Scale

The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales (see Appendix H). The instrument is comprised of 14 items: 7 related to anxiety and 7 to depression. Each item on the questionnaire is scored from 0-3; one can score between 0 and 21 for either anxiety or depression.

The HADS was found to perform well in assessing anxiety disorders and depression in both somatic and psychiatric cases and (not only in hospital practice for which it was first designed) in primary care patients and the general population (13). The MID for the HADS-A (anxiety) has been reported to be in the range of 0.41 (anxious and depressed subjects in active treatment controlled studies) to 1.32 (COPD patients), in the range of 0.50 (anxious and depressed subjects in active treatment controlled studies) to 1.40 (COPD patients) for HADS-D (depression) and approximately 1.5 (COPD patients) for the HADS Total score (14, 15)

Alternatively, a significant improvement in treatment versus placebo group was defined as the % of subjects who moved from a defined category of moderate to severe depression or anxiety (≥8 to not having the disease (<8) (16). Using this methodology Stelara (Ustekinumab) was able to make the claim in summary of product characteristics that "HADS was significantly improved in the treatment group compared with placebo" (17).

9.2.1.4.4 EQ-5D-5L

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (18). EQ-5D is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages – the EQ-5D descriptive system and the EQ VAS (see Appendix I). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. The MCID for the EQ-5D in asthma patients has been reported to be in the range of .001 to 0.074 (19, 20)

9.2.1.4.5 Standardized Rhinoconjunctivitis Quality Of Life Questionnaire (RQLQ(S))+12 in those patients with comorbid allergic rhinitis.

RQLQ(S)+12 (see Appendix J) is a self-administered questionnaire with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 12 to 75 years of age, as a result of perennial or seasonal allergic rhinitis. There are 28 items on the RQLQ(S) in 7 domains: 1. Activities (3 items), 2. Sleep (3 items), 3. Non-Hay Fever Symptoms (7 items), 4. Practical Problems (3 items), 5. Nasal Symptoms (4 items), 5. Eye Symptoms (4 items) and 7. Emotional (4 items). The RQLQ(S)+12 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. An MID of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (21).

9.2.2 Safety and tolerability endpoints

The same safety assessments will be applied across all arms. Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI), will be collected at every visit. The Investigator will ask the patient how he/she has felt since the last study visit. The study specific and general safety criteria are detailed in Section 10.4.1. 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.

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.
- 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.

9.2.2.1 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 Visit or till the rollover to the extension study, except for:

- SAEs
- AEs that are ongoing at database lock.

Adverse events, adverse events with special interest (AESI) and serious adverse events (SAEs) will be reported as described in Section 10.4.

9.2.2.2 Vital signs

Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), body weight (kg) and height (cm) will be measured. 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 if applicable.

9.2.2.3 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. All deviations from normal will be recorded, including those attributable to the patient's disease.

9.2.2.4 ECG

One recording of a standard 12-lead ECG will be performed centrally. At the post-randomization visits, ECGs will be performed prior to investigational product administration if applicable. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG. All ECG recordings will be centrally read by independent experts. Refer to central ECG reading manual for more details.

9.2.2.5 Clinical laboratory tests

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.

The clinical laboratory parameters that will be measured are:

- Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, 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), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. The blood sample must be taken with the patient in fasting state which means no intake of any food or drink except for water for at least 8 hours (If the visit can only be done at a different time of the day and the patient is not fasting, then he/she should be advised to eat light food and the site should document that serum chemistry was not obtained under fasting conditions).
- Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any assessment 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.

- Serum immunoglobulins: quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and IgA.
- Hepatitis screening: HBs Ag, HBs Ab, HBc Ab including HBcAb IgM and total, HCV Ab. In case of results showing HBs Ag (negative) and HBc Ab total (positive), a HBV DNA testing must be performed prior to randomization to determine eligibility. In case of results showing HCV Ab (positive), a HCV RNA testing must be performed prior to randomization to determine eligibility.
- HIV screening (Anti-HIV-1 and HIV-2 antibodies)
- Anti-nuclear antibody (ANA). Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

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

9.2.2.6 Hepatitis B viral load

Hepatitis B viral load (HBV DNA) must be tested at Visit 1 and Visit 17 (only applicable for patients who plan to participate in the OLE study) in case of results showing HBs Ag (negative), HBs Ab (negative or positive) and HBc Ab total (positive), refer to Section 9.2.2.5 for details.

In Japan or other countries/regions if there is local regulatory requirement, hepatitis B viral load (HBV DNA) will be tested at Visit 2, then every 12 weeks until Visit 14 and at end of treatment visit for patients who are HBs Ag negative and HBs Ab positive at screening.

9.2.2.7 Pregnancy test

A serum pregnancy test (β-human chorionic gonadotrophin) will be performed at screening (Visit 1) in women of childbearing potential, and a urine dipstick pregnancy test will be performed at Visit 2 prior to randomization and other visits. A negative result must be obtained at Visit 1 and 2 prior to randomization.

9.3 OTHER ENDPOINTS

9.3.1 Systemic drug concentration and anti-drug antibodies

9.3.1.1 Sampling time

Serum samples for determination of functional dupilumab and anti-dupilumab antibodies (also known as anti-drug antibodies (ADA)) will be collected as per study flow chart (see Section 1.2 and Section 1.3). 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. Patients who discontinue early from treatment or patients who choose not to participate in the long term extension study 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/or clinical presentation at the time of discontinuation or at the time of last study visit.

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

Pre-existing anti-drug antibodies are defined as:

- An ADA positive response in the assay at baseline with all post treatment ADA results negative, OR
- An ADA positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.

Treatment-emergent anti-drug antibodies are defined as:

- An ADA positive response in the assay post first dose, when baseline results are negative or missing.

Treatment-boosted anti-drug antibodies are defined as:

- An ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Treatment-emergent (TE) ADA responses are further classified as Transient, Persistent or Indeterminate

a) Persistent Response- defined as a treatment-emergent response with two or more consecutive ADA positive sampling time points, separated by more than 12-week period (with no ADA negative samples in between).

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

c) Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

Unused samples collected for drug concentration or ADA analyses may be used for research purpose.

9.3.1.2 Handling procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure of samples used in the determination of functional dupilumab concentration and ADA is provided in Table 1.

Table 1 - Summary of handling procedures for dupilumab

Sample type	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Blood sample volume	5 mL	5 mL
Anticoagulant	None	None
Blood handling procedures	See Operational Manual	See Operational Manual
Serum aliquot split	2 aliquots	2 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

9.3.1.3 Bioanalytic method

Serum PK and ADA samples will be assayed using validated methods as described in Table 2.

Table 2 - Summary of bioanalytical methods for dupilumab and anti-dupilumab antibody

Analyte	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	Electrochemiluminescence
Lower limit of quantification	0.078 mg/L	Not applicable
Site of bioanalysis	Regeneron	Regeneron

ELISA=enzyme-linked immunosorbent assay.

9.3.2 Pharmacodynamics

Several biomarkers related to asthmatic inflammation and Th2 polarization will be assessed for their value in predicting therapeutic response and/or in documenting the time course of drug response. In a prior asthma trial (ACT11457), treatment with dupilumab significantly suppressed systemic levels of serum TARC (CCL17; a ligand of CCR4 receptors that attracts Th2 cells), plasma eotaxin-3 (CCL26; a ligand of CCR3 receptors that attracts eosinophils and lung mast cells), and serum total IgE (a product of immunoglobulin class switching driven by IL-4), as well as reduced the concentrations of fractional exhaled nitric oxide (a marker of airway inflammation). Now added to these are the following serum biomarkers: eosinophil cationic protein (ECP; a stored protein released from activated eosinophils) and periostin, a protein reported to be elevated at baseline in patients responsive to treatment with anti-IL-13 antibodies.

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.

Eotaxin-3, eosinophil cationic protein (ECP), total IgE and Thymus and Activation-Regulated Chemokine (TARC) will all be assayed at the same time points as a biomarker set and as indicated in the study flow chart. Periostin and antigen-specific IgE panels will be collected individually per the study flow chart.

9.3.2.1 Whole blood biomarkers

Blood eosinophil count will be measured as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.

9.3.2.2 Plasma biomarkers

Eotaxin-3 will be measured in heparinized plasma with a validated enzyme immunoassay (Human Eotaxin-3 Quantikine ELISA kit; R&D Systems).

9.3.2.3 Serum biomarkers

Concentrations of eosinophil cationic protein (ECP) will be measured using a quantitative ImmunoCAP assay (Phadia).

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

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

TARC and periostin will be assayed with validated immunoassays.

9.3.2.4 Exhaled nitric oxide

Exhaled nitric oxide will be performed centrally and 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. All exhaled nitric oxide recordings will be centrally read by independent experts. Further details on the procedure for measuring exhaled nitric oxide with NIOX will be provided in a separate instruction manual.

9.3.3 Pharmacogenetics

9.3.3.1 Optional stored DNA and RNA samples

Pharmacogenetic testing is optional and voluntary. A separate written informed consent form must be signed before sampling.

For those patients who signed the optional pharmacogenetic informed consent form, blood samples for exploratory genetic analysis of DNA or RNA will be collected at the study visit as

specified in the study flow chart, and these samples will be stored for up to 15 years after completion of the final report of the main clinical trial or for a shorter time if there is local requirement. Specific procedures for collection, storage and shipping of pharmacogenetic samples will be provided in a lab manual.

DNA or RNA samples may be used to determine a possible relationship between genes and response to treatment with dupilumab, possible adverse reactions to dupilumab, and to study the genetics of asthma. The DNA may be subjected to a genome-wide association study by microarray analysis and/or to whole exome sequencing or whole genome analysis in order to thoroughly explore genetic associations with disease progression or treatment response. The RNA may be subjected to discrete panels of PCR analyses, microarray analyses or RNA sequencing analyses.

The blood DNA sample, and the DNA or RNA that is extracted, will be assigned a second number, a Genetic ID (de-identification code) that is different from the Subject ID. This "double coding" is performed to separate a subject's medical information and DNA data.

The clinical study data (coded by Subject ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

9.3.4 Vaccine response

Patients will be encouraged to provide vaccination plans for the following vaccines, tetanus (alone or combined), any injectable influenza, any pneumococcal and any meningococcal, which are in line with the patients age and local medical practice (live attenuated vaccines are excluded) during the study. Subjects planning to receive any of the above listed vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine: the first should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Pre-vaccine blood sample collection will not take place until patient is on treatment of IMP for at least 6 weeks. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits. The details on the date(s) of vaccination and the specific vaccines that are administered, such as brand and antigenic strains, should be collected (see Appendix L).

9.4 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For subjects who have consented to it, the samples that are archived, unused or left

over after planned testing may be used for additional research purposes (any genetic analysis subject to additional consent per Section 9.3.3). For subjects who have consented to it, archival blood samples will be collected at the visit specified in the study flow chart, 15 mL each, will be collected into a dry, red topped tube (or into smaller tubes of equivalent total volume) kept at room temperature for 30 minutes and then centrifuged at approximately 1500 g for 10 minutes at room temperature. The serum will then be transferred, in equal portions, into 3 storage tubes, which will be immediately capped and frozen in an upright position at -20°C or colder.

These archived serum samples, and any residual or leftover serum, plasma or blood remaining from planned laboratory work, may be used for research purposes related to asthma (eg, exploratory biomarkers of disease or drug effect), additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol. These samples will remain labelled with the same identifiers as the ones used during the study (ie, subject ID, sample ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 14.3 and Section 14.5).

9.5 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

10.1 VISIT SCHEDULE

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

- Screening Period (4±1 weeks; Visit 1)
- Randomized Treatment Period (52 weeks; Visits 2-18)
- Post-treatment Period (12 weeks; Visits 19-21)

The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within the ± 3 day visit window.

All the study visits should be scheduled in the morning, to have the spirometry performed and the patient should be fasting for serum chemistry tests. However, if the visit can only be done at a different time of the day and the patient is not fasting, then he/she should be advised to have a light meal and the site should document that serum chemistry was not obtained under fasting conditions. For spirometry, it should be 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 study visits and participate in assessments according to the visit schedule until the end of the study with a +/-5 day window (See Section 1.3). Under exceptional circumstances when a patient cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs, concomitant medication and asthma exacerbation events should be collected.

Patients who discontinue early from treatment or patients who choose not to participate in the OLE study 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/or clinical presentation at the time of discontinuation or at the time of last study visit.

Reminder: sexually active female patients of reproductive potential are required to practice an effective contraception throughout the participation in the study including a 12-week period after last IMP dose. Sites should counsel these patients, with special attention towards adolescent patients regarding the importance of practicing responsible and effective contraception throughout the participation in the study including a 12-week period after last IMP dose.

Prior to all screening assessments, after discussion of participation in the study, the written consent form (including voluntary participation in pharmacogenetic testing/future use of blood samples/vaccination testing) must be signed and dated.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, 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 (35 days) prior to Day1. These patients do not need to sign a new ICF 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 rescreened for study eligibility 1 additional time. Patients that are re-screened must sign a new consent form and will be allocated a new patient number; all of the Visit 1 procedures must be repeated (refer to Section 8.4 for further instructions related to rescreening) unless a prior assessment is performed within the time frame permitted prior to study entry.

Patients that fail the Screening Visit (Visit 1) or Randomization Visit (Visit 2) because of eDiary /spirometry equipment malfunction, or patient-related / site personnel-related unintentional errors may be rescreened one time after approval is granted by the Sponsor's clinical study director. In every case of rescreen 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.

When approaching the season appropriate for influenza vaccination, patients will be reminded to inform the clinic staff about vaccination plans. Similarly, when approaching the planned date of tetanus (alone or combined), any pneumococcal and any meningococcal vaccination, patients will be reminded about the related pre- and post-vaccination blood sampling for vaccine IgG testing. Those who have not yet signed the separate consent for collection of blood pre-vaccination (eg, those who make mid-study decisions about vaccinations) may do so just prior to blood collection.

It is recommended that assessments/procedures at a site visit are performed in the following order if applicable, and these assessments/procedures should be done prior to IMP administration:

1. Patient-reported outcomes and other questionnaires
2. Procedures:
    a) ECG
    b) FENO
    c) Spirometry
    d) Reversibility/Post-bronchodilator FEV_1
    e) eDiary download
3. Safety and laboratory assessments
4. IMP administration

10.1.1 Visit 1 (Week -4 ± 1, -35 days to -21 days)

Following a discussion of participation in the clinical trial, informed consent must be obtained and documented. These steps precede any study 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, asthma history (including smoking habits), other medical history and surgical history, and prior and concomitant medications
- Interview to collect vaccination information and vaccination plan during the treatment period for patient who agree to participate to the vaccine response assessment.
- Review entry criteria to assess eligibility, with special attention to verify the following:
  - Prescribed treatment dosage meets the pre-protocol definition of medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects aged 18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1. In addition, patients requiring a third controller for their asthma are considered eligible for this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are excluded).
  - Patient has experienced, within 1 year prior to Visit 1: 1) Treatment with ≥1 systemic (oral or parenteral) steroids 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, respiration rate, body temperature, weight (kg), height (cm)]
- Perform physical examination
- Administer ACQ-7
  - Verify 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 FEV_1 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.

  - Pre-bronchodilator Forced expiratory volume (FEV_1) must be ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents.

- Establish reversibility
  - Reversibility must be at least 12% and 200 mL in FEV_1 after 200 mcg to 400 mcg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice.
- Perform 12-lead electrocardiography (ECG)
- Perform chest X-ray or MRI (MRI is for Germany only) if no chest imaging (X-ray, CT, MRI) available within the previous 12 months as per local standard of care or if there is local requirement.
- Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis.
- Obtain (fasting if morning visit) blood samples for screening clinical laboratory determinations:
  - Hematology (see Section 9.2.2.5 for details)
  - Serum chemistry (see Section 9.2.2.5 for details)
- Obtain blood samples for hepatitis screen (HBs Ag, HBs Ab, HBc Ab including HBcAb IgM and total, and HCV Ab). In case of results showing HBs Ag (negative) and HBc Ab total (positive), a HBV DNA testing must be performed prior to randomization to determine eligibility. In case of results showing HCV Ab (positive), a HCV RNA testing must be performed prior to randomization to determine eligibility.
- Obtain blood sample for HIV screen (Anti-HIV-1 and HIV-2 antibodies)
- Obtain blood sample for ANA test. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).
- Obtain blood sample for serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA)
- Obtain serum β-HCG pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick) If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Dispense electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit within 21 to 35 days (Visit 2, Week 0) and request patient to come at approximately the same time of this visit (fasting if morning visit).

10.1.2 Visit 2 (Week 0, Day1)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Review entry criteria and reconfirm eligibility based on review of Inclusion/Exclusion Criteria.
- Administer ACQ-7 and all other scales (AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales)). Verify ACQ-5 score is ≥ 1.5.
- Compliance with use of the mandatory background therapy, ICS in combination with one or two other controller product as used just prior to screening, as defined as:
  - $\geq$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 $\geq$1 hour.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Perform spirometry

Entry criteria at Visit 2 include the requirement of a specific FEV_1 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.

- Pre-bronchodilator Forced expiratory volume (FEV_1) must be ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents.
- Post-bronchodilator FEV_1 should be determined
- Treatment Period stability limits will be established for FEV_1 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 if entry criteria are met, and receive the first assignment for 2 treatment kit numbers.
  - Note: Please screen-fail the patient if entry criteria are not met.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - Clinical lab testing: hematology/biochemistry (refer to Section 9.2.2.5)
  - Hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.
  - Systemic drug concentration and ADA (refer to Section 9.3.1)
  - Biomarker set, Periostin and Antigen-specific IgE (refer to Section 9.3.2)
  - Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer Section 9.4).
  - For those patients who have signed a specific pharmacogenetic informed consent form, collect blood samples for DNA and RNA sampling (prior to administration of investigational product during the Randomized Treatment Period), please refer to Section 9.3.3.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Dispense and administer IMP
  - For those patients willing to perform self-injection: The Investigator or delegate will train the patient (or caregiver) regarding preparation and injection of IMP at Visit 2 and will inject the first of the 2 injections. The patient (or caregiver) will perform the second injection under the supervision of the Investigator or delegate. Document the training for IMP self-injection in the patient's study file.
  - Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 2 ± 3 days) at approximately the same time of this visit.

10.1.3 Visit 3 (Week 2)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined
- Perform 12-lead electrocardiography (ECG)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following test:
  - Systemic drug concentration.
- Download electronic diary/PEF meter and remind patient 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 patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection under the supervision of the Investigator or delegate.

- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- 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 (fasting if morning visit).

10.1.4 Visit 4 (Week 4)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined
- Perform 12-lead electrocardiography (ECG)
- Administer health care resource utilization questionnaire
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:

  - Clinical laboratories, systemic drug concentration and Periostin (refer to Section 9.3.2).
- 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.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit two weeks later (Week 6 ± 3 days) at approximately the same time of this visit.

10.1.5 Visit 5 (Week 6)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for the following test:

- Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)

- 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.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- 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 (fasting if morning visit).

10.1.6 Visit 6 (Week 8)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.

  - Post-bronchodilator FEV_1 should be determined
- Administer health care resource utilization questionnaire
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - Clinical laboratories and systemic drug concentration
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
- 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.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 10 ± 3 days) at approximately the same time of this visit.

10.1.7 Visit 7 (Week 10)

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

- Administer ACQ-7
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for the following tests:
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
- 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.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- 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 (fasting if morning visit).

10.1.8 Visit 8 (Week 12)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick) If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - Clinical laboratories,
  - Serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),
  - Systemic drug concentration,
  - Anti-drug antibodies,
  - Biomarker set, Periostin and Antigen-specific IgE (refer to Section 9.3.2)
  - Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to Section 9.4).

  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
  - Hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who were HBs Ag negative and HBs Ab positive at screening.
- 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.
  - For patients (or caregivers) willing to self-administer IMP:
    - Provide instructions on preparation, self-injection and dose. Allow the patient (or caregiver) to perform the injection under the supervision of the Investigator or delegate, and provide feedback on technique. Verify that the training for IMP self-injection is documented in the patient's study file. Instruct patients to administer IMP at q2w intervals.
  - For patients (or caregivers) unable or unwilling to self-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.
- Dispense patient (self-injection) Home Dosing Diary
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- 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 (fasting if morning visit).

10.1.9 Visit 9 (Week 16)

- 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, respiration rate, body temperature, weight for all patients and height for adolescents only)
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to IMP administration) for the following tests:
  - Clinical laboratories,
  - Systemic drug concentration
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
- Administer health care resource utilization questionnaire.
- 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
- Review instructions on self-injection and dosing and dispense patient (self-injection) Home Dosing Diary
- Dispense and administer IMP
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP at q2w intervals.

- For patients (or caregivers) unable or unwilling to self-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 patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (Week 20 ± 3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.10 Visit 10, 12, 13, 15, 16, 17 (Week 20, 28, 32, 40, 44, 48)

- 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, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Measure exhaled nitric oxide (only applicable for Visit 10 and Visit 17)
  - 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Administer health care resource utilization questionnaire.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to IMP administration) for the following tests:

- Clinical laboratories include hematology and serum chemistry (see Section 9.2.2.5 for details)
- At Visit 17, for patients who will continue in the OLE study, obtain blood samples for hepatitis screen (HBs Ag, HBs Ab, HBc Ab including HBcAb IgM and total, and HCV Ab). In case of results showing HBs Ag (negative) and HBc Ab total (positive), a HBV DNA testing must be performed prior to inclusion to OLE in order to determine eligibility. In case of results showing HCV Ab (positive), a HCV RNA testing must be performed prior to inclusion to OLE in order to determine eligibility.
- At Visit 17, for patients who will continue in the OLE study, obtain blood sample for HIV screen (Anti-HIV-1 and HIV-2 antibodies)
- At Visit 17, for patients who will continue in the OLE study, obtain blood sample for ANA test. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).
- Obtain blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4).
- Obtain blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)

- At Visit 17, for patients who plan to participate in the OLE study, perform chest X-ray or MRI (MRI is for Germany only) if available chest imaging (X-ray, CT, MRI) is over 12 months from entry into the OLE study.
- 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
- Review instructions on self-injection and dosing and dispense patient (self-injection) Home Dosing Diary
- Dispense and administer IMP
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP at q2w intervals.
  - For patients (or caregivers) unable or unwilling to self-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 patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.

- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (±3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.11 Visit 11, 14, 18 (Week 24, 36, 52 / End-of-Treatment Visit)

- 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, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Perform physical examination (only applicable for Visit 11 and EOT visit)
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick) If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling(fasting if morning visit, prior to administration of IMP) for the following tests:
  - Clinical laboratories,

- Serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),
- Systemic drug concentration,
- Anti-drug antibodies (only applicable for Visit 11 and Visit 18),
- Biomarker set, Periostin (Only applicable for Visit 18, refer to Section 9.3.2) and Antigen-specific IgE (only applicable for Visit 11 and Visit 18, refer to Section 9.3.2)
- Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to Section 9.4)
- Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
- Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
- Blood sampling for hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.

- 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 (applicable for Visit 11 and Visit 14)
- Dispense and administer IMP (only applicable for Visit 11 and Visit 14)
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP at q2w intervals.
  - For patients (or caregivers) unable or unwilling to self-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 patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period (only applicable for Visit 11, Visit 14 and EOT visit after which patients continue to participate the open label extension trial) and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.

- Schedule a site visit 4 weeks (±3 days) and ask patient to come at approximately the same time of this visit (only for Visit 11 and Visit 14: fasting if morning visit).
- Call IVRS/IWRS to register the EOT date (only applicable for EOT visit)

At Visit 18 (EOT visit), for patients who will not continue with the open label extension, the controller medication regimen and dose used during the randomized period could be adjusted based on medical judgment of the patients' asthma control status.

Patients who permanently discontinue the study treatment will perform early treatment discontinuation visit (ETD) at the time of permanent treatment discontinuation as well as EOT visit (visit 18) at planned Week 52. See section 1.3 for assessments to be performed at ETD and EOT visits and Section 10.3.4 for additional details.

10.1.12 Visit 19 and Visit 20 (Week 56 and Week 60, Post-Treatment Period)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Administer health care resource utilization questionnaire
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling (fasting if morning visit) for the following tests:
  - Clinical laboratories,
  - Systemic drug concentration
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue the stable dose of ICS in combination with one or two other 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 patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (±3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.13 Visit 21 (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, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Perform physical examination
- 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 and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis), RQLQ(S)+12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick) If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit) for the following tests:

- clinical laboratories,
- serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),
- Systemic drug concentration,
- Anti-drug antibodies

- 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 CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of 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 AE is sufficiently resolved and unlikely to recur after resuming therapy with IMP.

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

- Infections or infestations that do not respond to medical treatment
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix K

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 treatment (ie, from any further investigational product administration) for the following reasons:

- At their own request or at the request of their legally authorized representative (Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- At the specific request of the Sponsor
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor
- Any code broken 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, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (See Appendix N).
- Serum ALT >3 ULN and Total Bilirubin > 2ULN (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.

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 with a +/-5 day window (See Section 1.3). Under exceptional circumstances when a patient cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs, concomitant medication and asthma exacerbation events should be collected.

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/or clinical presentation at the time of discontinuation.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time 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. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study.

Patients who withdraw should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.

Patients 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 are assessed using the procedure normally planned for the end-of-study visit including a systemic drug concentration sample, if appropriate, and three Post-treatment Period Visits.

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 subject 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 **adverse event** (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 asthma exacerbation events are collected as efficacy endpoints via the "Asthma Exacerbation Events" form. These events should not be reported as AEs unless they fulfill a seriousness criterion.

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 **serious adverse event** (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 as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Anaphylaxis (refer to Appendix M for Definition of Anaphylaxis)
  - 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 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 adverse event of special interest (AESI) is an AE (serious or non-serious) 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 or removed during a study by protocol amendment.

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

- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (refer to Appendix M for Definition of Anaphylaxis)
- Severe injection site reactions that last longer than 24 hours
- Any infection meeting at least one of the following criteria:
  - Any serious infection (SAE)
  - Requires parenteral (intravenous, intramuscular, subcutaneous) antimicrobial therapy
  - Requires oral antimicrobial therapy for longer than 2 weeks
  - Is a parasitic infection
  - Is an opportunistic infection (see Appendix N)

Note: antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents

- Significant ALT elevation
  - ALT >5 x the upper limit of normal (ULN) in patients with baseline ALT ≤2 x ULN; or
  - ALT >8 x ULN if baseline ALT >2 x ULN
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/Noninvestigational medicinal product (NIMP);
  - 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 will be qualified as an SAE only if it fulfills one 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 is an event suspected by the Investigator or spontaneously notified by the patient 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 adverse event 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 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 health authorities providing 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 Global Safety Officer (GSO) with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. The GSO must communicate this decision to the study team for inclusion in the protocol and AE 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 with immediate notification, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

The following table summarizes the reporting timelines:

Adverse event / laboratory abnormality		Reporting timeline
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	
Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment		Within 24 hours
Severe injection site reactions that last longer than 24 hours		Within 24 hours
Infections as defined in Section 10.4.1.3.		Within 24 hours

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator 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 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
- Increase in ALT
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

Note: In some clinical trials these laboratory abnormalities can be considered as AESIs. For this study, only significant ALT increase will be considered as AESIs (see Section 10.4.1.3)

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, IECs/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 suspected unexpected serious adverse drug reaction (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 an immunologically mediated response to a pharmaceutical and/or formulation agent in a sensitized person. Signs and symptoms are often experienced during

or shortly after therapeutic administration. Anaphylaxis may represent the most severe form of allergic reactions, refer to Appendix M "Definition of Anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis.

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

Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment must-be reported as an adverse event of special interest (AESI) (within 24 hours, for further details, see AESI definition in Section 10.4.1.3 and Appendix M) and study medication must be permanently discontinued. ADA 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 subcutaneous mode of administration of high doses of protein and on a higher incidence of local injection site reactions observed at the highest dose level (300 mg weekly), 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. 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 infection. As a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness.

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. 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 slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc.). Subsequent medical assessments (eg, stool exam, blood tests, etc.) must be performed in order to rule out parasitic infection/infestation. Patients with confirmed parasitic infections during the study should be reported as AESI with immediate notification.

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

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

Infections or infestations that do not respond to medical treatment should have study 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 Appendix N), patients must be permanently discontinued from study medication.

10.6.4 Elevated liver function tests

No pre-clinical 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 Visit 1, prior to randomization to exclude those patients with high risk of hepatitis infection or severe liver injury from this study (Refer to Section 7.2 and Section 9.2.2.5).

In order to closely follow potential liver abnormalities, assessment of total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing (Refer to Section 9.2.2.5).

Guidance for the investigation of elevated ALT as well as concurrent management of IMP 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 calculation of this study was based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary endpoints: annualized rate of severe exacerbations during the 52-week treatment period and absolute change from baseline in FEV_1 at Week 12. Assuming the number of severe exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline eosinophil count ≥300 cells/μL (0.3 giga/L), approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for the subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV_1 from baseline at Week 12 for the overall population, and 690 patients will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline eosinophil count ≥300 cells/ /μL (0.3 giga/L). The overall study recruitment will continue until at least 1638 patients in total and 690 patients with eosinophils ≥300 cells/μL (0.3 giga/L) are randomized. The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized into the study. In addition, approximately 84 adolescent patients will be randomized.

Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w and dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL respectively.

Randomization will be stratified by age (<18 years, ≥18 years) at screening, central eosinophil count (<300 cells/μL, ≥300 cells/μL) at screening, ICS dose level (medium, high) and country.

In addition, in order to have additional patients treated with drug manufactured using the intended commercial process, approximately 220 patients will be randomized in addition to the originally planned sample size (1638).

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the 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, but will be included in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The analysis population for the efficacy endpoints will be intent-to-treat (ITT) population. The two primary endpoints will also be analyzed in the HEos ITT population.

ITT population: all randomized population analyzed according to the treatment group allocated by randomization regardless of whether treatment kit is used or not.

HEos ITT population: ITT population with baseline eosinophils ≥300 cells/μL.

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. 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 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 population

The anti-drug antibody 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, regardless the actual amount of solution injected. The loading dose will be considered as two administrations. No imputation will be made for patients with missing or incomplete data.

Treatment compliance will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoints

The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed treatment duration will be the offset variable. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the additional off-treatment severe exacerbation events up to Week 52 will be included in the analysis and the last contact date at Week 52 will be used to calculate the offset variable.

The absolute change from baseline in FEV_1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline in FEV_1 values up to Week 12 as response variables, and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV_1 value and baseline-by-visit interaction as covariates. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in FEV_1 at Week 12 will be derived from the mixed-effect model. For patients discontinuing the treatment before Week 12, off study-treatment FEV_1 values measured up to Week 12 will be included in the primary analysis.

Subgroup analyses will be performed for the two primary endpoints using the same methods by baseline eosinophil levels (≥300 cells /μL vs <300 cells /μL and ≥150 cells /μL vs <150 cells /μL).

11.4.2.1.1 Analysis of annualized event rate

The annualized rate of exacerbation events, including severe exacerbation events resulting in hospitalization or emergency room visit and LOAC events, will be analyzed using the same way as for severe exacerbation events.

11.4.2.1.2 Analysis of Time to event variables

Time to event (eg, LOAC, severe exacerbation) will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, age, number of asthma exacerbation events within 1 year prior to the study, region (pooled country), baseline eosinophil strata and baseline ICS dose level as covariates. The Kaplan-Meier method will be used to respectively estimate the probabilities that a patient would experience events at Week 12, 24, 36 and 52 per each treatment group.

11.4.2.1.3 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 FEV_1. The covariates to be included are treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, corresponding baseline value and baseline-by-visit interaction. Sex and height will be included as covariates only in the models for spirometry parameters.

Descriptive statistics including number of patients, mean, standard error and LS means will be provided. 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.

Change from baseline at other time points will be analyzed in the same way.

11.4.2.1.4 Subgroup analysis

To assess the consistency in treatment effects across the subgroup levels, subgroup analyses will be performed for the primary efficacy endpoints with respect to baseline eosinophil level (≥300 cells /μL vs. <300 cells /μL and ≥150 cells /μL vs. < 150 cells /μL), age group, gender, region, race, background ICS dose levels, background controller medication type, baseline FEV_1, predicted FEV_1 %, ACQ-5, weight, BMI, smoking history, atopic medical history, age of onset of asthma and number of asthma exacerbation events within 1 year prior to the study.

11.4.2.2 Multiplicity considerations

To strongly control the type-I error rate for the primary family (two primary endpoints and two doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The

hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300 mg q2w versus placebo, 2) absolute change from baseline in FEV_1 at Week 12 for 300 mg q2w versus placebo, 3) annualized severe exacerbation rate for 200 mg q2w versus placebo, 4) absolute change from baseline in FEV_1 at Week 12 for 200 mg q2w versus placebo.

If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significant level. The list of secondary endpoints to be tested in the hierarchical order will be specified in SAP. The overall familywise error rate will be strongly controlled at a 2-sided 5% level for all tested endpoints across dose groups.

11.4.2.3 Handling of missing data

Sensitivity analyses excluding the additional off-treatment measurements up to Week 52 will be performed to corroborate the primary analyses. The reason and pattern of missing data will be carefully examined and tipping point analysis and additional sensitivity analyses may be performed. The details will be specified in the SAP.

11.4.2.4 Loading dose evaluation

To examine if inclusion of the loading dose may impact demonstration sustained efficacy regard to exacerbations, additional sensitivity analyses of the annualized rate of severe exacerbation will be performed by excluding severe exacerbation events occurring during the first four weeks and 12 weeks, respectively. The analyses will be performed the same way as the primary analysis. To avoid possible confounding effect due to off-treatment data, only on-treatment events will be included. Due to potential insufficient number of events after excluding data from the first 12 weeks, two dupilumab groups will be combined and two placebo groups will be combined.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group. The results of the two placebo groups will be presented separately. 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 IMP.

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 literature review and defined by the Sponsor for clinical laboratory tests, vital signs and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment 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.

Proportion of patients with at least one treatment emergent adverse event (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. None treatment emergent serious AE, None treatment emergent AE leading to study discontinuation will be summarized separately.

11.4.3.1.1 AESI

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group.
- The time-to-first event analyzed using K-M methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.
- An overview summary of the number (%) of patients with
  - any TEAE
  - any serious AE (regardless of treatment-emergent status)
  - any treatment-emergent SAE
  - any AE leading to death
  - any TEAE leading to permanent study drug discontinuation
  - any TEAE by maximum intensity, corrective treatment, and final outcome
  - cumulative incidence at specified time points (K-M estimates at 1 week, 4 weeks, 12 weeks, 24 weeks and 52 weeks)

AESI definitions 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 (TEAE, 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.

11.4.3.1.3 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, standard deviation, median, Q1, Q3, minimum and maximum.

The proportion of patients who had at least one incidence of PCSA at any time during the TEAE 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.

11.4.3.2 Vaccine response

For patients who receive vaccination, vaccine response parameters will be summarized by treatment groups with descriptive statistics.

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

Incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%), presented by study cohorts. Listing of all ADA titer levels will be provided for

patients positive in the ADA assay. All samples that are positive in the ADA assay will be further tested 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.

ADA 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.

ADA 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 treatment-emergent ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent ADA
- Number (%) of patients with transient treatment-emergent ADA
- Number (%) of patients with persistent treatment-emergent ADA

Titer values (Titer value category)

The minimum titer for samples positive in the ADA assay is based on the minimum required dilution of the assay.

Low (Titer < 1000)
Moderate (1,000 ≤ Titer ≤ 10,000)
High (Titer > 10,000)

More details will be specified in SAP.

11.4.4.3 Pharmacodynamics

The values to be used as baselines will be those collected on Day 1 (predose assessments). If any of the scheduled assessments on Day 1 are technically disqualified (eg, insufficient sample), then values determined at Screening 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 +/- standard error of the mean) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment group.

11.4.5 Analyses of Patient Reported Outcomes (Health-related Quality of Life/health economics variables

Change from baseline in the following variables: global measure of AQLQ(S) and the four domains, the quantitative variables of EQ-5D-5L (single index utility), the anxiety and depression scores of HADS will be analyzed with an MMRM approach described previously for the continuous efficacy variables. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 95% CI's and the p-values will be provided for comparison between dupilumab and placebo.

SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis) and RQLQ(S)+12 (only for those patients with comorbid allergic rhinitis) will be analyzed using the similar approach.

11.5 INTERIM ANALYSIS

There is no interim analysis planned for this study.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the 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, should fully inform the patient (and the parent[s] or guardian[s] for pediatric patients) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the Institutional Review Board / Institutional Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the informed consent form should be signed, name filled in and personally dated by the patients (for adult patients) or patient's parent(s) for pediatric patients or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient (for adult patients) or patient's parent(s) for pediatric patients. Local law must be observed in deciding whether 1 or both parents/guardians consent is required for pediatric patients. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian's signature.

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

Pediatric participants who can read the assent form will do so before writing their name and dating or signing and dating the form.

Pediatric participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Pediatric participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form 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 collection of blood for pharmacogenetics, the optional pharmacogenetic informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

Prior to collection of blood for evaluation of vaccine response, the optional vaccine response informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

Prior to collection of blood for archiving of serum, the optional Future Use of Specimens informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

The main study informed consent form, the optional Pharmacogenetic informed consent form, optional Vaccine Response informed consent form and the Future Use of Specimens informed consent form to be used by the Investigator for obtaining the 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.

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

12.3 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 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, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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 IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It 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.

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 Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the 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 CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form 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 CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

It is the responsibility of the Investigator to maintain adequate and accurate 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 CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the 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 Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

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

The Investigator should retain the study documents 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 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 Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for FDA, on Japanese population for the PMDA in Japan, or on Chinese population for the CFDA in China).

Analyses of subject genetic data will be conducted as described in the protocol as this is needed for pharmacogenetics analyses required for the purpose 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, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;

- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

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

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon 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 of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, 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 some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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