

NCT number: NCT02528214



AMENDED CLINICAL TRIAL PROTOCOL 02

COMPOUND: SAR231893 - dupilumab

A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma

STUDY NUMBER: EFC13691

VERSION DATE / STATUS: 25-Jan-2017 / Approved

STUDY NAME: VENTURE

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Amended Clinical Trial Protocol 01	Version number: 1 (electronic 3.0)	Date: 20-Jul-2016
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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR

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MONITORING TEAM'S REPRESENTATIVE

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SPONSOR

Company:
Address:

OTHER EMERGENCY TELEPHONE NUMBERS

CLINICAL TRIAL SUMMARY

COMPOUND: SAR231893	STUDY No: EFC13691 STUDY NAME: VENTURE
TITLE	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	<p>Primary objective</p> <ul style="list-style-type: none"> To evaluate the efficacy of dupilumab compared with placebo, for reducing the use of maintenance oral corticosteroids (OCS) in patients with severe steroid-dependent asthma. <p>Secondary objectives</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of dupilumab To evaluate the effect of dupilumab in improving patient-reported outcomes (PROs) To evaluate dupilumab systemic exposure and the incidence of treatment-emergent anti-drug antibodies (ADA) <p>Exploratory objectives</p> <ul style="list-style-type: none"> To evaluate baseline and on-treatment levels of biomarkers in association with treatment response and for their potential to predict treatment responses To evaluate patient genetic profiles and their potential to predict treatment responses To evaluate the effect of dupilumab on airway markers of inflammation (at selected study sites within Canada)
STUDY DESIGN	<p>General Design</p> <p>Multinational, multicenter, randomized, double-blind, placebo-controlled study assessing the effect of dupilumab administered subcutaneously (SC) for a maximum of 24 weeks in patients with severe steroid-dependent asthma.</p> <p>Periods</p> <p>The clinical trial will be divided into the following periods:</p> <ul style="list-style-type: none"> Screening and OCS Optimization period (from 3 to up to 8 weeks [up to 10 weeks for patients experiencing an asthma exacerbation that requires a change in OCS dose to allow for 2 weeks of stabilization prior to randomization]): to determine a patient's eligibility status and to ensure that patients enter the treatment period on the lowest dose of OCS that will manage their symptoms Treatment period (24 weeks): includes a 4-week induction phase, a 16-week OCS reduction phase, and a 4-week maintenance phase Post-treatment period (12 weeks): to monitor a patient's status after completing/withdrawing from study drug treatment for patients not rolling over into a long-term study.

	<p><u>Screening and OCS Optimization Period</u></p> <p>Patients who meet eligibility criteria at the Screening visit will enter the OCS Optimization Phase. Prednisone or prednisolone will be the only OCS used. During the Screening visit, patients currently using other OCS medications will be switched to either of these corticosteroids at a dose clinically equivalent to their current stable OCS dose. The definition of stable OCS maintenance dose in EFC13691 is no change of OCS dose within 4 weeks of Screening Visit 1.</p> <p><i>OCS optimization phase interruption criteria</i></p> <p>The lowest effective OCS dose will be defined during this phase as the lowest dose a patient can tolerate without experiencing any of the following criteria:</p> <ul style="list-style-type: none"> • Increase in Asthma Control Questionnaire (ACQ)-5 of at least 0.5 from the last ACQ-5 score recorded in the e-diary • Severe asthma exacerbation • Clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment <p>In general, the investigator can refer to the ACQ-5 score at Screening Visit 1 to guide the OCS dose adjustments made during the optimization phase of the study; however, the decision to titrate can be based on the investigator's clinical judgement. Once determined, the optimized dose must remain stable for 2 consecutive weeks along with baseline medications without meeting any of the OCS optimization phase interruption criteria prior to randomization.</p> <p>Investigators should adjust the OCS dose according to a prespecified titration schedule based on the OCS optimization phase interruption criteria, and in accordance with their clinical judgement. During the OCS optimization phase, the patient's asthma control will be assessed weekly by reviewing these criteria via scheduled phone calls after Visit 2. If the patient's asthma status remains controlled and none of the above criteria are met, the investigator should down-titrate the patient's OCS dose. The downward titration will continue until a point when at least 1 of the OCS optimization phase interruption criteria is met. If the down-titration is stopped, the investigator should up-titrate the OCS dose by 1 step per Table 1, unless the patient's medical condition requires treatment with a higher dose of OCS.</p> <p>Those patients who are able to down titrate their OCS dose to 2.5 mg during the OCS Optimization phase without experiencing any of the above bulleted criteria will be considered screen failures and will not be randomized.</p> <p>If a patient experiences a severe asthma exacerbation during the OCS Optimization Phase, the exacerbation should be treated with the use of oral or parenteral steroids at least double the dose of current maintenance dose of OCS. Following exacerbation treatment, the patient should be placed on the OCS dose 1 step higher than the dose they were on when the exacerbation occurred. Note that the optimization period can be extended to 10 weeks to allow for 2 weeks of stabilization prior to randomization.</p> <p><u>Randomized Treatment Period</u></p>
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	<p><i>Induction Phase (4 weeks)</i></p> <p>At Visit 3 (Week 0), patients who meet the eligibility criteria will be randomized in a 1:1 ratio to receive a 600 mg loading dose followed by 300 mg once every 2 weeks (q2w) of dupilumab or matching placebo, respectively. During this phase, patients will remain on their optimized dose of OCS along with their baseline asthma medications.</p> <p><i>OCS Reduction Phase (16 weeks)</i></p> <p>The OCS dose should be down-titrated during this phase following a predetermined schedule that is based upon the optimized OCS dose identified during the OCS Optimization Period. Dose reductions may occur every 4 weeks which should allow the minimization of any carryover effects from the previous dose and reduce the risk for adrenal insufficiency. The last possible dose reduction can occur at Week 20. No down-titration beyond this time point is permitted. The reduction in OCS dose should occur per the schedule unless the patient meets defined criteria indicating that it is not acceptable for the patient to reduce the dose. A clinical assessment should be completed prior to each dose reduction. Primary reasons for not following the scheduled dose reduction include:</p> <ul style="list-style-type: none"> • Mean morning peak expiratory flows (PEF) <70% of baseline stability limit • Forced expiratory volume in 1 second (FEV₁) 20% reduction from baseline stability limit • Rescue medication (metered dose inhaler) use requiring 4 or more puffs/day above the mean baseline value for any 2 consecutive days in the prior week, or 12 puffs or more on any 1 day in the prior week • Change in ACQ-5 score $\geq +0.5$ from the prior month OCS dose assessment • Clinically significant asthma exacerbation • Clinically significant event, based on investigator judgment, that requires treatment by OCS dose adjustment <p>The Investigator will decide, depending on the reason for not reducing the OCS dose per schedule, whether to maintain or increase his /her current OCS dose by 1 step.</p> <p><i>Maintenance Phase (4 weeks)</i></p> <p>Patients will be maintained for the last 4 weeks of the treatment period on the same OCS dose established at Week 20. However, when any of the above criteria for not reducing OCS dose is met, the Investigator should decide whether to maintain or increase the current OCS dose accordingly.</p> <p>If a severe asthma exacerbation occurs during the Reduction or Maintenance Phases, the exacerbation should be treated with the use of oral or parenteral steroids at a dose at least equivalent to double the dose of current maintenance dose of OCS. Following resolution, the patient should be placed on the OCS dose 1 step higher than that which he/she was on when the exacerbation occurred for at least 4 weeks and continue with dose reductions</p>
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	<p>(only during the Reduction phase) as per the predefined schedule at the following visit. If a patient experiences 2 exacerbations, no further OCS dose reductions will be allowed.</p> <p><u>Post-treatment Period</u></p> <p>After completing the treatment period, patients who do not rollover into a long-term study will be evaluated for 12 weeks in the post-treatment period. During this follow-up period, patients will continue treatment with their stable dose of controller medication (includes all medications used to control asthma symptoms, with the exception of the investigational medicinal product [IMP]) that can be modified based on their level of asthma control, as determined by the Investigator.</p> <p>During the post-treatment period, patients will continue to collect e-diary information that can be used to determine asthma control.</p> <p>Eligible patients completing the treatment period may have the opportunity to roll over into a long-term study with dupilumab. Patients subsequently enrolled in this long-term study will not participate in the Post-treatment period of this trial.</p> <p>Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits. In addition, patients who discontinue early from treatment or patients who choose not to roll over into a long-term 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 clinical presentation.</p>
<p>STUDY POPULATION</p> <p>Main selection criteria</p>	<p>Inclusion criteria</p> <p>I 01. Adult and adolescent (12 years of age or older) patients with a physician diagnosis of asthma for ≥ 12 months, based on the Global Initiative for Asthma (GINA) 2014 guidelines and the following criteria:</p> <ul style="list-style-type: none"> A) Patients with severe asthma and well-documented, regular prescribed treatment of maintenance systemic corticosteroids in the 6 months prior to Visit 1 and using a stable OCS dose (ie, no change of OCS dose) for 4 weeks prior to Visit 1. Patients must be taking 5 – 35 mg/day of prednisone/ prednisolone, or the equivalent, at Visit 1 and at the Randomization visit. In addition, the patient must agree to switch to study-required prednisone/prednisolone as their OCS and use it per protocol for the duration of the study. B) Existing treatment with high dose inhaled corticosteroid (ICS; $>500 \mu\text{g}$ total daily dose of fluticasone propionate or equivalent) in combination with a second controller (ie, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA]) for at least 3 months with a stable dose of ICS for ≥ 1 month prior to Visit 1. In addition, patients requiring a third controller for their asthma are considered eligible for this study. C) A forced expiratory volume in 1 second (FEV_1) $<80\%$ of predicted normal for adults and $\leq 90\%$ of predicted normal for adolescents at Visit 1. D) Evidence of asthma as documented by either: <ul style="list-style-type: none"> - Reversibility of at least 12% and 200 mL in FEV_1 after the

	<p>administration of 200 to 400 µg (2 to 4 puffs 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 or documented in the 12 months prior to Visit 1 OR</p> <ul style="list-style-type: none"> - Airway hyperresponsiveness (methacholine: provocative concentration that causes a positive reaction [PC₂₀] of <8 mg/mL) documented in the 12 months prior to Visit 1. <p>Exclusion criteria</p> <p>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, patient recruitment will be restricted to those who are ≥18 years of age).</p> <p>E 02. Patients who weigh <30 kg.</p> <p>E 03. Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc) which may impair lung function.</p> <p>E 04. Clinical evidence or imaging (eg, chest X-ray, computed tomography, magnetic resonance imaging) within 12 months of Visit 1 with clinically significant findings of lung disease(s) other than asthma, as per local standard of care.</p> <p>E 05. A patient who experiences a deterioration of asthma that results in emergency treatment or hospitalization within 4 weeks of Screening Visit 1.</p> <p>E 06. A patient who requires 12 puffs or more of rescue medication (eg, metered dose inhaler) on any 1 day in the week prior to Visit 1.</p> <p>E 07. A patient who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to Screening.</p> <p>E 08. Current smoker or cessation of smoking within 6 months prior to Visit 1.</p> <p>E 09. Previous smoker with a smoking history >10 pack-years.</p> <p>E 10. Comorbid disease that might interfere with the evaluation of the IMP (an example being, but not limited to, neuromuscular disease, etc).</p>
Total expected number of patients	Approximately 180 patients will be randomized to either dupilumab or placebo. Enrollment will be limited to approximately 46 (25% of total sample size) patients whose eosinophil level is <150 cells/µL. In addition, patients whose optimized OCS dose is 5 mg/day at Visit 3 will be limited to 54 patients (approximately 30% of the study population).
STUDY TREATMENT(s)	
Investigational medicinal products	Dupilumab (SAR231893/REGN668) or matching placebo.
Formulations	<p>Dupilumab: 150 mg/mL in a prefilled syringe to deliver 300 mg in 2 mL.</p> <p>Placebo: Prefilled syringe to deliver 2 mL.</p>
Route(s) of administration	Subcutaneously (SC)

Dose regimen	Dupilumab 300 mg SC q2w with a 600 mg loading dose on Day 1. Placebo SC q2w (matching the dupilumab 300 mg formulation) with a placebo loading dose on Day 1.																																																																																																																																																																
Noninvestigational medicinal products	Oral corticosteroids (prednisone/prednisolone), ICS with a second or third controller medication (LABA, LTRA, theophylline, etc), reliever medication (albuterol/salbutamol or levalbuterol/levosalbutamol)																																																																																																																																																																
Formulation	Oral corticosteroids will be provided in the appropriate formulation by each investigational site (except in selected countries).																																																																																																																																																																
Route(s) of administration	As appropriate for the formulation.																																																																																																																																																																
Dose regimen	<p><u>Screening/OCS Optimization Period</u></p> <p>Prior to and during the Screening Period, patients must be on a stable dose of high dose ICS in combination with a second controller medication (LABA, LTRA, theophylline, etc). Patients needing a third controller are eligible for this study. In addition, patients will receive prednisone/prednisolone at a variable dose based on a predefined titration schedule (see Table 1).</p> <p>Table 1: Titration schedule for optimizing oral corticosteroids during the OCS Optimization Phase</p> <table><tr><th>Time course</th><th colspan="9">OCS dose (mg/day)</th></tr><tr><td>Starting dose (Visit 1)</td><td>35</td><td>30</td><td>25</td><td>20</td><td>15</td><td>12.5</td><td>10</td><td>7.5</td><td>5</td></tr><tr><td>Dose reduction (Visit 2)</td><td>30</td><td>25</td><td>20</td><td>15</td><td>12.5</td><td>10</td><td>7.5</td><td>5</td><td>2.5</td></tr><tr><td>+1 week</td><td>25</td><td>20</td><td>15</td><td>12.5</td><td>10</td><td>7.5</td><td>5</td><td>2.5</td><td></td></tr><tr><td>+1 week</td><td>20</td><td>15</td><td>12.5</td><td>10</td><td>7.5</td><td>5</td><td>2.5</td><td></td><td></td></tr><tr><td>+1 week</td><td>15</td><td>12.5</td><td>10</td><td>7.5</td><td>5</td><td>2.5</td><td></td><td></td><td></td></tr><tr><td>+1 week</td><td>12.5</td><td>10</td><td>7.5</td><td>5</td><td>2.5</td><td></td><td></td><td></td><td></td></tr><tr><td>+1 week</td><td>10</td><td>7.5</td><td>5</td><td>2.5</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>+1 week</td><td>7.5</td><td>5</td><td>2.5</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table> <p>OCS=oral corticosteroid</p> <p><u>Randomized Treatment Period</u></p> <p>During this period, patients will continue taking their controller medication(s) and the optimized dose of prednisone/prednisolone (dose received during the 2 weeks prior to randomization). During the OCS Reduction Phase, the dose of OCS will be down-titrated based on a predefined schedule (see Table 2).</p> <p>Table 2: Titration schedule for oral corticosteroids during the OCS Reduction Phase of the Randomized Treatment Period</p> <table><tr><th>Time course</th><th colspan="9">OCS dose (mg/day)</th></tr><tr><td>Optimized OCS dose</td><td>35</td><td>30</td><td>25</td><td>20</td><td>15</td><td>12.5</td><td>10</td><td>7.5</td><td>5</td></tr><tr><td>First dose reduction</td><td>25</td><td>20</td><td>15</td><td>10</td><td>10</td><td>10</td><td>5</td><td>5</td><td>2.5</td></tr><tr><td>+4 week</td><td>15</td><td>10</td><td>10</td><td>5</td><td>5</td><td>5</td><td>2.5</td><td>2.5</td><td>0</td></tr><tr><td>+4 week</td><td>10</td><td>5</td><td>5</td><td>2.5</td><td>2.5</td><td>2.5</td><td>0</td><td>0</td><td></td></tr><tr><td>+4 week</td><td>5</td><td>2.5</td><td>2.5</td><td>0</td><td>0</td><td>0</td><td></td><td></td><td></td></tr><tr><td>+4 week</td><td>2.5</td><td>0</td><td>0</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>	Time course	OCS dose (mg/day)									Starting dose (Visit 1)	35	30	25	20	15	12.5	10	7.5	5	Dose reduction (Visit 2)	30	25	20	15	12.5	10	7.5	5	2.5	+1 week	25	20	15	12.5	10	7.5	5	2.5		+1 week	20	15	12.5	10	7.5	5	2.5			+1 week	15	12.5	10	7.5	5	2.5				+1 week	12.5	10	7.5	5	2.5					+1 week	10	7.5	5	2.5						+1 week	7.5	5	2.5							Time course	OCS dose (mg/day)									Optimized OCS dose	35	30	25	20	15	12.5	10	7.5	5	First dose reduction	25	20	15	10	10	10	5	5	2.5	+4 week	15	10	10	5	5	5	2.5	2.5	0	+4 week	10	5	5	2.5	2.5	2.5	0	0		+4 week	5	2.5	2.5	0	0	0				+4 week	2.5	0	0						
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	<p><u>Post-treatment Period</u></p> <p>Upon completing the Randomized Treatment Period, patients not rolling over into a long-term study will continue treatment with the controller medication regimen and dose used during the randomized period, which could be adjusted based on the medical judgment of the Investigator based on the patient's asthma control status.</p> <p><u>Reliever Medication</u></p> <p>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.</p>
ENDPOINTS	<p>Primary endpoint</p> <p>Percentage reduction of OCS dose at Week 24 compared with the baseline dose, while maintaining asthma control. A patient will be considered as having maintained asthma control between Week 20 and Week 24 if he/she does not have a clinically significant event, based on investigator judgment, that requires treatment by OCS dose adjustment during this period. For those patients who experience an exacerbation, the final OCS dose will be considered to be 1 step higher than the dose they were receiving at the time of the exacerbation.</p> <p>Secondary endpoints</p> <p><u>Key secondary endpoint</u></p> <ul style="list-style-type: none"> Proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24, while maintaining asthma control. The relative reduction for each patient will be calculated as (optimized OCS dose – final OCS dose at Week 24)/optimized OCS dose × 100. <p><u>Efficacy</u></p> <ul style="list-style-type: none"> Absolute reduction of OCS dose at Week 24 compared with the baseline dose while maintaining asthma control Proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24 while maintaining asthma control Proportion of patients no longer requiring OCS at Week 24 while maintaining asthma control Proportion of patients achieving their maximum possible reduction of OCS dose per protocol at Week 24 while maintaining asthma control <p><u>Safety and tolerability</u></p> <ul style="list-style-type: none"> Adverse events (AEs) Vital signs Electrocardiogram (ECG) Clinical laboratory tests <p><u>Pharmacokinetic and ADA</u></p> <ul style="list-style-type: none"> Serum functional dupilumab concentrations Anti-drug antibodies (ADA)

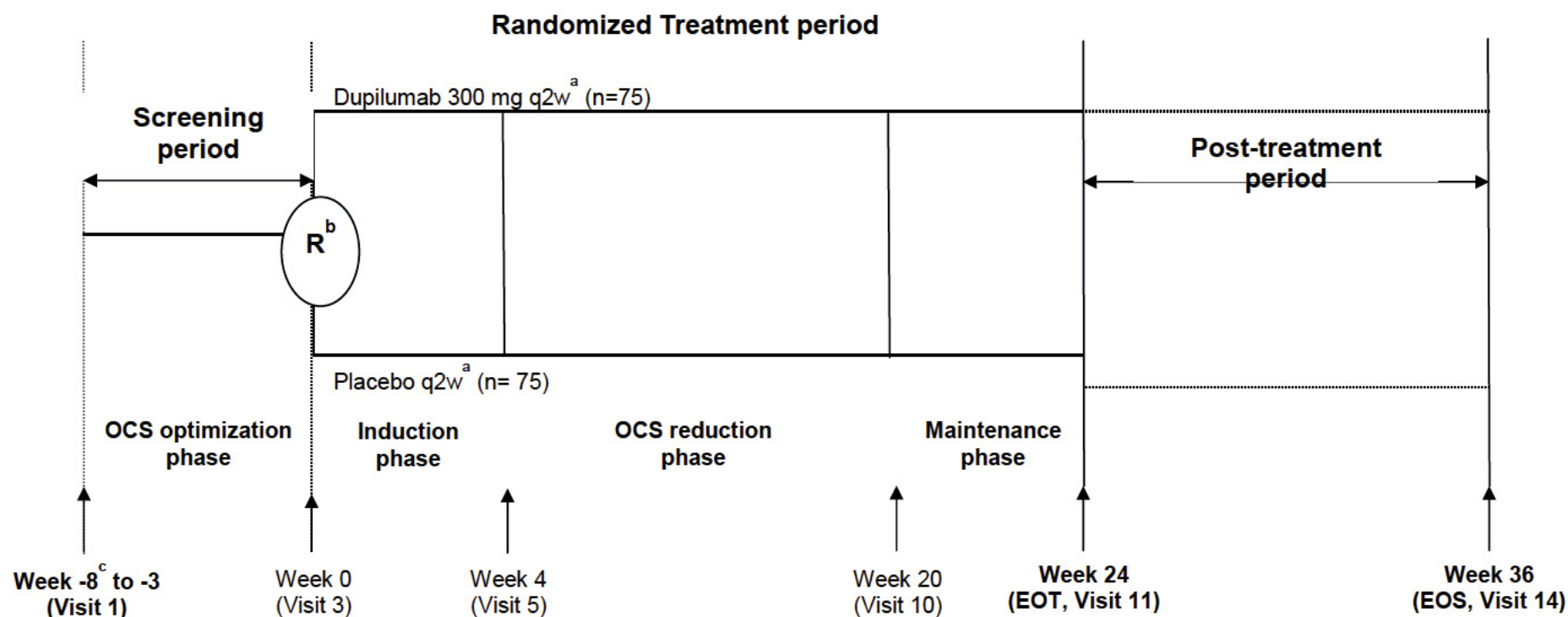
	<p>Other endpoints</p> <p><u>Efficacy</u></p> <ul style="list-style-type: none"> • Annualized rate of severe asthma exacerbation events defined as a deterioration of asthma during the 24-week treatment period requiring: <ul style="list-style-type: none"> - Use of systemic corticosteroids for ≥ 3 days (<u>at least double the dose currently used</u>); AND/OR - Hospitalization related to asthma symptoms, OR emergency room (ER) visit because of asthma requiring intervention with a systemic corticosteroid treatment. • Time to first severe asthma exacerbation event • Absolute change from baseline in pre-bronchodilator FEV₁ at Weeks 2, 4, 8, 12, 16, 20, and 24 • Percent change from baseline in pre-bronchodilator FEV₁ at Weeks 2, 4, 8, 12, 16, 20, and 24 • Change from baseline in other lung function measurements (percent predicted FEV₁, morning/evening PEF, forced vital capacity [FVC], forced expiratory flow over the 25% to 75% range of the vital capacity [FEF_{25-75%}]), at Weeks 2, 4, 8, 16, 20, 12 and 24 • Change from baseline in post-bronchodilator FEV₁ at Weeks 12 and 24 • Change from baseline in ACQ-5 score at Weeks 2, 4, 8, 12, 16, 20, and 24 • Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) score at Weeks 12, and 24 • Annualized rate of asthma exacerbations requiring hospitalization or ER visit • Time to first severe asthma exacerbation requiring hospitalization or ER visit • Change from baseline at weeks 12 and 24 in: <ul style="list-style-type: none"> - 22-Item Sino Nasal Outcome Test (SNOT-22) in patients with bilateral nasal polyposis/chronic rhinosinusitis - Hospital Anxiety and Depression Scale (HADS) - EQ-5D-5L • Change from baseline at Weeks 2, 4, 8 12, 16, 20, and 24 in: <ul style="list-style-type: none"> - Morning/evening asthma symptom score and nocturnal awakenings (eDiary) - Use of rescue medication - Health Care Resource Utilization <p><u>Exploratory endpoints</u></p> <ul style="list-style-type: none"> • Blood samples for exploratory genetic analysis of DNA and RNA to assess the relationship of DNA variants and/or gene expression with asthma and response to dupilumab treatment • Biomarkers <ul style="list-style-type: none"> - Fractional exhaled nitric oxide (FeNO) levels - Blood eosinophil count - Total and antigen-specific immunoglobulin (Ig)E
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	<ul style="list-style-type: none"> - Thymus and activation-regulated chemokine (TARC) - Periostin - Eotaxin-3 • Sputum and blood, interleukin (IL) C2 and CD34 cells, and cytokines (at selected study sites in Canada) • Change from baseline in airway hyperresponsiveness at Week 24 (at selected study sites within Canada)
ASSESSMENT SCHEDULE	<ul style="list-style-type: none"> • Screening period (from 3 to up to 8 weeks [up to 10 weeks for patients who experience an asthma exacerbation that requires a change in OCS dose to allow for 2 weeks of stabilization prior to randomization]) • Randomized Treatment period (up to 24 weeks) • Post-treatment period (12 weeks)
STATISTICAL CONSIDERATIONS	<p>Sample size determination</p> <p>The sample size estimation is based on the comparison between dupilumab versus placebo in regards to the primary endpoint and the key secondary endpoint: percentage reduction of OCS dose at Week 24 compared with the baseline dose and proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24, while maintaining asthma control. For the primary endpoint, assuming a common standard deviation of 50%, with 90 randomized patients per group, the study will have 94% power to detect a treatment difference of 27% at the 2-tailed significance level of $\alpha=0.05$. For the key secondary endpoint, with the same sample size of 90 randomized patients per group, the study will have 81% power to detect a difference in the proportion of patients achieving 50% or greater in their OCS dose of 33% in the placebo group, compared to 54% in the dupilumab group at the 2-tailed significance level of $\alpha=0.05$.</p> <p>Patients will be randomized using a 1:1 randomization ratio for dupilumab 300mg q2w and placebo. Randomization will be stratified by optimized OCS dose at Week 0 (≤ 10 mg/day, >10 mg/day) and country.</p> <p>Recruitment of patients whose eosinophil level is below 150 cells/μL will stop when approximately 46 (25% of the total sample size) of such patients are randomized. Recruitment will continue with patients whose eosinophil level is greater or equal to 150 cells/μL until reaching the total sample size of 180. In addition, the number of patients receiving 5 mg OCS at Visit 3 will be limited to approximately 54 patients (approximately 30% of the study population).</p> <p>Analysis population</p> <p>The analysis population for the efficacy endpoints will be the 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.</p> <p>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 patients actually received.</p> <p>Primary analysis</p> <p>The outcome of the percentage reduction of OCS dose at Week 24 compared with the baseline dose, while maintaining asthma control, will be calculated as: (optimized OCS dose – final OCS dose at Week 24)/optimized OCS dose $\times 100\%$. The percentage reduction will be analyzed using an analysis of</p>

	<p>covariance (ANCOVA) model. The model will include the percentage reduction of OCS dose at Week 24 as the response variable, and treatment group, baseline eosinophil level subgroups (<150 cells/μL and \geq150 cells/μL), optimized OCS dose at baseline, region as covariates. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the Investigator will continue to prescribe OCS at the dose specified for OCS titration. The off-treatment OCS dose at Week 24 will be used in the primary analysis.</p> <p>Analysis of secondary endpoints</p> <p>The absolute reduction of OCS dose at Week 24 will be analyzed using an ANCOVA model in the same fashion as for the primary endpoint (percent reduction of OCS dose at Week 24).</p> <p>The proportion of patients achieving OCS reduction will be analyzed using a logistic regression model including treatment, baseline eosinophil level subgroups, optimized OCS dose at baseline, and region as covariates.</p> <p>The annualized rate of severe asthma exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 24-week Randomized Treatment period as the response variable, with the treatment group, baseline eosinophil level subgroups, region, baseline optimized OCS dose strata, and number of severe exacerbation events prior to the study as covariates. Log transformed treatment duration will be the offset variable. For patients who permanently discontinue the treatment, the events which occurred up to Week 24 will be included and the last contact date will be used to calculate the offset variable. For patients lost to follow up prior to Week 24, events that occurred up to the last contact date will be analyzed, and the last contact date will be used to calculate the offset variable.</p> <p>Time to severe asthma exacerbation will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment group, baseline eosinophil level subgroups, region, baseline optimized OCS dose strata, number of asthma events prior to the study, and region as covariates. The Kaplan-Meier method will be used to derive the proportion of patients with an asthma exacerbation event at Weeks 12 and 24 for each treatment group.</p> <p>The change from baseline in FEV₁ will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline FEV₁ values up to Week 24 as response variables, and factors (fixed effects) for treatment, age, sex, height, baseline eosinophil level subgroups, region, baseline optimized OCS dose strata, visit, treatment by-visit interaction, baseline FEV₁ value, and baseline-by-visit interaction. 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 key secondary endpoint, percentage change from baseline in FEV₁ at each visit, will be derived from the mixed-effect model.</p> <p>The change from baseline for continuous endpoints will be analyzed using a MMRM in the same fashion as for the change in FEV₁. Data up to Week 24 will be included as response variables. Age, sex, and height will be included as covariates in the models for spirometry parameters only.</p> <p>The safety variables, including AEs, laboratory parameters, vital signs, ECG and physical examinations will be summarized using descriptive statistics.</p>
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	<p>Interim analysis</p> <p>No interim analysis is planned for this study. The primary analysis is planned when the last patient completes the week 24 visit or discontinues from the study before week 24.</p> <p>Data base lock</p> <p>The primary database lock will be based on the date when the last patient completes the week 24 visit or discontinues from the study before week 24. 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.</p>
DURATION OF STUDY PERIOD (per patient)	<p>Total duration of study (per patient) is expected to be up to 46 weeks:</p> <ul style="list-style-type: none">• Up to 10 weeks for screening• 24 weeks of treatment• 12 weeks of post-treatment follow-up

1 FLOW CHARTS



^a 600 mg (or matching placebo) loading dose on Day 1.

^b Randomization and first IMP administration occurs at this visit.

^c The Screening period can be increased to 10 weeks for patients experiencing an asthma exacerbation that requires a change in OCS dose to allow for 2 weeks of stabilization prior to randomization.

EOS=end of study; EOT=end of treatment; OCS=oral corticosteroid; q2w=every 2 weeks; R=Randomization visit

1.1 STUDY FLOW CHART

	Screening Period/ OCS Optimization Phase ^a		Randomized Treatment Period													Post-treatment Period		
			R N D ^b	Induction Phase		OCS Reduction Phase								Maintenance Phase				
Week	-8 to -3	-7 to -2	0	2	4	6	8	10 ^c	12	14 ^c	16	18 ^c	20	22 ^c	24	28	32	36
Visit	1	2 ^d	3	4	5	6	7		8		9		10		11/EOT	12	13	14
Informed consent	x																	
Inclusion/exclusion criteria	x	x	x															
Patient demography	x																	
Medical/surgical history	x																	
Reversibility ^e	x																	
Post-bronchodilator FEV ₁			x						x						x			x
Spirometry ^f	x	x	x ^g	x	x	x	x		x		x		x		x	x	x	x
CXR (if none within previous year) ^h	x												x					
Prior & concomitant meds ⁱ	x	x	x	X	x	x	x		x		x		x		x	x	x	x
Physical examination	x														x			
Randomization			x															
Call IVRS	x		x	X	x	x	x		x		x		x		x			x
Investigational product administration ^j			x	X	x	x	x	x	x	x	x	x	x	x				
Dispense or download e-diary/PEF meter ^k	x	x	x	X	x	x	x		x		x		x		x	x	x	x
Dispense/review home dosing diary							x		x		x		x		x			
ACQ ^l	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x

	Screening Period/ OCS Optimization Phase ^a		Randomized Treatment Period													Post-treatment Period		
			R N D ^b	Induction Phase		OCS Reduction Phase								Maintenance Phase				
Week	-8 to -3	-7 to -2	0	2	4	6	8	10 ^c	12	14 ^c	16	18 ^c	20	22 ^c	24	28	32	36
Visit	1	2 ^d	3	4	5	6	7		8		9		10		11/EOT	12	13	14
AQLQ	x		x						x						x			x
FeNO ^m	x	x	x	X	x	x	x		x		x		x		x	x	x	x
Vital signs ⁿ	x	x	x	X	x	x	x		x		x		x		x	x	x	x
OCS reduction criteria review ^o		x	x		x		x		x		x		x		x			
Begin OCS reduction if patient meets criteria ^p					x													
OCS dose adjustment ^q		x			x		x		x		x		x		x ^{q,r}			
ECG	x		x						x						x			x
Pregnancy test ^s	x		x		x		x		x		x		x		x			x
Clinical lab testing ^t	x		x		x		x		x		x		x		x			x
Urinalysis ^u	x		x						x						x			x
Serum IgG, IgM, IgA	x		x						x						x			x
PK sampling ^{v,w}			x		x		x		x						x			x
Anti-drug antibodies ^{w,x}			x						x						x			x
Pharmacodynamics/ biomarkers			x		x				x				x		x			
Archival serum ^y			x						x						x			
Pharmacogenetics: blood DNA and RNA (optional) ^z			x															
SNOT-22 ^{aa}	x		x						x						x			x
HADS	x		x						x						x			x

	Screening Period/ OCS Optimization Phase ^a		Randomized Treatment Period													Post-treatment Period		
			R N D ^b	Induction Phase		OCS Reduction Phase								Maintenance Phase				
Week	-8 to -3	-7 to -2	0	2	4	6	8	10 ^c	12	14 ^c	16	18 ^c	20	22 ^c	24	28	32	36
Visit	1	2 ^d	3	4	5	6	7		8		9		10		11/EOT	12	13	14
EQ-5D-5L	x		x						x						x			x
Health resource utilization	x	x	x	X	x	x	x		x		x		x		x	x	x	x
AE/SAE recording	x	x	x	X	x	x	x		x		x		x		x	x	x	x
Optional assessments (for select study sites in Canada)																		
Sputum and blood collection ^{bb}			x												x			x
Methacholine challenge ^{cc}			x												x			

ACQ=Asthma Control Questionnaire; ADA=anti-drug antibodies; AE=adverse event; AM=morning; ANA=anti-nuclear antibodies; AQLQ=Asthma Quality of Life Questionnaire; CXR=chest x-ray; ECG=electrocardiogram; DNA=deoxyribonucleic acid; ds=double-stranded; eDiary=electronic diary; EOT=end-of-study; FEF_{25-75%}=forced effective flow over the 25% to 75% range of the vital capacity; FeNO=fractional exhaled nitric oxide; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; HADS=Hospital Anxiety and Depression scale; HbA1c=hemoglobin A1c; HIV=human immunodeficiency virus; ICS=inhaled corticosteroid; Ig=immunoglobulin; IMP=investigational medicinal product; IVRS=interactive voice response system; LABA=long-acting beta agonist; LAMA=long-acting muscarinic antagonist; LTRA=leukotriene receptor antagonist; OCS=oral corticosteroid; PEF=peak expiratory flow; PK=pharmacokinetics; PM=evening; q2w=once every 2 weeks; RNA=ribonucleic acid; Rnd=randomization; SAE=severe adverse event; SNOT-22=22-item Sino Nasal Outcomes Test.

- a The Screening period is from 3 to up to 8 weeks in duration (for patients who experience an asthma exacerbation that requires a change in OCS dose this period can be extended to 10 weeks to allow for 2 weeks of stabilization prior to randomization) to collect baseline data on asthma and to optimize the OCS dose. A follow up visit/s or call/s may be added during this visit depending upon the patient's response to changes in OCS dosing.
- b Randomization Visit (Visit 3) is defined as Day 1. Visit windows for subsequent visits are +/- 3 days.
- c Weeks 10, 14, 18, and 22 are scheduled as phone visits. Patients who are not (or whose caregivers are not) comfortable with self-administering the IMP will return to the study clinic for these visits.
- d Visit 2 will occur over 2 weeks which are designated as Visit 2A (complete with all procedures) and Visit 2B (will consist of a review of the eDiary with the patient). Both visits (2A and 2B) must be done in the clinic.
- e Three attempts may be made during the Screening Period to meet the qualifying criteria for reversibility. (Note: this is only required if reversibility or airway responsiveness meeting eligibility criteria was not performed within 12 months prior to Visit 1).
- f FEV₁, FVC, FEF_{25-75%} at all visits; pulmonary function tests should be performed in the morning if possible, but if testing can only be done at another time during the day, then the testing should be done at approximately the same time of day at each visit throughout the study. Spirometry will be performed after withholding the last dose of salbutamol/albuterol or levalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours.
- g Treatment Period stability limits will be established for FEV₁ and PEF.

- h* At Visit 1, perform chest X-ray or magnetic resonance imaging (MRI) if no chest imaging (X-ray, computed tomography [CT], MRI) available within the previous year. At Visit 10, it is only applicable for patients who plan to roll over into a long-term study and available chest imaging is over 1 year from rolling over into a long-term study.
- i* Prior to screening, patients must be on a stable high-dose ICS (fluticasone propionate >500 µg total daily or equivalent) plus a second controller (LABA, LTRA, etc) for ≥1 month prior to Visit 1. Patients requiring a third controller are considered eligible for this study. Patients should be on well-documented, regular prescribed treatment of maintenance systemic corticosteroids in the 6 months prior to Visit 1 and using a stable OCS dose for 4 weeks prior to Visit 1. Patients must be taking 5 to 35 mg/day of prednisone or equivalent at Visit 1.
- j* Investigational product administrations (q2w) must be separated by at least 11 days. The randomized Treatment Period visits occur every 2 weeks up to Week 8 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 24. After Visit 7 (Week 8), 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.
- k* Electronic diary/PEF meter is used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, ICS, LABA, LAMA, LTRA, and other controller use, OCS requirements, nocturnal awakenings, morning and evening asthma symptom scores, and AM and PM PEF. The device is dispensed at Visit 1. The eDiary data must be reviewed on a weekly basis by the Investigator during the Optimization Period and prior to OCS dose reduction during the OCS Reduction Phase of the study, including Visit 5.
- l* During the OCS Optimization period, the ACQ-5 will be completed weekly in the patient's electronic diary. During the Treatment and Post-treatment periods, the ACQ-7 will be performed at clinic visits and the ACQ-5 will be completed on a weekly basis for those weeks that the patient does not have a scheduled clinic visit.
- m* FeNO assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- n* 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, 2 and 3) and every subsequent visit. Height (cm) will be measured at screening (Visit 1) only. 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.
- o* OCS dose adjustments can be made during scheduled phone visits or scheduled in-clinic visits.
- p* Patients who do not meet the criteria for OCS reduction at Visit 5 may begin reduction at a later visit.
- q* OCS titration during the OCS Optimization Phase can occur weekly following Visit 2 until the optimal OCS dose is determined and every 4 weeks during the OCS Reduction Phase but is not necessarily required to occur during a scheduled in-clinic visit.
- r* At the EOT visit (Visit 11), the final OCS dose the patient is receiving needs to be documented; no adjustments to the OCS dose will be permitted (except for those patients who experience an asthma exacerbation).
- s* Serum pregnancy test at Visit 1 and urine pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 3 prior to randomization.
- t* Hematology: hemoglobin, hematocrit, platelet count, total white blood cell count with 5-part differential count, and total red blood cell count. Serum chemistry: creatinine, blood urea nitrogen, glucose (only at Visits 3, 8, and 11), HbA1c, uric acid, total cholesterol, total protein, albumin, total bilirubin (reflex testing will be triggered by elevated 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 10 (only for patients who planned roll over into a long-term study) includes hepatitis screen (HBsAg, HBsAb, IgM and IgG/total-HBcAb, and HCVAb), HIV screen (anti-HIV-1 and anti-HIV-2 antibodies), and ANA. Patients who are IgG/Total-HBc Ab positive and HBs Ag negative at Visit 1 must undergo HBV DNA testing prior to randomization to determine eligibility (only applicable for patients who plan to roll over into a long term study). Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer). At Visits 3 (randomization), 8, and 11, the blood sample should 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 a light meal and the site should document that serum chemistry was not obtained under fasting conditions.
- u* Urine dipstick analysis, including specific gravity, pH, glucose, ketones, blood protein, nitrate, leukocyte esterase, urobilinogen, and bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis will be performed by central laboratory.
- v* Pharmacokinetic samples will be collected prior to dosing.
- w* Systemic drug concentration and ADA samples are to be collected prior to dosing. In the event of any SAE or any adverse event of special interest (AESI) of anaphylaxis or systemic allergic reaction related to IMP and requiring 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 9.2.5](#) for more details.

- x* ADA samples are to be collected prior to dosing.
- y* Archival serum will be collected for potential use in retrospective safety follow-up or additional biomarker analysis. Collection of archival serum is optional and requires the patient to sign consent.
- z* Optional sampling for exploratory analysis of DNA and RNA, requiring separate pharmacogenetics informed consent. Blood for DNA can be collected any time during the study; blood for RNA must be collected prior to any IMP administration.
- aa* For those patients with bilateral nasal polypsis/chronic rhinosinusitis.
- bb* Sputum and additional blood samples will be collected at selected Canadian sites as an optional assessment. At Visits 3 and 11, both sputum and blood will be collected. At Visit 14, only a sputum sample will be collected (for patients who have not rolled over into a long-term study). In addition, sputum collection will be obtained when a patient experiences symptoms of an asthma exacerbation (collected during an unscheduled visit).
- cc* An optional assessment to be done in selected Canadian sites (only for patients with a $FEV_1 \geq 70\%$ of predicted).

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3 LIST OF ABBREVIATIONS

ACQ-5:	Asthma Control Questionnaire-5 question version
ADA:	anti-drug antibodies
AE:	adverse event
AESI:	adverse events of special interest
ANA:	anti-nuclear antibody
ANCOVA:	analysis of covariance
AQLQ:	Asthma Quality of Life Questionnaire
ATS:	American Thoracic Society
BMI:	body mass index
CDMS:	clinical data management system
CI:	confidence interval
COPD:	chronic obstructive pulmonary disease
CT:	computed tomography
CV%:	coefficient of variation
CYP:	cytochrome P450
DMC:	data monitoring committee
DRF:	Discrepancy Resolution Form
ECG:	electrocardiogram
e-CRF:	electronic case report form
ELISA:	enzyme linked immunosorbent assay
EOT:	end-of-treatment
ER:	emergency room
ERS:	European Respiratory Society
FEF _{25-75%} :	forced expiratory flow from 25% to 75% of the vital capacity
FEV ₁ :	forced expiratory volume in 1 second
FVC:	forced vital capacity
GCP:	good clinical practice
GINA:	Global Initiative for Asthma
GSO:	Global Safety Officer
HADS:	Hospital Anxiety and Depression Scale
HbA1c:	hemoglobin A1c
HBsAb:	hepatitis B surface antibody
HCV:	hepatitis C virus
HCVAb:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
ICH:	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS:	inhaled corticosteroids
IEC:	Institutional Ethics Committee
Ig:	immunoglobulin

IL:	interleukin
IL-4R α :	interleukin-4 receptor alpha subunit
IMP:	investigational medicinal product
IRB:	Institutional Review Board
ISR:	injection site reaction
ITT:	intent-to-treat
IVRS:	interactive voice response system
IWRS:	interactive web response system
KM:	Kaplan Meier
LABA:	long-acting beta agonist
LS:	least squares
LTRA:	leukotriene receptor antagonist
MCID:	minimal clinically important difference
MDI:	metered dose inhaler
MMRM:	mixed effect model with repeated measures
MRI:	magnetic resonance imaging
mRNA:	messenger ribonucleic acid
OCS:	oral corticosteroids
PC ₂₀ :	provocative concentration that causes a positive reaction
PCR:	polymerase chain reaction
PCSA:	potentially clinically significant abnormality
PEF:	peak expiratory flow
PK:	pharmacokinetic
Pop:	population
PROs:	patient-reported outcomes
PT:	preferred term
Q1:	first quartile
q2w:	every 2 weeks
Q3:	third quartile
q4w:	every 4 weeks
RNA:	ribonucleic acid
SAE:	serious adverse event
SC:	subcutaneous
SD:	standard deviation
SEM:	standard error of the mean
SNOT-22:	22-item Sino Nasal Outcome Test
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reactions
TARC:	thymus and activation-regulated chemokine
TEAE:	treatment-emergent adverse event
Th-2:	T-helper cell-2
TSLP:	thymic stromal lymphopoietin
ULN:	upper limit of normal
VAS:	visual analogue scale
WBC:	white blood cells
β -HCG:	beta-human chorionic gonadotropin

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).

Although asthma is well controlled with inhaled therapy in most patients, approximately 10% of the patients have severe asthma that is associated with considerable morbidity and mortality. Severe asthma is a heterogeneous syndrome with multiple distinct phenotypes based on several clinical, functional, and inflammatory parameters (2,3). From a clinical perspective, severe asthma has been divided into 3 subgroups (1,4):

- Frequent asthma exacerbations with relatively stable periods in between
- Asthma with fixed airway obstruction
- Corticosteroid-dependent asthma

Corticosteroids are highly effective in patients with severe asthma; however, the regular use of systemic steroids can result in serious deleterious side effects affecting numerous body systems (eg, formation of cataracts, muscle weakening, central nervous system disorders, and osteoporosis) (5,6). There is a clear need for safe corticosteroid sparing therapies for these patients. Current available options do not offer a positive benefit-risk ratio. 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 (4).

In a recently published trial involving 135 patients with severe eosinophilic asthma, treated with oral corticosteroids (OCS) for more than 6 months in addition to high dose inhaled corticosteroids (ICS) in combination with a second controller, received mepolizumab (an anti-interleukin [IL]-5 monoclonal antibody) or placebo for 24 weeks. Patients treated with mepolizumab were 2.4 times more likely to have a dose reduction in their OCS daily dose. The median percentage reduction was 50% for the actively treated patients (7).

Recent therapeutic approaches in asthma have been focused on trying to control the T-helper cell-2 (Th-2) response. Up-regulation of IL-4 and IL-13 activity has been implicated as an

important inflammatory component of asthma disease progression. Dupilumab is under development as a potential novel treatment for asthma. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4R α), 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-4R α results in blockade of downstream signaling initiated by both IL-4 and IL-13. Recently published clinical data from a Phase 2 clinical trial, demonstrated that dupilumab had a significant clinical effect in reducing asthma exacerbations, improving lung function and asthma control in patients with moderate to severe uncontrolled asthma in comparison with placebo (8). For complete information regarding the preclinical and clinical evaluation of dupilumab to date, see the Investigator's Brochure.

4.2 RATIONALE

4.2.1 Rational for study design

This Phase 3 study will investigate the efficacy and tolerability of dupilumab, in comparison with placebo, in reducing the use of OCS while maintaining asthma control in patients with severe refractory asthma. The study will also investigate the effects of dupilumab on clinical markers of asthma control, including asthma exacerbation rate, quality of life, and lung function (eg, forced expiratory volume in 1 second [FEV₁]). The study will enroll patients with severe asthma and well-documented, regular prescribed treatment of maintenance systemic corticosteroids in the 6 months prior to screening. The clinical trial will be divided into 3 periods:

- Screening and OCS optimization period (from 3 to up to 8 weeks [up to 10 weeks for those patients who experience an asthma exacerbation that requires a change in OCS dose to allow for 2 weeks of stabilization prior to randomization]).
- Treatment period (24 weeks): includes a 4-week induction phase, a 16-week OCS reduction phase, and a 4-week maintenance phase.
- Post-treatment period (12 weeks): to monitor the patients' status following completion of study drug treatment. This period only applies for those patients not rolling over into a long-term study.

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 while still providing patients access to standard of care.

The OCS adjustments (increase or decrease) during the Optimization phase and the length of the Optimization phase are deemed suitable because the patients have been managed on a stable dose of OCS for a significant period of time prior to the start of the study (as per by the inclusion criteria). A similar optimization approach was successfully employed in 3 published OCS reduction studies (7,9,10).

The proposed study design provides the opportunity to better understand the efficacy of dupilumab on multiple asthma domains including lung function, prevention of severe asthma exacerbations, and symptom control while reducing the dose of OCS over a period of 24 weeks.

4.2.2 Rationale for dose selection

The dose regimen of subcutaneous (SC) dupilumab selected for this study is 300 mg every 2 weeks (q2w). All patients randomized to receive treatment with dupilumab will get an initial loading dose of 600 mg on Day 1. The administration of the loading dose of dupilumab will allow systemic concentrations to reach steady-state faster, 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/ μ L or a sputum eosinophil level of at least 3%, partially controlled or uncontrolled by medium-to-high doses of ICS plus long-acting beta agonist (LABA; fluticasone/salmeterol, budesonide/formoterol, or mometasone/formoterol) were randomized to the study. The study showed unprecedented efficacy in a population of mostly severe asthmatics with poor asthma control and decreased lung function inadequately controlled with mostly high doses of ICS in combination with a LABA.

In addition, in the Phase 2b study DRI12544, 776 patients were randomized in a 1:1:1:1:1 ratio to 1 of 4 dupilumab regimens or placebo. The doses tested were: 200 mg every 4 weeks (q4w), 300 mg q4w, 200 mg q2w, 300 mg q2w, and placebo. Patients on the 300 mg regimens received a 600 mg loading dose on Day 1, whereas those treated with 200 mg doses received a loading dose of 400 mg. Study treatment was administered for 24 weeks. A prespecified interim analysis, based upon all available data at that time, was performed when the last patient completed 12 weeks of treatment. The assessment, change from baseline in FEV₁ at Week 12, was the final analysis of the primary endpoint. The analysis of annualized rate of severe asthma exacerbation included all events that occurred during the treatment period, adjusted by the treatment duration. At the time of this analysis, the average observed treatment duration was approximately 21.4 out of 24 weeks (approximately 89% of study information), with 70% of patient having completed 24 weeks of treatment, and 30% of patients had completed the 16-week off-treatment follow-up.

Compared with placebo, treatment with dupilumab demonstrated dose-dependent improvement in FEV₁ and reduction in the annualized severe asthma exacerbation rate. In general, the q2w dosing regimens demonstrated greater efficacy than the q4w dosing regimen. Both the 200 mg q2w and 300 mg q2w dose regimens demonstrated statistically significant improvements in FEV₁ and a significant reduction in the annualized rate of severe asthma exacerbations versus placebo in the overall intent-to-treat (ITT) population, patients with a baseline high eosinophil count (≥ 300 cells/ μ L), and patients with a lower baseline blood eosinophil (< 300 cells/ μ L). In contrast to the q2w regimen, the q4w dosing regimens demonstrated a consistently lower improvement in FEV₁ from baseline compared with placebo than the q2w dosing regimens and the 200 mg q4w dose did not reach a statistically significant improvement in FEV₁ in all patients as well as those with high baseline blood eosinophils. Secondary efficacy analysis on endpoints such as patient reported outcomes (Asthma Control Questionnaire-5 question version [ACQ-5] and Asthma Quality of Life Questionnaire [AQLQ]) also support the superiority of the q2w regimens compared with the q4w dosing.

Although the results of the Phase 2b study didn't show a clear differentiation between the 2 biweekly regimens, modeling and simulation data suggest that the 300 mg q2w may exhibit

better clinical efficacy. Because this trial will enroll patients with greater asthma severity than those randomized in the Phase 2b and in the planned pivotal Phase 3 trial, the Sponsor prefers to optimize the chances for these patients for exhibiting the best clinical response to dupilumab. For these reasons, the 300 mg q2w dose regimen has been selected for this trial.

A population pharmacokinetic (PK) model prediction demonstrated that exposure in adolescents at the 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 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 in healthy volunteers, patients with atopic dermatitis, nasal polyposis with chronic sinusitis, or asthma dosed for up to 16 weeks with a maximum dose of 300 mg administered every week. 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. Furthermore, patients on placebo demonstrated a higher discontinuation rate in comparison to those on dupilumab. The reported rate of suspected unexpected serious adverse reactions (SUSARs) has also been low. In addition, no imbalance in the frequency of treatment-emergent adverse events (TEAEs) between patients treated with dupilumab versus those treated with placebo has been observed, with the exception of injection site reactions (ISRs). In summary, the safety data observed so far in completed and currently ongoing studies in patients with atopic dermatitis, asthma, or nasal polyps with chronic sinusitis have demonstrated a very positive profile for dupilumab in comparison with placebo.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to evaluate the efficacy of dupilumab, compared with placebo, for reducing the use of maintenance OCS in patients with severe steroid-dependent asthma.

5.2 SECONDARY

Secondary objectives of the study include:

- To evaluate the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab in improving patient-reported outcomes (PROs)
- To evaluate dupilumab systemic exposure and the incidence of treatment-emergent anti-drug antibodies (ADA)

5.3 EXPLORATORY

The following objectives will be exploratory:

- To evaluate baseline and on-treatment levels of biomarkers in association with treatment response and for their potential to predict treatment responses
- To evaluate patient genetic profiles and their potential to predict treatment responses
- To evaluate the effect of dupilumab on airway markers of inflammation (at select study sites within Canada)

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a multinational, multicenter, randomized, double-blind, placebo-controlled study assessing the effect of dupilumab administered SC for a maximum of 24 weeks in patients with severe steroid-dependent asthma. Patients will be treated on an outpatient basis and will be stratified by optimized OCS dose at Week 0 (≤ 10 mg/day, >10 mg/day) and country.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Screening is from signed informed consent to randomization and the study observation period starts at randomization and lasts until the end of the study.

The total duration of the study (per patient) is expected to be up to 44 weeks (or up to 46 weeks in patients who experience an asthma exacerbation that requires a change in OCS dose to allow for 2 weeks of stabilization prior to randomization) and consists of:

- Up to 10 weeks for the Screening period/OCS Optimization phase
- 24 weeks for the Treatment period
- 12 weeks for the Post-treatment period (for patients not rolling over into a long-term study)

Patients who discontinue early from treatment or patients who choose not to roll over into a long-term 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 clinical presentation.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur when the last patient either completes the end-of-treatment (EOT) visit (Visit 11) and rolls over into long-term study, or at the end of the 12-week safety follow-up period if the patient completes treatment and elects not to roll over into long-term study or discontinues treatment early, or withdraws during the Post-treatment period for any reason, whichever occurs last.

6.3 INTERIM ANALYSIS

No interim analysis is planned for this study. The primary analysis is planned when the last patient completes the week 24 visit or discontinues from the study before week 24.

The primary database lock will be based on the date when the last patient completes the week 24 visit or discontinues from the study before week 24. 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.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

A data monitoring committee (DMC) is independent from the 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.

6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

The study design (including reductions in OCS dosing) and choice of a control group is based on similar optimization approach of studies that have been successfully employed in 3 published OCS reduction studies (7,9,10).

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

- I 01. Adult and adolescent (12 years of age and older) 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) Patients with severe asthma and well-documented, regular prescribed treatment of maintenance systemic corticosteroids in the 6 months prior to Visit 1 and using a stable OCS dose (ie, no change of OCS dose) for 4 weeks prior to Visit 1. Patients must be taking 5-35 mg/day of prednisone/ prednisolone, or the equivalent, at Visit 1 and at the Randomization visit. In addition, patients must agree to switch to study-required prednisone/prednisolone as their OCS at Visit 1 (see [Section 10.1.1](#)) and use it per protocol for the duration of the study (see [Appendix A](#) for a steroid conversion chart).
 - B) Existing treatment with high dose ICS (>500 μg total daily dose of fluticasone propionate or equivalent) in combination with a second controller (ie, LABA, leukotriene receptor antagonist [LTRA]) for at least 3 months with a stable dose of ICS for ≥ 1 month prior to Visit 1. In addition, 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 (see [Appendix A](#) for a steroid conversion chart).
 - C) An FEV_1 $<80\%$ of predicted normal for adults and $\leq 90\%$ of predicted normal for adolescents at Visit 1.
 - D) Evidence of asthma as documented by either:
 - Reversibility of at least 12% and 200 mL in FEV_1 after the administration of 200 to 400 μg (2 to 4 puffs 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 or documented in the 12 months prior to Visit 1
- OR**
- Airway hyperresponsiveness (methacholine: provocative concentration that causes a positive reaction [PC_{20}] of <8 mg/mL) documented in the 12 months prior to Visit 1.
- 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, patient recruitment will be restricted to those who are ≥ 18 years of age).
- E 02. Patients who weigh <30 kg.
- E 03. Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis, cystic fibrosis) which may impair pulmonary function tests.
- E 04. Clinical evidence or imaging (eg, chest X-ray, computed tomography, magnetic resonance imaging) within 12 months of Visit 1 with clinically significant findings of lung disease(s) other than asthma, as per local standard of care.
- E 05. A patient who experiences a deterioration of asthma that results in emergency treatment or hospitalization within 4 weeks of Screening Visit 1.
- E 06. A patient who requires 12 puffs or more of rescue medication (eg, metered dose inhaler) on any 1 day in the week prior to Visit 1.
- E 07. A patient who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to Screening.
- E 08. Current smoker or cessation of smoking within 6 months prior to Visit 1.
- E 09. Previous smoker with a smoking history >10 pack-years.
- E 10. Comorbid disease that might interfere with the evaluation of the investigational medicinal product (IMP) (an example being, but not limited to, neuromuscular disease, etc).
- E 11. Known or suspected alcohol and/or drug abuse.
- E 12. Inability to follow the procedures of the study (eg, due to language problems or psychological disorders).
- E 13. 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 14. Anti-immunoglobulin (Ig) E therapy (omalizumab) within 130 days of Visit 1.
- E 15. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy or change dose during the Screening period or the Randomized Treatment period.

- E 16. 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 17. 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 3 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 1.
- E 18. Patients receiving medications that are prohibited as concomitant medications (See [Section 8.8](#)).
- E 19. Patients who have previously been treated in any clinical trial of dupilumab.
- E 20. The 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 21. A patient 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 insulin-dependent diabetes, uncontrolled hypertension, active hepatitis, active or latent untreated tuberculosis, bronchiectasis. 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 breastfeeding woman
- E 23. Women of childbearing potential (pre-menopausal female biologically capable of becoming pregnant) who do not fulfill:

- A confirmed negative serum beta-human chorionic gonadotropin test at Visit 1.

And either:

- An established use of an acceptable contraceptive method:
 - Oral, injected, inserted, or implanted hormonal contraceptive.
 - Intrauterine device with or intrauterine system with progestogen.
 - Barrier contraceptive (condom, diaphragm, or cervical/vault caps) used with spermicide (foam, gel, film, cream, or suppository).

Or:

- 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 vasectomized male partner should be the sole partner for that patient.
- True abstinence; 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. Positive for human immunodeficiency virus (HIV) infection or HIV serology at Visit 1.

E 27. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, or aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per the Investigator's judgment. Tuberculosis testing will be performed on a country by country basis according to local guidelines, if required by regulatory authorities or ethic committees.

E 28. Evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1, significant viral infections within 4 weeks before Visit 1 that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment). Exceptions may be considered for uncomplicated mild viral or fungal infections requiring antiviral or antifungal therapy respectively only after discussion with the Investigator and approval by the Sponsor.

E 29. Live, attenuated vaccinations within 4 weeks prior to Visit 1 or planned live, attenuated vaccinations during the study; see [Appendix B](#) for list of prohibited live, attenuated vaccines.

E 30. Patients with active autoimmune disease or patients using immunosuppressive therapy (including OCS) for an autoimmune disease (eg inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) or patients with high titer of autoantibodies at Screening who are suspected by the Investigator or the Sponsor of having a high risk for developing an autoimmune disease.

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 systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

E 33. Patients with:

- Positive (or indeterminate) test for hepatitis B surface antigen (HBs-Ag),
- Positive IgM hepatitis B core antibody,
- Positive IgG/total hepatitis B core antibody confirmed by positive hepatitis B virus DNA (HBV DNA)
- Positive hepatitis C virus antibody (HCVAb) confirmed by positive hepatitis C virus RNA (HCV RNA)

E 34. Patient has evidence of liver injury, as defined by any of the following criteria:

- Clinically significant/active hepatobiliary disease
- Alanine aminotransferase $>3 \times$ upper limit of normal (ULN)

E 35. Patient has any of the following abnormal lab values at Screening:

- Creatine phosphokinase $>10 \times$ ULN
- Platelets $<100,000$ cells/mm³
- Eosinophils >1500 cells/mm³

7.2.4 Additional exclusion criteria during or at the end of the Screening period/OCS optimization period before randomization

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

E 37. Despite screening of the patient, enrolment/randomization is stopped at the study level.

E 38. Patient did not experience an increase in ACQ-5 ≥ 0.5 during the OCS optimization phase.

E 39. Noncompliance with completion of the electronic diary (eDiary) defined as :

- Documented use of each asthma controller medication (including OCS, ICS/LABA, etc) dose as instructed during the OCS Optimization phase for at least 80% of the duration of that period.
- Completion of weekly ACQ-5 scores.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

8.1.1 Dupilumab

Sterile dupilumab will be provided in 150 mg/mL in glass prefilled syringes (2.25 mL total volume) to deliver 300 mg in 2 mL.

8.1.2 Placebo

Sterile placebo for dupilumab will be provided in identically matched glass prefilled syringes to deliver 2 mL.

8.1.3 Preparation of investigational product

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

8.1.4 Dosing schedule

The IMP will be administered every 14 ± 3 days (ie, q2w). The doses of the IMP must be separated by ≥ 11 days to avoid an overdose.

Patients will receive q2w SC injections of 300 mg dupilumab or placebo following a loading dose of 600 mg on Day 1 during the 24-week Treatment period.

Prophylactic treatment/premedication for an ISR is not permitted.

Patients will have the option to self-administer the study drug (or have a caregiver administer study drug) outside the study site during weeks in which no clinic visit is scheduled. The study staff will train the patient/caregiver on the preparation and administration of study drug on Day 1 and will administer the first of the 2 injections required for the loading dose. The patient/caregiver will administer the second injection required for the loading dose under the supervision of the clinic staff. This training must be documented in the patient's study file. At subsequent study visits, patients are trained to self-inject the IMP, and the patients are allowed to self-inject IMP at home after 5 injections at the investigational site (starting on Week 10).

When the patient has a study visit, the IMP will be administered following clinic procedures and blood collection. Patients will be monitored for signs or symptoms of a hypersensitivity reaction at the study site for a minimum of 30 minutes.

For doses not given at the study site, a Home Dosing Diary will be provided to record information related to the injections. The diary will be kept as source data in the patient's study file and the information will be recorded in the eCRF.

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 the IMP for the doses that are not scheduled to be given at the study site. Patients who prefer to have the clinic staff administer study drug may choose to have injections administered in the clinic.

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 the 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 does not develop the comfort to inject the investigational drug at home, or the Investigator determines that the 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 the IMP are provided to the patient. Patients will complete a Home Dosing Diary to document compliance with self-injection (or caregiver) injection of IMP.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

Oral corticosteroids will be provided by each investigational site.

8.2.1 Inhaled corticosteroid with a second or third controller

Prior to and during the Screening period, patients must be on a stable dose of high dose ICS with a second controller medication (LABA, LTRA, theophylline, etc). 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.

During the Randomized Treatment period and Post-treatment period (for those patients not rolling over into a long-term study), patients will continue taking their controller medication(s).

The recognized controllers in this study will include the following 5 classes: ICS, LABA, LAMA, anti-leukotrienes and methylxanthine. For examples of commonly used asthma controller therapies, refer to [Appendix M](#) for a list of controller medications approved for this study.

8.2.2 Oral corticosteroids

During the course of the study, patients will receive variable doses of OCS (prednisone/prednisolone). Prednisone/prednisolone use will be captured on a daily basis by the patient using an eDiary.

8.2.2.1 Screening Period/Oral Corticosteroid Optimization Phase (Visits 1 and 2)

Patients who meet eligibility criteria at the Screening visit will enter the OCS Optimization Phase. Prednisone or prednisolone will be the only OCS used. At the Screening visit (V1), patients currently using other forms of maintenance OCS will have their corticosteroids switched to either of these corticosteroids at a dose clinically equivalent to their current stable OCS maintenance dose. The definition of stable OCS maintenance dose in EFC13691 is no change of OCS dose within 4 weeks of Screening Visit 1

OCS optimization phase interruption criteria

The lowest effective or optimized OCS dose will be defined during this phase as the lowest dose a patient can tolerate without experiencing any of the following criteria:

- Increase in ACQ-5 of ≥ 0.5 from the last ACQ-5 score recorded in the e-diary
- Severe asthma exacerbation
- Clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment

In general, the investigator can refer to the ACQ-5 score at Screening Visit 1 to guide the OCS dose adjustments made during the optimization phase of the study; however, the decision to titrate can be based on the investigator's clinical judgement. Once determined, the optimized dose must remain stable for 2 consecutive weeks along with baseline medications without meeting any of the OCS optimization phase interruption criteria in order to be eligible for randomization.

Investigators should adjust the OCS dose according to a prespecified titration schedule ([Table 1](#)) based on the OCS optimization phase interruption criteria, and in accordance with their clinical judgement. The decision rule of the titration schedule will be based on changes in the patient's asthma control, assessed by the above criteria. In the absence of a severe asthma exacerbation or a clinically significant event, the change in OCS dose should be guided directly by the ACQ-5 score.

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

- Use of systemic corticosteroids for ≥ 3 days (at least double the dose currently used) and/or

- Hospitalization or emergency room (ER) visit because of asthma requiring intervention with a systemic corticosteroid treatment (at least double the dose currently used)

No change in OCS dose will be made at Visit 1. One week after the Screening visit (Visit 1), patients will return to the clinic for Visit 2. At Visit 2, and weekly throughout the Optimization phase, patient stability will be assessed by the above outlined criteria.

If at Visit 2, the patient's asthma status remains controlled (ie, none of the above criteria are met), the Investigator should down titrate the patient's OCS dose. The downward titration will continue until a point when at least 1 of the OCS optimization phase interruption criteria are met. If the down-titration is stopped, the investigator should up-titrate the OCS dose by 1 step per [Table 1](#), unless the patient's medical condition requires treatment with a higher dose of OCS.

Deterioration is defined as an increase in the ACQ-5 score of ≥ 0.5 from the last ACQ-5 score recorded in the e-diary, the occurrence of a severe asthma exacerbation, or a clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment. In these cases, the patient will return to the prior OCS dose at which none of the OCS optimization phase interruption criteria were met.

If at Visit 2, or weekly thereafter, the patient's asthma status deteriorates as outlined above their OCS dose should be increased by 1 step ([Table 1](#)). In this manner, the Screening/OCS Optimization phase can range from 3 to 8 weeks until an optimized dose of OCS is achieved (Note: If an asthma exacerbation occurs that requires a change in OCS dose, this period can be extended up to 10 weeks to allow for 2 weeks of stabilization prior to randomization.)

In cases where the stable OCS dose for 4 weeks prior to Visit 1 does not conform to a dose found on [Table 1](#), the initial dose reduction should be the most conservative decrease that approximates the [Table 1](#) protocol guidance. As an example, 6 mg could be reduced to 5 mg and then per protocol to 2.5 mg thereafter, or 8 mg to 7.5 mg and then 5 mg, depending upon the individual patient and the investigator's judgment. In the event of any uncertainty, the Investigator will discuss the therapy directly with the Sponsor prior to the first OCS dose reduction.

Those patients who are able to down titrate their OCS dose to 2.5 mg during the OCS Optimization phase without meeting any of the above criteria, will be considered screen failures and will not be randomized.

Table 1 Oral corticosteroid optimization titration schedule

Time course	OCS dose (mg/day)								
Starting dose (Visit 1)	35	30	25	20	15	12.5	10	7.5	5
Dose reduction (Visit 2)	30	25	20	15	12.5	10	7.5	5	2.5
+1 week	25	20	15	12.5	10	7.5	5	2.5	
+1 week	20	15	12.5	10	7.5	5	2.5		
+1 week	15	12.5	10	7.5	5	2.5			
+1 week	12.5	10	7.5	5	2.5				
+1 week	10	7.5	5	2.5					
+1 week	7.5	5	2.5						

OCS=oral corticosteroid

If a patient experiences a severe asthma exacerbation during the OCS Optimization phase, the exacerbation should be treated with the use of oral or parenteral steroids at least double the dose of the current maintenance dose of OCS (see [Section 8.2.5](#)). Following exacerbation treatment, the patient should be placed on the OCS dose 1 step higher than the dose they were on when the exacerbation occurred, in accordance with [Table 1](#).

Once the optimized OCS dose has been identified, the patient will be maintained on their optimized OCS dose, along with their baseline medications, for 2 weeks prior to randomization. If a patient is unable to maintain their optimized OCS dose and experiences an increase in ACQ-5 of at least 0.5 or a severe asthma exacerbation, the dose of OCS should be increased 1 step or as detailed for a severe asthma exacerbation in [Section 8.2.5](#) unless there is a clinically significant contraindication to an increase in the OCS dose. The patient will be eligible for randomization after the increased OCS dose remains stable for a 2-week period (provided there is sufficient time remaining in the Screening Period [up to 10 weeks]).

8.2.2.2 Randomized Treatment Period

Induction Phase

During the 4-week Induction phase patients will remain on their optimized dose of OCS along with their baseline asthma medications.

Oral Corticosteroid Reduction Phase

The OCS dose will be down-titrated during this phase following a predetermined schedule, provided in [Table 2](#), dependent upon the patient's optimized OCS dose (the OCS dose the patient was receiving at the time of randomization). Dose reductions will occur every 4 weeks which should allow for carryover effects from the previous dose to be minimized and also minimize the risk for clinically significant events. The last possible dose reduction can occur at Week 20 with no further dose adjustments beyond this time point.

Table 2 Oral corticosteroid titration schedule during the Oral Corticosteroid Reduction phase

Time course	OCS dose (mg/day)								
Optimized OCS dose	35	30	25	20	15	12.5	10	7.5	5
First dose reduction	25	20	15	10	10	10	5	5	2.5
+4 week	15	10	10	5	5	5	2.5	2.5	0
+4 week	10	5	5	2.5	2.5	2.5	0	0	
+4 week	5	2.5	2.5	0	0	0			
+4 week	2.5	0	0						

OCS=oral corticosteroid

A clinical assessment should be completed prior to each dose reduction. The reduction in OCS dose should occur per the schedule provided in [Table 2](#).

OCS Reduction Phase Interruption Criteria

Primary reasons for not following the scheduled dose reduction include:

- Change in ACQ-5 score ≥ 0.5 from the prior month OCS dose assessment
- Clinically significant asthma exacerbation(s)
- FEV₁ 20% reduction from baseline stability limit
- Mean morning peak expiratory flow (PEF) <70% of baseline stability limit as assessed in the week prior to the clinical visit
- Rescue medication use requiring 4 or more puffs/day above the mean baseline value for any 2 consecutive days in the prior week, or ≥ 12 puffs on any 1 day in the week prior to the clinical visit
- Clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment

The Investigator should decide, depending on the reason for not reducing the OCS dose per schedule, whether to maintain or increase his/her current OCS dose by 1 step.

Maintenance Phase

Patients will be maintained for the last 4 weeks of the Randomized Treatment period on the same OCS dose established at Week 20; however, the Investigator should decide whether to maintain or increase the current OCS dose by 1 step based on the OCS reduction phase interruption criteria.

Oral Corticosteroid Dose after an Asthma Exacerbation

If a severe asthma exacerbation occurs during the Reduction or Maintenance phase of the Randomized Treatment period, the exacerbation should be treated (see [Section 8.2.5](#) for treatment of severe asthma exacerbations). Following resolution, the patient should be placed on the OCS dose 1 step higher than that which he/she was on when the exacerbation occurred for at least

4 weeks and continue with dose reductions as per [Table 2](#) at the following visit. If a second exacerbation occurs, the OCS dose should be increased 1 step; however, no further OCS dose reductions will be allowed.

8.2.3 Posttreatment/Follow-up Period

During this follow-up period, patients will continue treatment with their stable dose of OCS. The dose of OCS can be modified based on their level of asthma control, as determined by the Investigator.

8.2.4 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.

8.2.5 Treatment of severe asthma exacerbations

Severe asthma exacerbations will be treated with the use of oral or parenteral corticosteroids at a dose at least equivalent to double the dose of current maintenance dose of OCS for a minimum of 3 days to a maximum of 7 days, this is to ensure that exacerbations are managed in a timely manner and consistently, when possible, for all patients participating in this study. If the exacerbation is not resolved after 7 days, the treatment of the exacerbation may continue at the discretion of the Investigator.

8.2.6 Treatment after the end of the study

The Investigator is responsible for ensuring that consideration has been given to the post study care of the patient's medical condition.

Patients who complete the 24-week treatment period, and return for the EOT visit at Week 24, may be eligible to roll over into a long-term study.

At the end of the study, patients who do not roll over into a long-term study may be prescribed appropriate alternative asthma therapy if needed and as determined by the study Investigator.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched 2 mL prefilled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab or placebo) glass prefilled syringe will be prepared such that the treatments (dupilumab or placebo) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Both the patient and the Investigator will be blinded to the assigned active drug or placebo. 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](#).

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 IMP because these values have the potential for unblinding. Furthermore, neither patients, investigators, nor site personnel will have access to eotaxin-3, antigen-specific IgE, thymus and activation-regulated chemokine (TARC), or periostin while the study is ongoing or upon study completion, as the related data are not essential for patient care and have the potential for unblinding.

The DMC will receive blinded results 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.

8.3.2 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.

Patient withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the emergency unblinding transaction is performed by the Investigator (ie, at the site level), then the patient 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 patient will not be withdrawn from treatment. At the facilities where the systemic drug concentration measurements, ADA, 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.

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 any exclusion criteria may be rescreened once during the open enrollment of the study. A different patient identification will be issued for these patients. Rescreening is not permitted if the patient fails to meet all inclusion criteria. There is no requirement for a waiting period between the screen-failure date and the rescreening date. The IVRS/IWRS report will flag rescreened patients. Patients that are rescreened must 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 IVRS/IWRS that will be available 24 hours a day.

Patients will be randomized using a 1:1 randomization ratio for dupilumab 300 mg q2w and placebo q2w. Randomization will be stratified by the optimized OCS dose (≤ 10 mg/day and >10 mg/day) at Week 0 and country.

Recruitment of patients whose eosinophil level is <150 cells/ μL will stop when approximately 46 (25% of the total sample size) of such patients are randomized. Recruitment will continue with patients whose eosinophil level is ≥ 150 cells/ μL until reaching the total sample size of 180. In addition, the number of patients receiving 5 mg OCS at Visit 3 will be limited to approximately 54 patients (approximately 30% of the study population).

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 1 glass prefilled syringe packed in a patient kit box. Both glass prefilled 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), 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 patient 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, 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 accountability include:

- Proper recording of treatment kit number as required on the 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 provides this information in the treatment log.
- Patients will record IMP dosing self-administered through the use of a Home Dosing Diary. Site personnel will review the diary at each clinic visit and follow up with the patient accordingly.
- Prednisone/prednisolone use will be captured on a daily basis by the patient (or caregiver) through the use of a daily eDiary. The Investigator or designee will review the eDiary at each clinic visit and follow up with the patient accordingly.

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.

Prednisone/prednisolone, tracking and reconciliation has to be completed by the Investigator or designee according to the system proposed by the Sponsor.

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 sharps container by the patients and be returned to sites for destroy. A detailed treatment log of the returned 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.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). All concomitant medications taken during the study will be recorded in the eCRF, including the drug name and the dates of administration.

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

- Anti-immunoglobulin E (IgE) therapy (eg, omalizumab)
- Other biologic therapies such as mepolizumab, benralizumab, anti-TNF, anti-IL-17, or other intravenous Ig therapies
- Systemic immunosuppressant
- Bronchial thermoplasty
- Beta-adrenergic receptor blockers (beta-blockers)
- Investigational drugs
- Live/attenuated vaccines: refer to [Appendix B](#)
- 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.

Of note, the following medications will be permitted during the study

- Antihistamines
- Ocular, topical, or intranasal corticosteroids
- Continuous positive airway pressure for the treatment of obstructive sleep apnea, if initiated prior to the Screening visit.

Cytochrome P450 substrates:

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized. However, IL-4 was reported to upregulate CYP2E1, 2B6, 3A4 messenger ribonucleic acid (mRNA) expression or down regulate CYP1A2 mRNA in human hepatocyte or human peripheral blood mononuclear cell culture (11,12). Human peripheral blood mononuclear cells incubated with various Th-2 cytokines showed that IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (13). 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 (11,12,13). 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 efficacy endpoint

The primary efficacy endpoint for this study is the percentage reduction of OCS dose at Week 24 compared with the baseline dose, while maintaining asthma control. The percent reduction in OCS dose will be calculated as: $(\text{optimized OCS dose} - \text{final OCS dose at Week 24}) / \text{optimized OCS dose} \times 100$. A patient will be considered as having maintained asthma control between Week 20 and Week 24 if he/she does not have a clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment during this period. For those patients who experience an exacerbation, the final OCS dose will be considered to be 1 step higher than the dose they were receiving at the time of the exacerbation. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the Investigator will continue to prescribe OCS at the dose specified for OCS titration. The off-treatment OCS dose at Week 24 will be used in the primary analysis.

9.1.1.1 Oral corticosteroid dose adjustments

The dose adjustment of OCS through the OCS Reduction phase of the study will be based on the following:

- Asthma symptom data collected through the eDiary (ACQ-5 score)
- Clinically significant asthma exacerbation(s)
- Mean morning PEF <70% of baseline stability limit as assessed in the week prior to the clinical visit
- FEV₁ 20% reduction from baseline stability limit
- Rescue medication use requiring 4 or more puffs/day above the mean baseline value for any 2 consecutive days in the prior week, or ≥ 12 puffs on any 1 day in the week prior to the clinical visit
- Clinically significant event, based on Investigator judgment that requires treatment by OCS dose adjustment

The patient will complete the ACQ-5 on a weekly basis and record the score in the eDiary (starting with Visit 1 onwards). The Investigator will review the eDiary data on a weekly basis during the OCS Optimization phase and monthly during the Randomized Treatment period.

Daily OCS dose will be recorded using the eDiary.

9.2 ADDITIONAL EFFICACY ENDPOINTS

9.2.1 Secondary efficacy endpoints related to adjustments in oral corticosteroid dosing

The key secondary endpoint is:

- Proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24 while maintaining asthma control. The relative reduction for each patient will be calculated as (optimized OCS dose – final OCS dose at Week 24)/optimized OCS dose \times 100.

Other secondary efficacy endpoints include:

- Absolute reduction of OCS dose at Week 24 compared with the baseline dose while maintaining asthma control
- Proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24 while maintaining asthma control
- Proportion of patients no longer requiring OCS at Week 24 while maintaining asthma control
- Proportion of patients achieving their maximum possible reduction of OCS dose per protocol at Week 24 while maintaining asthma control.

9.2.2 Disease-specific efficacy measures

The following additional disease-specific efficacy endpoints will be evaluated:

Annualized rate of severe asthma exacerbation events (see [Section 9.2.2.1](#))

- Time to first severe asthma exacerbation event
- Change from baseline in pre-bronchodilator FEV₁ at Weeks 2, 4, 8, 12, 16, 20, and 24
- Percent change from baseline in pre-bronchodilator FEV₁ at Weeks 2, 4, 8, 12, 16, 20, and 24
- Change from baseline in other lung function measurements (percent predicted FEV₁, morning/evening PEF, forced vital capacity [FVC], forced expiratory flow from 25% to 75% of the vital capacity [FEF_{25-75%}]), at Weeks 2, 4, 8, 12, 16, 20, and 24
- Absolute change from baseline in post-bronchodilator FEV₁ at Weeks 12 and 24
- Change from baseline in ACQ-5 score at Weeks 2, 4, 8, 12, 16, 20, and 24
- Change from baseline in AQLQ score at Weeks 12, and 24
- Annualized rate of severe asthma exacerbations requiring hospitalization or ER visit
- Time to first severe asthma exacerbation requiring hospitalization or ER visit
- Change from baseline at Weeks 12 and 24 in:

- 22-item Sino Nasal Outcome Test (SNOT-22) in patients with bilateral nasal polyposis/chronic rhinosinusitis
- Hospital Anxiety and Depression Scale (HADS)
- EQ-5D-5L
- Change from baseline at Weeks 2, 4, 8, 12, 16, 20, and 24 in:
 - *Morning/evening asthma symptom score and nocturnal awakenings (eDiary)*
 - Use of rescue medication
 - Health Care Resource Utilization
- Change from baseline in airway hyperresponsiveness at Week 24 (for select study sites in Canada)

9.2.2.1 Severe asthma exacerbation events

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

- Use of systemic corticosteroids for ≥ 3 days (at least double the dose currently used); and/or
- Hospitalization because of asthma symptoms or emergency room visit because of asthma requiring intervention with additional systemic corticosteroid treatment

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

The period of time for which severe asthma exacerbation information will be included in the endpoint analysis will be from randomization until the Week 24 visit.

For safety reasons, alerts will be programmed into the eDiary that will notify both the patient and the site to monitor the clinical situation closely in case the patient's asthma worsens. However, an alert in itself will not be classified as a clinically significant asthma exacerbation.

The reasons (eg, infections including viral and bacterial, allergen exposure, exercise, or others) of the severe asthma exacerbation events will be collected on the eCRF.

9.2.2.2 Spirometry

The following parameters will be measured using spirometry: FEV₁ (pre- and post-bronchodilator), percent predicted FEV₁, FVC, and FEF_{25-75%}.

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 (3). For pre-bronchodilator measured parameters, including FEV₁, FVC, and FEF_{25-75%}, spirometry will be performed after 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 and withholding the last dose of LAMA for at least 24 hours.

For post-bronchodilator FEV₁, the measure should follow the steps described for reversibility validation.

At all visits, spirometry should be performed in the morning if possible, but if the test can only be done at a different time of the day, the testing 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. Please refer to the Operational Manual for additional information.

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

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

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

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

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

Reversibility/post-bronchodilator FEV₁

Reversibility, which is defined as an increase in absolute FEV₁ of 12% over the baseline value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of bronchodilator administration.

A reversibility test will be administered (if not done and documented within 12 months of Visit 1) following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Patients will receive 2 to up to 4 puffs of albuterol/salbutamol. Alternatively, and only if it is consistent, with usual office practice (to be documented),

reversibility may be performed using inhalation of nebulized albuterol/salbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator.

If the patient does not meet the reversibility at Visit 1, 2 additional assessments can be performed at any time (ie, unscheduled visits) prior to randomization (Visit 3).

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

9.2.2.3 *Electronic diary/peak expiratory flow 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
- Record daily prednisone/prednisolone usage
- Indicate the number of puffs/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
- Record the use of daily controller medications
- Record the number of nocturnal awakenings due to asthma symptoms
- Record oral steroids use for asthma exacerbation event

At Screening (Visit 1), patients will be issued an eDiary/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:

- Morning PEF performed within 15 minutes after arising (between 5:30 AM and 10 AM) prior to taking any albuterol or levalbuterol
- Evening PEF performed in the evening (between 5:30 PM and 10 PM) prior to taking any albuterol or levalbuterol
- 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 morning PEF will be the mean AM measurement recorded for the 7 days prior to randomization, and baseline evening PEF will be the mean PM measurement recorded for the 7 days prior to randomization. Period stability limit is defined as the respective mean morning or evening 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. Please refer to the Operational Manual for additional information.

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

9.2.2.4 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. During the OCS Optimization period, the ACQ-5 will be completed weekly in the patient's eDiary. During the treatment period, the ACQ-7 will be performed at clinic visits and the ACQ-5 will be completed on a weekly basis for those weeks that the patient does not have a scheduled clinic visit.

9.2.2.4.1 Asthma Control Questionnaire-5 question version

The ACQ-5 is a 5-item questionnaire, which has been developed as a measure of patients' asthma control that can be quickly and easily completed in clinical practice (14). The questions are designed to be self-completed by the patient. The 5 questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, shortness of breath, and wheezing). The response options for all these questions consist of a 0 (no impairment/limitation) to 6 (total impairment/ limitation) scale (Appendix D). The ACQ-5 score is a mean of the values recorded for the individual questions.

Throughout the study patients should complete the ACQ-5 on a weekly basis using their eDiary. The results from the ACQ-5 will be used as a part of the assessment to determine patient eligibility for OCS dose adjustment. The patient should complete the questionnaire within the eDiary. The patient should be instructed to complete the questions as accurately as possible. The patient should be reassured that there are no right or wrong answers. If the patient requests help or clarification with any of the questions, he/she will be asked to reread the instructions and give the answer that best reflects how he/she felt over the previous week. The Investigator should not provide the patient with any answer or attempt to interpret any portion of a question.

If the ACQ-5 is completed through the eDiary while the patient is at a scheduled in-clinic visit, it is recommended that the ACQ-5 be administered at the same time during the visit. To avoid biasing responses, the patients should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed before any procedures are performed on the patient to avoid influencing the patient's response. Adequate time should be allowed to complete all items on the ACQ-5.

9.2.2.4.2 Asthma Control Questionnaire-7 question version

The ACQ-7 consists of 7 questions. The first 5 questions 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. FEV₁ (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; Appendix E).

Clinic staff scores the FEV₁% 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 (14).

9.2.2.5 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 each visit.

9.2.2.6 Airway hyperresponsiveness (optional; only for patients enrolled in select sites in Canada)

Airway hyperresponsiveness will be assessed through a bronchial provocation test using methacholine (to be done only if the patient's FEV₁ is $\geq 70\%$ of predicted). A 20% decrease in the FEV₁ will be considered as a positive test and the PC₂₀ of agonist to cause this decrease is calculated by interpolation from the dose-response curve.

9.2.3 Safety and tolerability endpoints

The same safety assessments will be applied across both arms. Adverse events, including serious adverse events (SAEs) and AEs 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. To assure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in [Section 6.4.1](#).

Safety observations

- The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow up the outcome of SAEs /AESI until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor.

- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- In case of any SAE/AESI with immediate notification brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor.

9.2.3.1 Adverse events

Adverse events for each patient will be monitored and documented from the time the patient gives informed consent at Visit 1 until the End-of-Study visit (Visit 14) or until the rollover to a long-term study, except for:

- Serious AEs
- Adverse events that are ongoing at database lock

Adverse events, AESI, and SAEs will be reported as described in [Section 10.4](#).

9.2.3.2 Vital signs

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 every visit. Height (cm) will be measured at the Screening visit (Visit 1) only.

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.

Refer to [Section 1.1](#) for the schedule of vital signs performed throughout this study.

9.2.3.3 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.

Refer to [Section 1.1](#) for the schedule of physical examinations performed throughout this study.

9.2.3.4 ECG

One recording of a standard 12-lead electrocardiogram (ECG) will be performed centrally. Refer to [Section 1.1](#) for the schedule of ECGs performed throughout this study. At the post-randomization visits in which an ECG is scheduled, the ECG will be performed prior to investigational product administration.

All measurements will be made from a single lead: lead II, lead I (if lead II is not possible), or lead V5 (if leads II and I are not possible). 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.

Please refer to the Operational Manual for additional information.

The ECGs will be manually read at a central reading vendor.

9.2.3.5 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 must be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of the persistent abnormality is determined.

Refer to [Section 1.1](#) for the description of the clinical laboratory evaluations and the schedule of laboratory evaluations performed throughout this study.

The clinical laboratory parameters that will be measured are:

- Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with 5-part differential count, and total red blood cell count.
- Serum chemistry: To include creatinine, blood urea nitrogen, glucose, hemoglobin A1c (HbA1c), 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 (ALT), AST, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. At Visits 3 (randomization), 8, and 11, the blood sample should 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 a light meal and the site should document that the serum chemistry was not obtained under fasting conditions.
- Urine dipstick analysis: To include specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- Serum immunoglobulins: quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and IgA (after the first administration of IMP, results are blinded to the sites and sponsor study team).

- Clinical laboratory testing at Visit 1 and Visit 10 adds hepatitis screen including HBsAg, HBsAb, IgM and IgG/total-HBcAb, HCVAb, HIV screening (anti-HIV-1 and anti-HIV-2 antibodies), and anti-nuclear antibody (ANA). Note: anti-double-stranded DNA antibody will be tested if ANA is positive ($\geq 1:160$ titer). Patients who are IgG/total-HBcAb positive and HBsAg negative at Visit 1 must undergo HBV DNA testing prior to randomization to determine eligibility (only applicable for patients who plan to roll over into a long term study). In case of results showing HCVAb positive, HCV RNA testing must be negative prior to randomization.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix F](#).

9.2.3.6 Pregnancy test

A serum pregnancy test (β -human chorionic gonadotropin) will be performed at Screening (Visit 1) in women of childbearing potential, and a urine dipstick pregnancy test will be performed at Visit 3 prior to randomization and other visits prior to investigational product administration. A negative result must be obtained at Visits 1 and 3 prior to randomization.

Refer to [Section 1.1](#) for the schedule of pregnancy test performed throughout this study.

9.2.4 Patient Reported Outcomes (Health-related Quality of Life/health economic variables/other endpoints)

Patients should complete PROs before undergoing spirometry testing.

9.2.4.1 Asthma Quality of Life Questionnaire

The AQLQ was designed as a self-administered PRO to measure the functional impairments that are most troublesome to patients as a result of their asthma (see [Appendix G](#)). The instrument is comprised of 32 items, each rated on a 7-point Likert scale (from 1 to 7). The AQLQ 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 the AQLQ is 0.5 (15).

9.2.4.2 SNOT-22

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on health related quality of life (see [Appendix H](#)). The SNOT-22 has 22 items, 5 domains and a global score. The 5 domains include:

- Nasal (range 0-30) with a MCID of -2.5
- Ear (range 0-15) with a MCID of -1.25
- Sleep (0-20) with a MCID of -1.67
- General and practical (0-30) with a MCID of -2.50
- Emotional (0-15) with a MCID of -1.25.

The range of the global score is 0-110 and an MCID of 8.9 ([16](#)). Lower scores indicate less impact. The recall period of the assessment is within the past 2 weeks.

9.2.4.3 Hospital Anxiety and Depression Scale

The HADS is a general scale used to detect states of anxiety and depression and has been validated in patients with asthma (see [Appendix I](#)). The instrument is comprised of 14 items: 7 items each related to anxiety and depression. Each item on the questionnaire is scored from 0-3; with a score for either anxiety or depression ranging between 0 and 21.

The minimal important difference for the HADS-A (anxiety) has been reported to be in the range of 0.41 (anxious and depressed patients in active treatment controlled studies) to 1.32 (COPD patients), in the range of 0.50 (anxious and depressed patients 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 ([17,18](#)).

Alternatively, a significant improvement in treatment versus placebo group was defined as the percentage of patients who moved from a defined category of moderate to severe depression or anxiety (≥ 8) to not having the disease (< 8) ([19](#)). 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” ([20](#)).

9.2.4.4 EQ-5D-5L

The 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 ([21](#)). The 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 visual analogue scale (VAS; see [Appendix J](#)). 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 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 0.001 to 0.074 (22,23).

9.2.4.5 Asthma symptom score

Patients will record overall symptom scores in an eDiary twice a day prior to measuring their PEF. Symptoms experienced during the night will be recorded upon arising (AM symptom score). 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. Scores can 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 will be used.

9.2.5 Systemic drug concentration and anti-drug antibodies

9.2.5.1 Sampling time

Blood samples of serum functional dupilumab and anti-dupilumab antibodies will be collected as designated in the study flow chart (Section 1.1). Patients who discontinue early from treatment or patients who choose not to roll over into a long-term study may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall clinical presentation at that time.

In the event of an SAE or any AESI of anaphylaxis or systemic allergic reaction related to IMP and requiring 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

- 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).
- Indeterminate Response- defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
- Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

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

9.2.5.2 Handling procedures

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

Table 3 - Summary of handling procedures for dupilumab

Sample type	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Blood sample volume	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

9.2.5.3 Bioanalytic method

Serum PK and ADA samples will be assayed using validated methods as described in [Table 4](#).

Table 4 Summary of bioanalytical methods for dupilumab and anti-dupilumab antibody

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

ELISA=enzyme-linked immunosorbent assay.

9.2.6 Pharmacodynamics

Pharmacodynamics is an exploratory endpoint.

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 2 prior asthma trials (ACT11457 and DRI12544), 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 FeNO (a marker of airway inflammation). Periostin (a protein reported to be elevated at baseline in patients responsive to treatment with anti-IL-13 antibodies) is included to differentiate dupilumab from the anti-IL-13 therapeutic class.

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.

9.2.6.1 Whole blood biomarkers

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

9.2.6.2 Plasma biomarkers

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

9.2.6.3 Serum biomarkers

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.

A validated immunoassay will be used to quantify levels of TARC and periostin.

9.2.6.4 Fractional exhaled nitric oxide

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

9.2.6.5 ILC2 and CD34 cells and cytokines in sputum and blood (optional; only for patients enrolled in select sites in Canada)

Innate lymphoid type 2 cells (ILC2) secrete IL-5 and IL-13, and to a lesser extent IL-4, when stimulated by several factors released from inflamed respiratory epithelium such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) and are thought to have a pivotal role in perpetuating asthma. CD34+ eosinophil progenitor cells are known to be elevated in the sputum of patients with asthma and may participate in asthmatic inflammation. To assess the effect of IL-4R blockade on the trafficking of ILC2 and CD34+ cells into the airway, these cells will be measured in the blood and induced sputum using flow cytometry. Cytokines will be assayed in the sputum and blood using immunoassays.

Please refer to the Operational Manual for additional information regarding sputum and blood collection.

9.2.7 Pharmacogenetic assessment

Pharmacogenetic testing is optional and voluntary.

For those patients who sign 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 up to 15 years after completion of the final report of the main clinical trial or as appropriate according to local regulations. Specific procedures for collection, storage, and shipping of pharmacogenetic samples will be provided in a lab manual.

The 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 whole genome array (common single nucleotide polymorphisms) 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 polymerase chain reaction (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 Patient ID. This “double coding” is performed to separate a patient’s medical information and DNA data.

The clinical study data (coded by Patient 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 Patient 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 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 patients who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes (excluding genetic analysis, patient to sign additional consent per [Section 9.2.6](#)). For patients 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 with clot activator (or into smaller tubes of equivalent total volume) kept at room temperature for 30 minutes and then centrifuged at approximately $1500 \times g$ 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 labeled with the same identifiers as the ones used during the study (ie, patient 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 patient confidentiality and personal data (see [Section 14.3](#) and [Section 14.5](#)).

9.4 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 study consists of 3 periods:

1. Screening and OCS Optimization Period (from 3 to up to 8 weeks for those patients who experience an asthma exacerbation that requires a change in OCS dose this period can be extended to 10 weeks to allow for 2 weeks of stabilization prior to randomization; Visits 1 and 2)
2. Treatment Period (24 weeks): includes the randomization visit (Visit 3) and a 4-week induction phase (Visits 4 and 5), a 16-week OCS reduction phase (Visits 6-10), and a 4-week maintenance phase (Visit 11)
3. Post-treatment Period (12 weeks; Visits 12-14)

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

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and participate in follow-up assessments according to the visit schedule. Under exceptional circumstances when a patient cannot come to the site for the scheduled visit/s, a phone contact can be made after sponsor approval is given. During the phone contact information about AEs, concomitant medications and exacerbation events should be collected.

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

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) must be signed and dated.

Although the screening assessments for this study are grouped under the heading of 2 visits in this protocol, it is possible for them to be performed over more than the 2 scheduled site visits if necessary, as long as the screening 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 prior to Day 1. 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 rescreened must sign a new

consent form and 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 who fail the Screening Visit because of eDiary/spirometry equipment malfunction, or patient-related/site personnel-related unintentional errors may be rescreened 1 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.

All clinical assessments and blood samples should be performed/collected prior to the administration of the IMP, unless otherwise specified.

For patients at select sites in Canada who have agreed to participate in the optional assessment, a sputum sample will be collected at the time of an asthma exacerbation during an unscheduled visit.

10.1.1 Screening and Oral Corticosteroid Optimization Period

Patients who meet eligibility criteria at the Screening visit (Visit 1) will enter the OCS Optimization phase. The Screening/OCS Optimization Period will be from 3 to up to 8 weeks (if an asthma exacerbation occurs that requires a change in OCS dose this period can be extended to 10 weeks to allow for 2 weeks of stabilization prior to randomization) in duration, dependent upon the length of time the patient requires to optimize their OCS dose.

Prednisone or prednisolone will be used as the OCS. At the Screening visit, patients currently using other forms of maintenance OCS must have their corticosteroids switched to the corresponding equivalent daily dose of prednisone/prednisolone.

Follow up visits/phone calls may be added during this period depending on the patient's response to OCS dose changes.

10.1.1.1 Visit 1 (Week -8 to -3)

Following a discussion of participation in the clinical trial, informed consent must be obtained and documented. These steps precede any study procedures. In patients who experience an asthma exacerbation during the OCS Optimization phase, this visit may occur at Week -9 or -10.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number and register screening visit
- Interview to collect patient demographic information including gender, ethnic origin, race, date of birth, height, weight, and body mass index (BMI).
- Collect other medical history and surgical history, and prior and concomitant medications

- Medical history will include smoking status; history of diabetes, hypertension, sinusitis, polyposis, osteoporosis, cataracts, aspirin sensitivity, previous intubations, asthma exacerbations in the previous years, gastrointestinal bleeding, myopathy, signs of adrenal insufficiency/crisis, and susceptibility to infections; and triggers of worsening asthma.
- Therapy history should include current treatments for asthma including the duration of prior use of maintenance OCS for the treatment of asthma, coursed of rescue corticosteroid (oral or parenteral).
- Review entry criteria to assess eligibility, with special attention to verify the following:
 - Patients must be on a stable dose high-dose ICS (fluticasone propionate >500 µg total daily or equipotent) plus a second controller (LABA, LTRA, etc.) for ≥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 should be on a well-documented, regular prescribed treatment of maintenance systemic corticosteroids in the 6 months prior to Visit 1 with a stable OCS dose for the 4 weeks prior to Visit 1. Patients must be taking 5-35 mg/day of prednisone or equivalent at Visit 1.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg], height [cm])
- Perform physical examination including an assessment for any clinically significant adverse effects associated with the use of maintenance OCS.
- Perform a nasal exam to check for the presence/absence of nasal polyps.
- Dispense eDiary and PEF meter, provide instructions for daily use, and remind patient to bring the eDiary to the next visit.
- Instruct the patient on how to complete the ACQ-5. The first ACQ-5 will be collected at Visit 1 and then weekly thereafter throughout the duration of the study.
- Administer the following PROs:
 - AQLQ
 - HADS
 - EQ-5D-5L
 - SNOT-22 (only for patients with bilateral nasal polypoid/chronic rhinosinusitis)
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour
- Perform spirometry

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

- Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Pre-bronchodilator FEV₁ must be <80% predicted normal for adults and ≤90% of predicted normal for adolescents.
- Establish reversibility
 - Reversibility must be at least 12% and 200 mL in FEV₁ after 200 µg to 400 µg (2 to 4 puffs of albuterol/salbutamol, or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol. (Note: This is only required if reversibility or airway responsiveness was not performed within 12 months prior to Visit 1.)
 - Three total attempts may be made during the Screening Period to meet the qualifying criteria for reversibility.
- Perform 12-lead ECG
- Perform chest X-ray or magnetic resonance imaging (MRI), as per local standard of care, if no chest imaging (X-ray, computed tomography [CT], MRI) is available from the previous year or if there is local requirement.
- Obtain blood samples for screening clinical laboratory determinations:

Hematology (see [Section 9.2.3.5](#) for details)

- Serum chemistry (see [Section 9.2.3.5](#) for details)
- Obtain blood samples for hepatitis screen (HBsAg, HBsAb, IgM and IgG/total-HBcAb, and HCVAb), HIV screen (anti-HIV-1 and anti-HIV-2 antibodies), and anti-nuclear antibody (ANA). Patients who are IgG/total-HBcAb positive and HBsAg negative at Visit 1 must undergo HBV DNA testing prior to randomization to determine eligibility (only applicable for patients who plan to roll over into a long term study). In case of results showing HCVAb positive, HCV RNA testing must be negative/not detected prior to randomization.
- Obtain blood sample for serum immunoglobulins (total IgG, IgM, and IgA)
- Perform parasitic screening if there is a clinical suspicion per Investigator judgment (to be done using local testing as per local guidelines).
- Obtain serum β-human chorionic gonadotropin (β-HCG) pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.

- Record any AEs/SAEs
- For those patients who were previously receiving an OCS other than prednisone or prednisolone, switch their OCS to the equivalent daily dose of prednisone/prednisolone (see [Appendix A](#)).
- Dispense salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.1.2 Visit 2 (Week -7 to -2)

Visit 2 will occur 1 week after Visit 1. Visit 2 will then occur over 2 weeks which are designated as Visit 2A (complete with all procedures), and 1 week later, Visit 2B (will consist of a review of the eDiary with the patient). For both Visit 2A and 2B, patients must report to the clinical site and will be instructed on completing the ACQ-5 which will be collected at both visits; however, all other procedures will be performed only at Visit 2A.

The following procedures will be performed during this visit:

- Complete and review the ACQ-5 – recommended to be completed at the visit, when possible, prior to other procedures being performed
- Review entry criteria to confirm continued eligibility
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning, if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.

- Establish reversibility (Note: This is only required if reversibility or airway responsiveness was not performed within 12 months prior to Visit 1 or established at Visit 1.)
 - Reversibility must be at least 12% and 200 mL in FEV₁ after 200 µg to 400 µg (2 to 4 puffs of albuterol/salbutamol or of a nebulized solution of albuterol/salbutamol), if considered as a standard office practice.
 - Three total attempts may be made during the Screening Period to meet the qualifying criteria for reversibility for those patients who do not have documented reversibility in the previous year.
- Record any AEs/SAEs
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Review ACQ-5 score and asthma exacerbations and determine appropriate OCS dose adjustment according to the schedule provided in [Table 1](#).
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.1.3 Weekly phone calls to optimize oral corticosteroid dose

Patients will continue to assess their ACQ-5 score on a weekly basis reducing their OCS dose in accordance with [Table 1](#) until they achieve their optimal OCS dose. The lowest effective OCS dose will be identified as the OCS dose that the patient was taking just before the ACQ 5 score increased by 0.5. Once the optimized dose is determined, the patient must be able to remain on the optimized prednisone/prednisolone dose, along with their baseline ICS plus second (or third) controller medication, for 2 consecutive weeks prior to randomization.

The following procedures will be performed during the weekly phone calls:

- Review ACQ-5 score and determine appropriate OCS dose adjustment according to the schedule provided in [Table 1](#).
- Review any asthma exacerbations that have occurred.
- Review compliance with OCS and controller medications.
- Record any AEs/SAEs that occurred during the previous week.

10.1.2 Randomized Treatment Period

10.1.2.1 Visit 3/Randomization (Week 0)

At Visit 3 (Week 0), patients who meet the entry and randomization eligibility criteria will be randomized in a 1:1 ratio to receive a 600 mg loading dose (2 injections of 300 mg) followed by 300 mg q2w of dupilumab or matching placebo, respectively.

During this visit, the following procedures will be performed **prior to randomization**:

- Review inclusion/exclusion criteria to confirm continued eligibility
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the following PROs:
 - ACQ-5
 - AQLQ
 - HADS
 - EQ-5D-5L
 - SNOT-22 (only for patients with bilateral nasal polyposis/chronic rhinosinusitis)
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning, if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Measure post-bronchodilatory FEV₁
- Perform 12-lead ECG
- Obtain (fasting) blood samples for the following:
 - Clinical laboratory determinations (hematology and serum chemistry)
 - Serum immunoglobulins (total IgG, IgM, and IgA)
 - Pharmacokinetic sample
 - ADA
 - Biomarkers

- Archival serum
- Pharmacogenetics (optional, for those patients who sign the Pharmacogenetic informed consent form) Perform urine dipstick pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Collect sputum and additional blood sample (only for those patients enrolled in the optional assessment at selected sites within Canada)
- Perform methacholine challenge (only for those patients enrolled in the optional assessment at selected sites within Canada if the patient's FEV₁ is $\geq 70\%$ predicted normal)
- Record any AEs/SAEs
- Record any concomitant medications
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit
- Review OCS reduction criteria (ACQ-5 score and asthma exacerbations) and determine optimized OCS dose at baseline
- Call IVRS/IWRS to register visit and to randomize the patient to IMP (dupilumab or placebo)

After randomization:

- Administer IMP SC (dupilumab 300 mg or placebo). Two injections of IMP will be administered. The patient or caregiver receives training on administering the second injection, if the patient or caregiver is willing to self-inject.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.2.2 Induction Phase (4 weeks)

The Induction Phase of the Randomized Treatment Period will consist of 4 weeks (V4 and V5). During this period, patients will remain on their optimized dose of OCS along with their baseline asthma medications and return to the clinic for 2 visits. Visit 5 is the end of the 4 week period. Patients will be assessed and, if determined appropriate, will begin OCS dose adjustment at visit 5.

10.1.2.2.1 Visit 4 (Week 2 ± 3 days)

The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the ACQ-7
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Record any AEs/SAEs
- Administer IMP SC (dupilumab 300 mg or placebo). For those patients or caregivers willing to perform self-injection, the patient or caregiver will perform the injection under the supervision of the investigator or designee.
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.2.2.2 Visit 5 (Week 4 ± 3 days)

The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the ACQ-7
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Obtain blood samples for the following:
 - Clinical laboratory determinations (hematology and serum chemistry)
 - Pharmacokinetic sample
 - Biomarkers
- Perform urine dipstick pregnancy test if female of childbearing potential
- Record any AEs/SAEs
- Review OCS reduction criteria (ACQ-5 score, asthma exacerbations, PEF, rescue medication use, and signs of adrenal insufficiency) and determine appropriate OCS dose adjustment according to the schedule provided in [Table 2](#).
- Administer IMP SC (dupilumab 300 mg or placebo). For those patients or caregivers willing to perform self-injection, the patient or caregiver will perform the injection under that supervision of the investigator or designee.
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.

- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.2.3 OCS Reduction Phase (16 weeks)

During the OCS Reduction Phase, patients will return to the clinic once every 4 weeks.

The OCS dose will be titrated during this phase following a predetermined schedule ([Table 2](#)) and based on the starting optimized OCS dose. Dose reductions should be attempted every 4 weeks. The last possible dose reduction can occur at Week 20 with no further dose adjustments beyond this time point.

During Weeks 10, 14, and 18, patients will self-administer the IMP. They do not need to return to the clinic during these weeks. Study personnel will follow-up with the patient with a phone call.

For patients, or those with caregivers, who are not comfortable with self-administering the IMP, they will return to the study clinic for these visits.

10.1.2.3.1 Visit 6 (Week 6 ± 3 days)

The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the ACQ-7
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Record any AEs/SAEs

- Administer IMP SC (dupilumab 300 mg or placebo). For those patients or caregivers willing to perform self-injection, the patient or caregiver will perform the injection under that supervision of the investigator or designee.
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.2.3.2 Visit 7 (Week 8 ± 3 days)

The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the ACQ-7
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Obtain blood samples for the following:
 - Clinical laboratory determinations (hematology and serum chemistry)
 - Pharmacokinetic sample

- Perform urine dipstick pregnancy test if female of childbearing potential
- Record any AEs/SAEs
- Review ACQ-5 score, if any asthma exacerbations occurred, morning PEF, use of rescue medications, and signs of adrenal insufficiency. Determine appropriate OCS dose adjustment according to the schedule provided in [Table 2](#).
- Administer IMP SC (dupilumab 300 mg or placebo). For those patients or caregivers willing to perform self-injection, the patient or caregiver will perform the injection under that supervision of the investigator or designee.
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Review/dispense Home Dosing Diary.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.2.3.3 Visit 8 (Week 12 ± 3 days)

The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the following PROs:
 - ACQ-7
 - AQLQ
 - HADS
 - EQ-5D-3L
 - SNOT-22 (only for patients with bilateral nasal polyposis/chronic rhinosinusitis)
- Complete the Health Resource Utilization questionnaire
- Measure FeNO

- Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Measure post-bronchodilatory FEV₁
- Perform 12-lead ECG
- Obtain fasting blood samples for the following:
 - Clinical laboratory determinations (hematology and serum chemistry)
 - Pharmacokinetic sample
 - Biomarkers
 - Serum immunoglobulins (total IgG, IgM, and IgA)
 - Archival serum
- Perform urine dipstick pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Record any AEs/SAEs
- Review ACQ-5 score, if any asthma exacerbations occurred, morning PEF, use of rescue medications, and signs of adrenal insufficiency. Determine appropriate OCS dose adjustment according to the schedule provided in [Table 2](#).
- Administer IMP SC (dupilumab 300 mg or placebo)
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Review and dispense the Home Dosing Diary
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.2.3.4 Visit 9 (Week 16 ± 3 days)

The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the ACQ-7
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Obtain blood samples for the following:
 - Clinical laboratory determinations (hematology and serum chemistry)
- Perform urine dipstick pregnancy test if female of childbearing potential
- Record any AEs/SAEs
- Review ACQ-5 score, if any asthma exacerbations occurred, morning PEF, use of rescue medications, and signs of adrenal insufficiency. Determine appropriate OCS dose adjustment according to the schedule provided in [Table 2](#).
- Administer IMP SC (dupilumab 300 mg or placebo)
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Review and dispense the Home Dosing Diary
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.2.3.5 Visit 10 (Week 20 ± 3 days)

Week 20 is the last week that the patient's OCS dose can be changed. The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the ACQ-7
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Obtain blood samples for the following:
 - Clinical laboratory determinations (hematology, serum chemistry)
 - For patients who plan to roll over into a long-term study, obtain blood samples for HIV screen (anti-HIV-1 and anti-HIV-2 antibodies), ANA, and hepatitis screen (HBsAg, HBsAb, IgM and IgG/total-HBcAb, HCVAb). Patients who are IgG/total-HBcAb positive and HBsAg negative must undergo HBV DNA testing prior to randomization to determine eligibility (only applicable for patients who plan to roll over into a long-term study). In case of results showing HCVAb positive, HCV RNA testing must be "not detected" prior to randomization.
 - Biomarkers

- Perform chest x-ray or MRI if chest imaging (x-ray, CT, MRI) is over 1 year from entry into a long-term study as per local standard of care or if there is local requirement (only applicable for patients who plan to roll over into a long-term study)
- Perform urine dipstick pregnancy test if female of childbearing potential
- Record any AEs/SAEs
- Review ACQ-5 score, if any asthma exacerbations occurred, morning PEF, use of rescue medications, and signs of adrenal insufficiency. Determine appropriate OCS dose adjustment according to the schedule provided in [Table 2](#).
- Administer IMP SC (dupilumab 300 mg or placebo)
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Review/dispense Home Dosing Diary
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.2.4 Maintenance Phase

The Maintenance Phase consists of 4 weeks. During this phase, patients will be maintained on the same OCS dose established at Week 20.

During Week 22, patients do not need to return to the clinic and can self-administer the IMP.

10.1.2.4.1 Visit 11 (Week 24 ± 3 days; end-of-treatment visit)

The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Perform physical examination
- Administer the following PROs:

- ACQ-7
- AQLQ
- HADS
- EQ-5D-5L
- SNOT-22 (only for patients with bilateral nasal polyposis/chronic rhinosinusitis)
- Complete the Health Resource Utilization questionnaire
- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Measure post-bronchodilator FEV₁
- Perform 12-lead ECG
- Obtain fasting blood samples for the following:
 - Clinical laboratory determinations (hematology and serum chemistry)
 - Pharmacokinetic sample
 - ADA sample
 - Biomarkers
 - Serum immunoglobulins (total IgG, IgM, and IgA)
 - Archival serum
- Perform urine dipstick pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Collect sputum and additional blood sample (only for those patients enrolled in the optional assessment at selected sites within Canada)
- Perform methacholine challenge (only for those patients enrolled in the optional assessment at selected sites within Canada, if the patient's FEV₁ is $\geq 70\%$ predicted normal)
- Record any AEs/SAEs

- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Review ACQ-5 score, if any asthma exacerbations occurred, morning PEF, use of rescue medications, and signs of adrenal insufficiency and document the final OCS dose that the patient is receiving.
- Review Home Dosing Diary
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.3 Post-treatment Period

After completing the treatment period, patients will be evaluated for 12 weeks in the Post-treatment Period. During this follow-up period, patients will continue treatment with their stable dose of controller medication that can be modified based on their level of asthma control, as determined by the Investigator.

Eligible patients completing the treatment period will be offered the opportunity to roll over into a long-term study with dupilumab. Patients subsequently enrolled in this long-term study will not participate in the off-treatment safety phase of this trial.

Patients who discontinue early from treatment or patients who choose not to roll over into a long-term 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 clinical presentation.

10.1.3.1 Visits 12 and 13 (Week 28 ± 3 days and Week 32 ± 3 days, respectively)

The following procedures will be performed during each of these visits:

- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the ACQ-7
- Complete the Health Resource Utilization questionnaire
- Measure FeNO

- Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Record any AEs/SAEs
- Download electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their controller medication (including OCS and ICS in combination with 1 or 2 other controllers) and instruct patient to record daily usage in the electronic diary.
- Remind patient to 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 and withholding the last dose of LAMA for at least 24 hours prior to next visit.

10.1.3.2 Visit 14 (Week 36 \pm 3 days; end-of-study visit)

The following procedures will be performed during this visit:

- Call IVRS/IWRS to register visit
- Collect concomitant medications
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg])
- Administer the following PROs:
 - ACQ-7
 - AQLQ
 - HADS
 - EQ-5D-5L
 - SNOT-22 (only for patients with bilateral nasal polyposis/chronic rhinosinusitis)
- Complete the Health Resource Utilization questionnaire

- Measure FeNO
 - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥ 1 hour
- Perform spirometry
 - Spirometry will be performed in the morning if possible, but if the testing can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study, after 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 and withholding the last dose of LAMA for at least 24 hours.
- Measure post-bronchodilator FEV₁
- Perform 12-lead ECG
- Obtain blood samples for the following:
 - Clinical laboratory determinations (hematology and serum chemistry)
 - Pharmacokinetic sample
 - ADA
 - Serum immunoglobulins (total IgG, IgM, and IgA)
- Perform urine dipstick pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Collect sputum sample (only for those patients enrolled in the optional assessment at selected sites within Canada)
- Record any AEs/SAEs
- Download and collect the eDiary.

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, patient electronic diary/PEF meter, and the Home Dosing Diary 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 eCRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal products

Temporary treatment discontinuation may be considered by the Investigator because of AEs. Re-initiation of treatment with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the AE is sufficiently resolved and unlikely to recur after resuming therapy with IMP.

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

- Infections or infestations that do not respond to medical treatment.
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per [Appendix F](#).

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 e-CRF.

Patients must be withdrawn from treatment (ie, from any further investigational treatment) 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 breaking requested by the Investigator will lead to permanent treatment discontinuation.
- Pregnancy
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection, such as tuberculosis or other infections whose nature or course may suggest an immunocompromised status ([Appendix L](#)).
- Serum ALT >3 ULN and total bilirubin > 2ULN ([Appendix F](#)).
- Serum ALT > 5 ULN if baseline ALT < 2 ULN, or ALT >8 ULN if baseline ALT > 2 ULN ([Appendix F](#)).

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. Study investigators should continue OCS dose adjustment after treatment discontinuation, as guided by their medical judgment, including up-titration and down-titration in accordance with [Table 2](#) (Titration schedule for oral corticosteroids during the OCS Reduction Phase of the Randomized Period).

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

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

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for remaining study visits and participate in follow-up assessments according to the visit schedule.

Under exceptional circumstances when a patient cannot come to the site for the scheduled visit/s, a phone contact can be made after sponsor approval is given. During the phone contact information about AEs, concomitant medications and exacerbation events should be collected.

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. All study withdrawals should be recorded by the investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

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 patient should only be designated as lost to follow-up if the site is unable to establish contact with the patient 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.

Asthma exacerbations should only be reported as AEs if 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 K](#) for the 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 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × 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 10.4.2](#), 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 K](#) for the definition of anaphylaxis)
- Severe injection site reactions that last longer than 24 hours
- Any infection meeting at least 1 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 ([Appendix L](#))

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

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

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Not applicable.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- Protocol defined asthma exacerbation events are collected as efficacy endpoints via the asthma exacerbation form. These events should not be reported as AEs unless they fulfill a seriousness criterion.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s). In studies that require the use of combined/multiple IMPs/NIMPs, the GSO with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. The GSO must communicate this decision to the study team for inclusion in the protocol and AE CRF.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected. The duration of poststudy follow-up and reporting of AEs will be specified (eg, until recovery).

- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
 - Symptomatic and/or
 - Requiring either corrective treatment or consultation, and/or
 - Leading to IMP discontinuation or modification of dosing, and/or
 - Fulfilling a seriousness criterion, and/or
 - Defined as an AESI

Table 5 summarizes the reporting timelines for select AEs and laboratory abnormalities.

Table 5 Summary of adverse event reporting instructions

Adverse event/laboratory abnormality		Reporting timeframe
Serious adverse event		Within 24 hours
Pregnancy		Within 24 hours
Overdose	Symptomatic	Within 24 hours
	Asymptomatic	Routine
ALT elevation	ALT >5 ULN if baseline ALT is ≤2 ULN	Within 24 hours
	ALT >8 ULN if baseline ALT is >2 ULN	Within 24 hours
Anaphylactic 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

ALT=alanine aminotransaminase; ULN=upper limit of normal.

10.4.4 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

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

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix F](#).

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

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, Institutional Ethics Committees (IECs)/Institutional Review Boards (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 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 immunologically-mediated responses to a pharmaceutical and/or formulation agent in a sensitized person. Signs and symptoms are often experienced during or shortly after therapeutic administration. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Refer to [Appendix K](#) "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 at least 30 minutes after administration.

Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment must be reported as an adverse event of special interest (AESI) (within 24 hours; for further details, see AESI definition in [Section 10.4.1.3](#) and [Appendix K](#)) 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 SC 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-4R α , 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.

[Section 10.4.1.3](#) defines infections that should be reported as AESIs (ie, within 24 hours).

A complete diagnostic work-up should be performed (ie, 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 (Appendix L), patients must be permanently discontinued from study medication.

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.

10.6.4 Elevated liver function tests

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

In order to closely follow potential liver function abnormalities, assessment of total protein, albumin, total bilirubin, ALT, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing. Clinical laboratory testing at Visit 1 and Visit 10 (only applicable for patients who planned to roll over into a long-term study) adds hepatitis screen (HBsAg, HBsAb, IgM and IgG/total-HBcAb, and HCVAb). Patients who are IgG/total-HBcAb positive and HBsAg negative at Visit 1 or Visit 10 must undergo HBV DNA testing prior to randomization to determine eligibility (only applicable for patients who plan to roll over into a long-term study). Furthermore, it is recommended that patients who are receiving potentially immunosuppressive therapy and are IgG HBcAb positive and HBV DNA negative undergo surveillance HBV DNA studies every 1 to 3 months depending upon the individual potential therapeutic risk and comorbidities. If necessary, a hepatologist should be consulted on a case-by-case basis.

Hepatitis virus tests and liver function tests (LFTs) 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 ([Section 7.2](#) and [Section 9.2.3.5](#)).

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 nonconjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing ([Section 9.2.3.5](#)).

Guidance for the investigation of elevated LFTs is provided in [Appendix F](#).

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 estimation is based on the comparison between dupilumab doses versus placebo with regard to the primary endpoint and the key secondary endpoint: percentage reduction of OCS dose at Week 24 compared with the baseline dose and proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24, while maintaining asthma control. For the primary endpoint, assuming a common standard deviation of 50%, with 90 randomized patients per group, the study will have 94% power to detect a treatment difference of 27% (24) at the 2-tailed significance level of $\alpha=0.05$. For the key secondary endpoint, with the same sample size of 90 randomized patients per group, the study will have 81% power to detect a difference in the proportion of patients achieving 50% or greater in their OCS dose of 33% in the placebo group, compared to 54% in the dupilumab group (22), at the 2-tailed significance level of $\alpha=0.05$. Calculations were made using nQuery Advisor 7.0.

Patients will be randomized using a 1:1 randomization ratio for dupilumab 300mg q2w and placebo. Randomization will be stratified by optimized OCS dose at Week 0 (≤ 10 mg/day, >10 mg/day) and country.

Recruitment of patients whose eosinophil level is below 150 cells/ μ L will stop when approximately 46 (25% of the total sample size) of such patients are randomized. Recruitment will continue with patients whose eosinophil level is greater than or equal to 150 cells/ μ L until reaching the total sample size of 180. In addition, the number of patients receiving 5 mg OCS at Visit 3 will be limited to approximately 54 patients (approximately 30% of the study population).

11.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all patients with a treatment kit number allocated and recorded in the IVRS database, 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.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The population considered for the efficacy analysis will be the ITT population.

11.3.1.1 Intent-to-treat population

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

11.3.2 Safety population

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 patients actually received.

The treatment-emergent period for the safety population is defined as the time between the first administration of study medication to the end of the Post-treatment period (12 weeks after the end of study treatment) or until the patient rolls over into a long-term 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.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be the dupilumab group.

11.3.3 Systemic drug concentration population

The systemic drug concentration population will consist of all patients in the safety population with at least 1 evaluable functional dupilumab concentration result. Patients will be analyzed according to the treatment they actually received.

11.3.4 Anti-drug antibody population

The ADA population will consist of all patients in the safety population who had at least 1 reportable ADA result (either “ADA negative” or “ADA positive”) after the first dose of the study treatment.

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

Compliance with the IMP will be summarized in the following manner.

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

The percentage of compliance for a patient will be defined as the number of administrations the patient was compliant divided by the total number of administrations the patient was planned to take during the treatment period (ie, from the 1st to the last administration).

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, mean, standard deviation [SD], median, minimum, and maximum). The percentage of patients with a compliance <80% will be summarized. In addition, the number and percentage of patients with at least 1 dose greater than the planned dosing administration will be provided, as well as the number and percentage of patients with 0, (0, 20%), and >20% under-planned dosing administrations.

Compliance to OCS and controller medications will be summarized separately and will be specified in the SAP.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint

The outcome of the percentage reduction of OCS dose at Week 24 compared with the baseline dose, while maintaining asthma control, will be calculated as (optimized OCS dose at baseline – final OCS dose at Week 24)/optimized OCS dose at baseline × 100%.

The percentage reduction will be analyzed using an analysis of covariance (ANCOVA) model. The model will include the percentage reduction of OCS dose at Week 24 as the response variable, and the treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (<150 cells/μL, ≥150 cells/μL) as covariates. A review of the residuals will be done to determine whether the normality assumption is met. If the normality assumption is not met, a rank ANCOVA model will be used to corroborate the result.

The treatment difference will be tested at the 2-sided significance level of $\alpha=0.05$. Descriptive statistics for the primary efficacy endpoint will be provided, including the number of patients, means, standard errors, and least squares (LS) means by the treatment groups, as well as the difference in LS means and the corresponding 95% confidence interval (CI).

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the Investigator will continue to prescribe OCS at the dose specified for OCS titration (as described in [Section 8.2.2.2](#)). The off-treatment OCS dose at Week 24 will be used in the primary analysis. For patients with an ongoing severe asthma exacerbation and who has not completed treatment of the exacerbation at Week 24, the

patient should be placed on the OCS dose 1 step higher than that which he/she was on when the exacerbation occurred.

A sensitivity analysis for the primary efficacy endpoint will be specified in the SAP.

11.4.2.1.1 Subgroup analysis

To assess the consistency in treatment effects across the subgroup levels, subgroup analyses will be conducted for the primary efficacy endpoint with respect to baseline optimized OCS dose strata, age group, gender, region, race, baseline FEV₁, predicted FEV₁ %, ACQ-5, weight, BMI, smoking history, atopic medical history, age of onset of asthma, number of prior asthma exacerbations, baseline eosinophil level (<150 cells/μL or ≥150 cells/μL), and select baseline biomarker levels. The details will be provided in the SAP.

11.4.2.2 Analyses of secondary efficacy endpoints

11.4.2.2.1 Analysis of the key secondary efficacy endpoint

The proportion of patients achieving a reduction of 50% or greater in their OCS dose at Week 24 compared with baseline will be analyzed using a logistic regression model. The model will use the binary status of whether or not a patient achieved the 50% OCS dose reduction criterion as the response variable, and treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (<150 cells/μL or ≥150 cells/μL) as covariates. For patients who permanently discontinue the treatment, their final dose used for the primary efficacy endpoint will be used to determine whether or not they achieve the OCS dose reduction criterion.

11.4.2.2.2 Analysis of the absolute reduction of OCS dose

The absolute reduction of OCS dose at Week 24 will be analyzed using an ANCOVA model in the same fashion as for the primary endpoint, percent reduction of OCS dose at Week 24.

11.4.2.2.3 Analysis of proportion of patients achieving a certain reduction of OCS dose

The proportion of patients achieving a certain reduction of OCS dose will be analyzed in the same manner as the key secondary endpoint. The model will use the binary status of whether or not a patient achieves the prespecified OCS dose reduction criterion as the response variable, and the treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (<150 cells/μL or ≥150 cells/μL) as covariates. For patients who permanently discontinue the treatment, their final dose used for the primary efficacy endpoint will be used to determine whether or not they achieve the OCS dose reduction criterion.

11.4.2.3 Analyses of other efficacy endpoints

11.4.2.3.1 Analysis of annualized event rate

The annualized event rates (eg, severe asthma exacerbation, exacerbations requiring hospitalization or ER visit) will be analyzed using a negative binomial regression model. The model will include the total number of the events occurring during the 24-week Treatment Period as the response variable, and the treatment groups, baseline optimized OCS dose strata, regions (pooled countries), number of the events within 1 year prior to the study, and baseline eosinophil level subgroups (<150 cells/ μ L, ≥ 150 cells/ μ L) as covariates. Log-transformed treatment duration will be the offset variable. For patients who permanently discontinue the treatment, the events which occurred up to Week 24 will be included and the last contact date at Week 24 will be used to calculate offset variable. For patients who are lost to follow up prior to Week 24, events that occurred up to the last contact date will be analyzed, and the last contact date will be used to calculate the offset variable.

11.4.2.3.2 Analysis of time to event variables

Time to event parameters (eg, first severe asthma exacerbation, first exacerbation requiring hospitalization or ED visit) will be analyzed using a Cox regression model with the time to event as the response variable, and the treatment groups, baseline optimized OCS dose strata, regions (pooled countries), number of the events within 1 year prior to the study, and baseline eosinophil level subgroups (<150 cells/ μ L, ≥ 150 cells/ μ L) as covariates. The Kaplan-Meier (KM) method will be used to derive the proportion of patients with an event at Weeks 12 and 24 specific to each treatment group. For patients who are lost to follow up or who discontinue the study prior to Week 24, events that occurred up to the last contact date will be analyzed.

11.4.2.3.3 Analysis of change/ percentage change from baseline for other continuous variables

The change/percentage change from baseline for other continuous variables (eg, FEV₁, PEF, FVC, FEF_{25-75%}, ACQ, asthma symptom scores) will be analyzed using a mixed effect model with repeated measures (MMRM) approach. For a continuous variable, the corresponding MMRM model will include the change/percent change from baseline as response variables, and factors (fixed effects) for the treatment groups, baseline optimized OCS dose strata, regions (pooled countries), baseline eosinophil level subgroups (<150 cells/ μ L, ≥ 150 cells/ μ L) visits, treatment-by-visit interaction, the corresponding baseline value of the endpoint, and baseline-by-visit interaction. Additionally, age, gender, and height will be included as covariates in the models for spirometry variables but not for other variables. 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 an endpoint will be derived from the corresponding mixed-effect model.

11.4.2.4 Multiplicity considerations

The primary endpoint will be tested at a 2-sided 5% significance level. If the primary endpoint meets the significance level, the following secondary endpoints will be tested at a 2-sided 5% significance level in the hierarchical order defined below:

- Proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24 while maintaining asthma control;
- Proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24 while maintaining asthma control
- Proportion of patients achieving their maximum possible reduction of OCS dose per protocol at Week 24 while maintaining asthma control;
- Proportion of patients no longer requiring OCS at Week 24 while maintaining asthma control.

11.4.3 Analyses of safety data

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

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

- The baseline value is defined generally as the last available value before the first dose of study drug.
- The following definitions will be applied to laboratory parameters, vital signs and ECG.
 - The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on a review of the literature and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
 - The criteria for PCSA will determine which patients had at least 1 PCSA during the treatment-emergent period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.3.1 Adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT), and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

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

leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

11.4.3.1.1 Adverse events of special interest

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group.
- An overview summary of the number (%) of patients with
 - any 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 (KM estimates at 1, 4, 12, 24, and 36 weeks)

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

11.4.3.1.2 Deaths

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
- Treatment-emergent AEs 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 the internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

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

11.4.3.2 Clinical laboratory evaluation, vital signs, and electrocardiogram data

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

The proportion of patients who had at least 1 incidence of PCSA at any time during the treatment-emergent period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

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

11.4.4 Analyses of systemic drug concentration, anti-drug antibodies, and pharmacodynamics 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 serum functional dupilumab will be used in the population (Pop) PK analysis. Additional details of the Pop PK analysis plan and the results will be provided in separate documents.

11.4.4.2 Anti-drug antibodies analysis

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

11.4.4.3 Pharmacodynamic analysis

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) and the parameters are measured at any of the screening visits, then values determined at Screening can be used as the baseline.

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

Summary plots (mean +/- SEM) 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 and the 4 domains, the quantitative variables of EQ-5D-5L (single index utility), the anxiety and depression scores of

HADS will be analyzed using an MMRM approach, described previously for the continuous efficacy variables. Descriptive statistics including number of patients, mean, SEM, and LS means will be provided. In addition, the difference in LS means, the corresponding 95% CIs, and the p-values will be provided for comparison between dupilumab and placebo.

The SNOT-22 (only for those patients with bilateral nasal polyposis) will be analyzed using a similar approach.

11.5 INTERIM ANALYSIS

No interim analysis is planned for this study. The primary analysis is planned when the last patient completes the week 24 visit or discontinues from the study before the week 24 visit. The primary database lock will be based on the date when the last patient completes the week 24 visit or discontinues from the study before the week 24 visit. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR (Clinical Study Report). Additional data between database lock and last patient completing last visit will be summarized in a CSR addendum.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, 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 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

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

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB or 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 patient'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 patient.

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 patient'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 patient.

The main study informed consent form, the optional Pharmacogenetic 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.

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, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the 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 will be 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 will be responsible for inventory of OCS (including counting of pills at each study visit during the Treatment and Post-treatment periods).

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 AND ADDITIONAL REQUESTS

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.

Patient 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 patient 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
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP
- The total number of patients are included earlier than expected

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

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon 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 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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