NCT Number: NCT02912468

AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: SAR231893 (dupilumab)

A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids

STUDY NUMBER: EFC14146

STUDY NAME: SINUS-24

VERSION DATE / STATUS: Approval date (17-May-2017) / Approved

Protocol Amendment 01	Version number: 1 (electronic 1.0)	Date : 17-May-2017
Clinical Trial Protocol	Version number: 1 (electronic 2.0)	Date : 04-Aug-2016

Version Number:	1	EudraCT IND Number(s)	2015-003101-42 105379
Date:	17-May-2017	Total number of pages:	143

NAMES AND ADDRESSES OF

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

CLINICAL TRIAL SUMMARY

COMPOUND: SAR231893 (dupilumab)	**STUDY No.: EFC14146**
TITLE	A randomized, 24-week treatment double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVES	**Primary objective:** • To evaluate the efficacy of dupilumab 300 mg every 2 weeks (q2w) compared to placebo on a background of mometasone furoate nasal spray (MFNS) in reducing nasal congestion/obstruction (NC) severity and endoscopic nasal polyp score (NPS) in patients with bilateral nasal polyposis (NP). In addition for Japan, reduction in computed tomography (CT) scan opacification of the sinuses will be also a coprimary objective. **Secondary objectives:** • To evaluate the efficacy of dupilumab in improving total symptom score (TSS). • To evaluate the efficacy of dupilumab in improving sense of smell. • To evaluate the efficacy of dupilumab in reducing CT scan opacification of the sinuses (for Japan, this is part of the primary objective) • To evaluate the ability of dupilumab to reduce the proportion of patients who require treatment with systemic corticosteroids (SCS) or surgery for NP. • To evaluate the effect of dupilumab on patient reported outcomes (PROs) and health-related quality of life (HRQoL). • To evaluate the effect of dupilumab in the subgroups of patients with prior surgery and comorbid asthma (including nonsteroidal anti-inflammatory drug [NSAID] Exacerbated Respiratory Disease [NERD]). • To evaluate the residual effect of dupilumab through the 24-week follow-up period. • To evaluate the safety of dupilumab in patients with bilateral NP. • To evaluate functional dupilumab concentrations (systemic exposure) and incidence of treatment-emergent antidrug antibodies (ADA). **Exploratory objectives:** • To explore the effects of dupilumab on nasal microbiome, total and allergen-specific immunoglobulin Es (IgEs) in blood, and urinary leukotriene E4 and a metabolite of prostaglandin D2 (PGDM). • To evaluate the effect of dupilumab on healthcare resource utilization. • To evaluate the effect of dupilumab on SNOT-22 items: ‘decreased sense of smell/taste’, 'difficulty falling asleep,' 'wake up at night,' 'lack of a good night's sleep,' 'wake up tired,' 'fatigue,' and 'reduced productivity’. • To assess the effect of dupilumab in improving sense of taste.

STUDY DESIGN	**General design** Multinational, multicenter, randomized, double-blind, Phase 3, placebo-controlled, parallel group study comparing the efficacy of dupilumab to placebo, in patients with bilateral NP on a background treatment with intranasal corticosteroids (INCS). **Study periods** The clinical trial consists of 3 periods: **Run-in period (4 weeks +/-3 days):** All patients will enter a run-in period of 4 weeks receiving MFNS of 2 actuations (50 µg/actuation) in each nostril twice daily (BID), total daily dose of 400 µg, starting at Visit 1 (V1), unless the patients are unable to tolerate or there is a specific regulatory requirement preventing use of this dose, in which case they can stay on a lower dose regimen (200 µg once daily) of MFNS. **Randomized treatment period (up to 24 weeks +/-3 days):** Patients will be randomized to one of the following treatments: • Arm A: dupilumab 300 mg subcutaneous (SC) q2w. • Arm B: placebo matching dupilumab SC q2w. All patients will continue on the stable dose of MFNS used during the run-in period except if dose is changed due to adverse event (AE). **Rescue:** During the study treatment period and off-treatment follow-up, based on clinical evaluation, in case of worsening of signs and/or symptoms requiring medical intervention, the Investigator may consider rescue treatment with: • Nasal lavage with saline and/or systemic antibiotics (up to 2 weeks in case of acute infection). • Short course OCS (prednisone or prednisolone). • Sino-nasal surgery for nasal polyps (based on previous observations, 8 weeks of IMP treatment it is recommended prior to surgery to allow onset of treatment effect) Patients receiving rescue treatment other than surgery during the study should continue on study drug unless the Investigator decides to withdraw the study treatment (see Section 8.2.2). Before starting treatment with SCS, patients should come to the study site for clinical assessments including endoscopy and PROs. For patients undergoing surgery for NP the Investigator may decide to continue IMP up to the time of surgery or end of treatment (EOT), whichever date comes first (see Section 9.2.1.5 for details). At the time of surgery patients will be permanently discontinued from study treatment and assessed as soon as possible using the procedures normally planned for the EOT Visit and will be instructed to return to the study site as described in Section 10.3.1. **Post treatment period (24 weeks +/-3 days):** After completing 24 weeks of treatment with the investigational medicinal product (IMP) (or following early discontinuation of IMP or discontinuation from the study), patients will be instructed to: • Return to the study site for all the last scheduled study visits for evaluations of pharmacokinetics (PK) and ADA, physical examination, nasal peak inspiratory flow (NPIF), University of Pennsylvania smell identification test (UPSIT), NPS, CT

	scan (unless not approved by local ethics committee), PROs (SNOT-22, visual analog scale [VAS]), asthma control questionnaire-6 [ACQ-6] and forced expiratory volume in 1 second [FEV1] for patients with asthma and safety. • Continue to complete daily the e-diary for symptom evaluation. • Continue on MFNS stable dose during the post treatment period except if dose is changed due to AE. • Contact the Investigator during the post treatment period up to the EOS visit if the symptoms worsen requiring medical attention. • Report any adverse event (AE). For procedure to be followed for early discontinuation of IMP refer to Section 10.3.1.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** Patients with bilateral sino-nasal polyposis that despite prior treatment with SCS anytime within the past 2 years; and/or have a medical contraindication / intolerance to SCS; and/or had prior surgery for NP at the screening visit, have: • An endoscopic bilateral NPS at V1 of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity). • Ongoing symptoms (for at least 8 weeks prior to V1) of: - Nasal congestion/blockage/obstruction with moderate or severe symptom severity (score 2 or 3) at V1 and a weekly average severity of greater than 1 at the time of randomization (V2), and - Another symptom such as loss of smell, rhinorrhea (anterior/posterior). • Signed written informed consent. **Exclusion criteria:** See Section 7.2 for the complete list of exclusion criteria • Patients <18 years of age. • Patient who has previously been treated in dupilumab studies. • Patient who has taken: - Biologic therapy/systemic immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.) within 2 months before V1 or 5 half-lives, whichever is longer. - Any experimental monoclonal antibody (mAB) within 5 half-lives or within 6 months before V1 if the half-life is unknown. - Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days prior to V1. - Patients who are receiving Leukotriene antagonists/modifiers at V1 unless they are on a continuous treatment for at least 30 days prior to V1. • Initiation of allergen immunotherapy within 3 months prior to V1 or a plan to begin therapy or change its dose during the run-in period or the randomized treatment period. • Patients who have undergone any intranasal and/or sinus surgery (including polypectomy) within 6 months prior to V1. • Patients who have had a sino-nasal or sinus surgery changing the lateral wall structure of the nose making impossible the evaluation of NPS. • Patients with conditions/concomitant diseases making them nonevaluable at V1 or for the primary efficacy endpoint such as:

	- Antrochoanal polyps. - Nasal septal deviation that would occlude at least one nostril. - Acute sinusitis, nasal infection or upper respiratory infection. - Ongoing rhinitis medicamentosa. - Allergic granulomatous angiitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, concomitant cystic fibrosis. - Radiologic suspicion, or confirmed invasive or expansive fungal rhinosinusitis. • Patients with nasal cavity malignant tumor and benign tumors (eg, papilloma, blood boil etc). • Patients with forced expiratory volume in 1 second (FEV1) 50% or less (of predicted normal).
Total expected number of patients	A total of approximately 240 patients with bilateral NP will be randomized to 2 treatment arms (120 patients/arm). The randomization will be stratified based on asthma status, prior NP surgery, and country. In order to have adequate number of patients for the subgroup analysis of patients with asthma/NERD and patients with prior surgery, respectively, enrollment of the following categories of patients will be limited as follows (see rationale Section 4.2): • Patients without asthma and/or NERD history will be limited to 120 patients (out of the total 240 randomized patients). • Patients without prior surgery will be limited to 120 patients (out of the total 240 randomized patients). Patients may fall in more than one category without limitation in numbers.
Expected number of sites	Approximately 80 sites.
STUDY TREATMENTS	Dupilumab (SAR231893/REGN668) or matching placebo.
Investigational medicinal product Formulation	Dupilumab: 150 mg/mL in prefilled syringe to deliver 300 mg in 2 mL. Placebo: Prefilled syringe to deliver 2 mL.
Route of administration:	Subcutaneous (SC) injection.
Dose regimen	Randomized 1:1 to the following regimens until Week 24: • Arm A: dupilumab 300 mg SC q2w. • Arm B: placebo matching dupilumab SC q2w.
Noninvestigational medicinal product Formulation	• Mometasone furoate (NASONEX®) 50 µg/actuation nasal spray, suspension. Nasal spray is provided in a bottle that contains 18 g (140 actuations) of product formulation.
Route of administration	Mometasone furoate (NASONEX): Nasal spray.
Dose regimen	Mometasone furoate nasal spray 2 actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg), or once daily (total daily dose of 200 µg) if the patients are unable to tolerate BID or there is a specific regulatory requirement preventing use of this dose, in which case they can stay on a lower dose regimen (200 µg) of MFNS.

ENDPOINTS	**Coprimary endpoints:** Change from baseline at Week 24: • Nasal congestion/obstruction (NC) symptom severity score based on the patient daily morning (AM) assessment. • Nasal polyp score, as assessed by central video recordings of nasal endoscopy. For Japan, in addition to the coprimary endpoints above, the following will also be a coprimary endpoint. • Change from baseline in opacification of sinuses assessed by CT scans using the Lund Mackay score (LMK) at Week 24. **Secondary endpoints:** **Efficacy key secondary** • Change from baseline in TSS at Week 24: composite severity score consisting of the patient daily AM assessed NC, decreased/loss of sense of smell, anterior/posterior rhinorrhea. • Change from baseline in the UPSIT smell test at Week 24. • Change from baseline in the severity of decreased/loss of smell daily assessed by the patient at Week 24. • Change from baseline in opacification of sinuses assessed by CT scans using the LMK score at Week 24. (This endpoint will not be assessed as a secondary endpoint for Japan as it is already a coprimary endpoint.) • Change from baseline in SNOT-22 at Week 24. • Proportion of patients during study treatment receiving SCS and/or planned to undergo surgery for nasal polyps. **Other secondary** • Change from baseline at Week 24 in: - VAS for overall rhinosinusitis. - Nasal peak inspiratory flow (NPIF). - Rhinorrhea (anterior/posterior nasal discharge) daily symptom score assessed by the patient. • Efficacy endpoints for the subgroups of patients with prior surgery and patients with comorbid asthma (including NERD history). • Efficacy endpoints through the 24-week follow up period. • Safety (incidence of treatment-emergent AEs (TEAE), of treatment-emergent serious AEs (TESAEs), and TEAEs leading to treatment discontinuation), laboratory values, vital signs. • Dupilumab concentration in serum and ADA. • Total SCS rescue dose prescribed (in mg) during the treatment period. • Total SCS rescue intake in days during the treatment period. • Patient reported outcomes including HRQoL scales (EQ-5D-5L VAS score, self-rated health). Details in the statistical analysis for other secondary endpoints in the intent-to-treat (ITT) and predefined subgroups will be provided with the final statistical analysis plan (SAP). Additional ITT and subgroup exploratory analyses are discussed in Section 9 and Section 11.4.2. **Exploratory endpoints:**

	• Healthcare resource utilization. • Proportion and time-to-event of patients with SCS rescue for nasal polyps. • Proportion and time-to-event of patients planned for surgery of nasal polyps. • Change from baseline in decreased/loss of sense of taste symptom severity. • SNOT-22 items: 'decreased sense of smell/taste', 'difficulty falling asleep,' 'wake up at night,' 'lack of a good night's sleep,' 'wake up tired,' 'fatigue,' and 'reduced productivity'. • Pharmacodynamic biomarkers in blood and urine. • Microbiome in nasal mucus swab. • [redacted] • FEV1, forced vital capacity (FVC), and forced expiratory flow 25% to 75% (FEF 25-75) in patients with asthma. • Efficacy endpoints for the subgroup of patients with systemic corticosteroid use prior to study V1. • Patient reported outcomes including HRQoL scale (Index Score of EQ5D-5L)
ASSESSMENT SCHEDULE	Run-in period: 4 weeks +/-3 days. Randomized treatment period: 24 weeks +/-3 days. Post treatment period: 24 weeks +/-3 days. For detailed assessment schedule across the study randomized treatment period, refer to the study flow chart (see Section 1.2).
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size is chosen to enable an adequate characterization of the efficacy between dupilumab 300 mg q2w and placebo with regard to the 2 coprimary endpoints, changes from baseline in NC and NPS at Week 24. The observed mean NC reduction of the dupilumab group with weekly dosing (qw) in ACT12340 is 0.95 and the observed mean NC reduction of the placebo group is 0.26. To calculate the power, a conservative estimate is used that assumes the placebo-adjusted NC reduction of the dupilumab 300 mg q2w group is 80% of the placebo-adjusted effect observed with dupilumab 300 mg qw. Thus, the mean NC reduction of the dupilumab 300 mg q2w is then assumed to be 0.81 = 0.8 * (0.95 – 0.26) + 0.26 at Week 24. Assuming normal distribution of the change in NC, a common standard deviation (SD) of 1.03, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 120 patients per group, the study will have 95% power to detect an effect size of 0.534 using a two-sided test with alpha = 0.05 for the change in NC at Week 24 in the dupilumab 300 mg q2w group versus placebo. The observed mean NPS reduction of the dupilumab group with qw dosing in ACT12340 is 1.85 and the observed mean NPS reduction of the placebo group is 0.30. Using the same conservative approach that assumes the placebo-adjusted NPS reduction with the dupilumab 300 mg q2w is 80% of the placebo-adjusted effect observed with dupilumab 300 mg qw, the mean NPS reduction of the dupilumab 300 mg q2w group is then assumed to be 1.54 = 0.8 * (1.85 – 0.30) + 0.30. Assuming normal distribution of the change in NPS, a common SD of 2.11, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 120 patients per group, the study will have 98% power to detect an effect size of 0.588 using a two-sided test with alpha = 0.05 for the change in NPS at Week 24 in the dupilumab 300 mg q2w group versus placebo. Therefore, with a sample size of 120 patients per group, the combined power of the two coprimary efficacy endpoints is at least 93% for dupilumab 300 mg q2w group with

	alpha = 0.05 assuming no negative correlation between the two endpoints. The observed mean LMK reduction of the dupilumab group with qw dosing in ACT12340 is 9.07 and the observed mean LMK reduction of the placebo group is 0.23. Using same conservative approach that assumes the placebo-adjusted LMK reduction of the dupilumab 300 mg q2w group is 80% of the dupilumab 300 mg qw, the mean LMK reduction of the dupilumab 300 mg q2w group is then assumed to be 7.30 = 0.8*(9.07-0.23)+0.23. Assuming normal distribution of the change in LMK, a common standard deviation (SD) of 5.50, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 120 patients per group, the study will have 99% power to detect an effect size of 1.285 using a two-sided test with alpha = 0.05 for the change in LMK at Week 24 in the dupilumab 300 mg q2w group. With the same sample size of 120 patients per group, the combined power of the 3 coprimary efficacy endpoints for Japan is at least 92% for dupilumab 300 mg q2w group with alpha = 0.05 assuming no negative correlation between the 3 endpoints. The sample size calculations were performed using nQuery Advisor 7.0. **Randomization:** Patients will be randomized using a 1:1 randomization ratio to dupilumab 300 mg q2w or placebo. The randomization will be stratified based on asthma status, prior surgery, and country. **Analysis population:** The primary analysis population for the efficacy endpoints will be the randomized ITT population which includes all patients who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. The efficacy analyses will be conducted according to the treatment to which they were randomized. The analysis population for safety endpoints is 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 is defined as the time from the first administration of study medication to Week 12 of the post treatment period. **Coprimary efficacy variables:** For all countries except Japan, the coprimary efficacy variables are: change from baseline in NC and in NPS at Week 24 assessed for dupilumab 300 mg q2w versus placebo. For Japan only, in addition to the 2 coprimary endpoints above, the following will also be a coprimary endpoint: • Change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 24. The following null hypothesis and alternative will be tested for dupilumab versus placebo: • H0: No treatment difference between the dupilumab dose regimen and placebo. • H1: There is a treatment difference between the dupilumab dose regimen and placebo. **Analysis of the coprimary efficacy variables:** Each of the 2 coprimary efficacy endpoints (3 coprimary endpoints for Japan) will be analyzed using a hybrid method of the worst-observation carried forward (WOCF) and the multiple imputation (MI). With this approach, for patients who undergo surgery for NP or receive SCS for any reason, data collected postsurgery or post-SCS will be set to missing, and the worst postbaseline value on or before the time of surgery or SCS will be used to

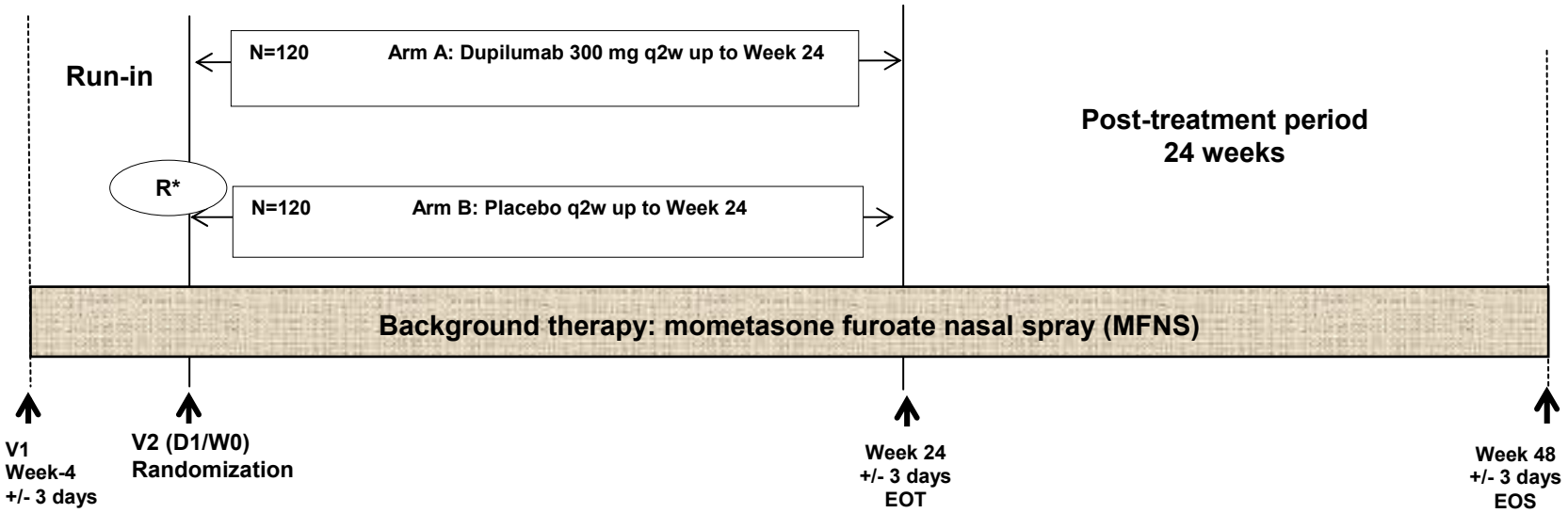
	impute missing Week 24 value (for patients whose postbaseline values are all missing, the baseline will be used to impute). For patients who discontinue the treatment without being rescued by surgery or receiving SCS, an MI approach will be used to impute missing Week 24 value, and this MI will use all patients who have not been rescued by surgery or receiving SCS at Week 24 and data collected after treatment discontinuation will be included in the analysis. Each of the imputed complete data will be analyzed by fitting an analysis of covariance model with the baseline covariate and factors for treatment, asthma status, prior surgery history, and regions. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of subjects mean, standard error, and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values. **Analyses of key secondary efficacy endpoints** *Analysis of the change from baseline in TSS, UPSIT score, daily loss of smell assessment, LMK, and SNOT-22 scores at Week 24 for dupilumab 300 mg q2w versus placebo* The change from baseline in TSS, SNOT-22, UPSIT, daily loss of smell and LMK at Week 24 will be analyzed using the hybrid method of the WOCF and the MI in the same fashion as for the coprimary endpoints. *Analysis of proportion of patients receiving SCS and/or planned to undergo surgery for NP during the 24-week treatment period for dupilumab 300 mg q2w versus placebo* Proportion of patients with first SCS rescue or surgery (actual or planned) for NP during the 24-week treatment period will be derived and analyzed using the Cox proportional hazards model and log rank test stratified by asthma status, prior surgery history, and regions, by considering the first SCS rescue use or surgery for NP (actual or planned) as the event. Descriptive statistics including number of patients with rescue or surgery and number of patients without rescue or surgery (censored) and the corresponding rates will be provided by treatment group. The estimates of the hazard ratio and corresponding 95% CI will be provided for the dupilumab group versus the placebo group. **Analysis of other secondary endpoints:** Changes from baseline in continuous endpoints at Week 24 will be analyzed using the hybrid method of the WOCF and the MI in the same fashion as for the coprimary endpoints. For each subgroup factor, interaction tests will be carried out to investigate consistency of the dupilumab effect across different subgroups identified by that factor. In addition to the analysis in the current study, statistical analysis for these subgroups with comorbid asthma/NERD and prior surgery will be further conducted using the pooled data of EFC14146 and EFC14280, and the details will be provided in the SAP for the Integrated Summary of Efficacy. For any responder type endpoints, the Cochran-Mantel-Haenszel test stratified by asthma status, prior surgery history, and region will be used. Comparisons of the proportions of responders between dupilumab 300 mg q2w and placebo will be derived. Patients who undergo surgery for NP or receive SCS for any reason will be considered as nonresponders for time points after using SCS or surgery. For patients who discontinue treatment without using SCS or surgery, data collected during the off-treatment period will be used to determine the responder/nonresponder status. Missing data will be considered as nonresponders. Proportion and time-to-event of patients with SCS rescue for any airway exacerbated disease will be analyzed using a similar approach as the key secondary endpoint of the proportion of patients with SCS rescue or surgery (actual or planned) for NP. For the change from baseline in continuous endpoints through the 24-week follow up period, descriptive statistics including number of subjects, mean, standard error of the mean (SEM),

	and the corresponding 95% confidence interval (CI) will be provided by treatment. The safety variables, including AEs, laboratory parameters, vital signs, electrocardiogram (ECG) and physical examinations will be summarized using descriptive statistics. **Missing data handling:** For all continuous efficacy endpoints, in the primary approach for missing data handling, for patients who undergo surgery for NP or receive SCS for any reason, data collected postsurgery or post-SCS will be set to missing, and the worst postbaseline value on or before the time of surgery or SCS will be used to impute missing value at the certain analyzed visit (for patients whose postbaseline values are all missing, the baseline will be used to impute), and for patients who discontinue the treatment without being rescued by surgery or receiving SCS on or before the analyzed visit, a MI approach will be used to impute missing value at the certain analyzed visit, and this MI will use all patients who have not been rescued by surgery or receiving SCS at that analyzed visit and data collected after treatment discontinuation will be included in the analysis. For responder type endpoints, patients who undergo surgery for NP or receive SCS for any reason will be considered as nonresponders for time points after using SCS or surgery; for patients who discontinue treatment without using SCS or surgery, data collected during the offtreatment period will be used to determine the responder/nonresponder status, and missing data will be considered as nonresponders. In addition, the reason and pattern of missing data will be carefully examined and tipping point analyses and other sensitivity analyses will also be performed. **Multiplicity considerations:** The multiplicity procedure is proposed to control the overall type-I error rate for testing the coprimary and selected secondary endpoints. The overall alpha is 0.05. The comparisons with placebo will be tested based on the hierarchical order below at 2-sided $\alpha = 0.05$ for 300 mg q2w dose regimen versus placebo: 1. Coprimary efficacy endpoints: In countries other than Japan: • Change from baseline in NC and in NPS at Week 24. In Japan: • Change from baseline in NC, in NPS and in CT LMK at Week 24. 2. Secondary efficacy endpoints: • Change from baseline to TSS at Week 24. • Change from baseline in UPSIT at Week 24. • Change from baseline in loss of smell daily symptoms at Week 24. • Change from baseline in SNOT-22 at Week 24. • Change from baseline in CT LMK score at Week 24 (this will not be a secondary endpoint for Japan as it is already a coprimary endpoint). • Proportion of patients with SCS rescue or surgery for NP during the treatment period. In countries other than Japan, the study is considered positive when both coprimary endpoints, the change from baseline in NC and NPS at Week 24, achieve statistical significance. In Japan, the study is considered positive when all coprimary endpoints, the change from baseline in NC, in NPS, and in CT LMK at Week 24, achieve statistical significance.

	First step analysis: A first step analysis may be performed when all patients complete the Week 24 visit, including early dropouts. Since this analysis is the final analysis of the coprimary endpoints and other 24-week endpoints, and no decision on the conduct of the study will be made based on the first step analysis (in particular, no decision to prematurely stop the study), there will be no alpha adjustment due to the EOT analysis. Specific steps will be taken to maintain the blind of the study to all individuals involved in the conduct of the study and/or analysis. Individuals involved in the first step analysis of the study will not be involved in the conduct of the study afterwards; individual patient identification will not be released to anyone who is directly involved in the conduct of the study.
DURATION OF STUDY PERIOD (per patient)	The total duration of the study (per patient) is expected to be approximately 52 weeks: • Run-in period (4 weeks +/- 3 days). • Randomized treatment period (24 weeks +/- 3 days). • Post treatment period (24 weeks +/- 3 days).

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



BID twice daily; D day; EOS end of study; EOT end of treatment; IMP investigational medicinal product; q2w every 2 weeks; MFNS mometasone furoate nasal spray; R* randomization; QD once daily; SC subcutaneous; V visit; W week

IMP: Regardless of the treatment group, all randomized patients will receive q2w SC administrations of dupilumab or placebo. Every other week IMP administrations must be separated by at least 11 days. At V2 the Investigator or delegate will perform the injection. After V2, every other week administration of IMP will be performed at the investigational site up to at least Week 8 (Visit 6). Patients will be monitored at the study site for at least 30 minutes or the minimum time required by your local regulator after injections. From Week 10, every other week home administration of IMP (patient, caregiver, or health care professional) is possible if the patient (or the caregiver) has been trained. If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or healthcare professionals to administer IMP for the doses not scheduled to be given at the study site.

Non-investigational medicinal product: MFNS will be self-administered by the patient BID or QD (if they cannot tolerate BID). At each visit the Investigator must ensure that the patient has the necessary doses up to the next visit, knowing that one MFNS device (1 bottle) contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen.

1.2 STUDY FLOW CHART

	Run-in[a]	Randomized treatment period								EOT[c]	FU1	FU2 (EOS)
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**	**9**	**10**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12,14[b]**	**16**	**18, 20, 22[b]**	**24**	**36**	**48**
Day +/- 3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**	**D253**	**D337**
Informed Consents	X											
Inclusion and Exclusion Criteria[d]	X	X										
Patient Demography	X											
Medical/Surgical/Medication History[d]	X											
Physical Examination	X									X	X	X
Spirometry[e]	X					X		X		X		X
Chest X-ray[f]	X											
Randomization		X										
Treatment:												
IMP: Dupilumab/placebo injection[g]		X	X	X	X	X	X	X	X			
Call IVRS (IWRS) at scheduled and unscheduled visits as needed	X	|----------X----------|								X	X	X
Review IMP and/or NIMP compliance		|----------X----------|								X		
Dispense or download electronic diary for symptoms[h]	|----------X----------|											
NIMP	|----------X----------|											
Record concomitant medication	|----------X----------|											

	Run-in[a]	Randomized treatment period								EOT[c]	FU1	FU2 (EOS)
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**	**9**	**10**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12,14[b]**	**16**	**18, 20, 22[b]**	**24**	**36**	**48**
Day +/- 3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**	**D253**	**D337**
Record planned surgery for NP, SCS use, and other rescue medication use[j]	|----------X----------|											
Efficacy												
Nasal endoscopy[j]	X	X				X		X		X	X	X
CT scan[k]	X[k]									X		X
Smell test (UPSIT)		X	X			X		X		X		X
NPIF	X	|----------Daily AM ----------|									X	X
Patient reported outcomes/HRQoL[l]												
SNOT-22		X				X		X		X	X	X
Visual analog scale (VAS) for rhinosinusitis		X	X	X		X		X		X	X	X
Severity score (0-3) for reduced sense of taste		X	X	X		X		X		X		
EQ-5D		X								X		
SF-36		X										
ACQ-6 in patients with asthma		X				X		X		X		X
Healthcare resource utilization		X				X		X		X		
Safety												
AE/SAE recording (if any)	|----------X----------|											
Vital Signs[m]	X	X				X		X		X	X	X
ECG (local reading)		X								X		

	Run-in[a]	Randomized treatment period								EOT[c]	FU1	FU2 (EOS)
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**	**9**	**10**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12,14[b]**	**16**	**18, 20, 22[b]**	**24**	**36**	**48**
Day +/- 3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**	**D253**	**D337**
Laboratory Testing												
Clinical laboratory testing[n]	X	X						X		X		
Hepatitis B viral load[o]		X								X		
Pregnancy test (for WOCBP) [p]	X	X		X		X	X (W12)	X	X (W20)	X	X	X
Sampling for serum dupilumab concentration[q]		X		X		X		X		X	X	X
Antidrug antibody sampling[q]		X				X		X		X	X	X
Blood biomarkers (TARC, eotaxin-3, periostin)		X										
Serum Total IgE, allergen-specific IgE panel sampling including Staph enterotoxins IgE		X								X		
Spot urine for biomarker sampling (LTE4, PGDM, creatinine)		X								X		
Nasal swabs for microbiome		X								X		
[redacted]		X										
[redacted]		X								X		
[redacted]		X										

a The run-in period is 28 days in duration to run in any patient on MFNS, and to collect baseline data. Patients receiving rescue medication with systemic corticosteroid (SCS) or and surgery during this period will not be randomized. V2 will take place 28 days +/-3 day window after V1. Windows for subsequent visits are also +/- 3 days. Assessments/procedures at a site visit are performed in the following order if applicable: patient-reported outcomes and other questionnaires; procedures; safety and laboratory assessments; IMP administration,

b Optional interim visit may be scheduled at site for IMP/NIMP supply or IMP administration.

c Patients who discontinue treatment early will be assessed as soon as possible using the procedures normally planned for the EOT Visit and will be instructed to return to the study site as described in Section 10.3.1.

d Past medical history including allergic comorbidities (asthma, aspirin sensitivity, allergic rhinitis etc.). Surgeries for NP will be assessed including number, type and dates of sino-nasal surgeries, polypectomies in the past. Systemic corticosteroids (SCS) use (number of courses, doses, way of administration and duration) in the past 2 years before V1 and/or contraindication/intolerance to SCS, as well as long term antibiotics use (>2 weeks) in the previous year will be entered in the e-CRF. NERD: NSAID (nonsteroidal anti-inflammatory drug) Exacerbated Respiratory Disease will be assessed through a specific questionnaire (Appendix F).

e Spirometry (FEV1, FVC and FEF25-75): should be performed anytime during the run-in period (between V1 and V2) before a first administration of IMP for all patients, locally after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. FEV1, FVC and FEF25-75 will be determined at the designated treatment visits. All patients should have the result of FEV1 (% of predicted normal) recorded in e-CRF: anytime during the run-in period (before V2). Patients with FEV1 50% or less (of predicted normal) will not be randomized. For the other scheduled visits during the randomized treatment period, spirometry will be performed only in patients with asthma at V6, V7, V8 and V10 and the result of FEV1, FVC and FEF25-75 will be recorded in e-CRF at the study scheduled visits.

f Chest X-ray if no chest imaging (X-ray, CT, MRI) is available within the previous year of V1. In countries for which a specific approval procedure for the x-ray or CT scan is required by a different committee than the local EC/IRB, a chest MRI between V1 and V2 can be performed.

g Refer to Section 1 and Section 6 Study Design for details on treatment arms. IMP will be administered after completion of all scheduled clinical assessments and sample collections at the visit or at home.

h Electronic diary/NPIF meter is used for daily recording of MFNS use, AM NPIF (daily up to Week 24 and afterwards at Week 36 and Week 48 during the follow up) and daily symptoms severity from V1 to end of study: 1) nasal congestion/obstruction, 2) anterior rhinorrhea (runny nose), 3) posterior rhinorrhea (post nasal drip), and 4) loss of sense of smell, scored using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). This device is dispensed at V1 and information is downloaded from this device on the other indicated days. For nasal congestion, a severity ≥2 on V1 and a weekly average severity >1 at the time of randomization (V2) is required and will be made available to the site to determine patient eligibility. If there are 4 or more measurements collected within 7 days prior to randomization, the baseline will be the average of these measurements; if less than 4 measurements are collected, the baseline will be the average of the most recent 4 prior to randomization.

i At baseline (V1 and V2) eligibility to surgery based on Investigator opinion will be assessed. During the study treatment and follow-up, if rescue medication with systemic corticosteroids is required, oral prednisone or prednisolone will be dispensed by the site to the patient through a scheduled or unscheduled in-clinic visit. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF and the date and dosing information (daily dose, duration, INN) will be informed. Details on actual or planned date for surgery for NP, type and outcome (wherever possible) will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up, an AE or SAE page will be completed. They will be discontinued from study treatment and assessed as soon as possible using the procedures normally planned for the EOT visit and will be instructed to return to the study site as described in Section 10.1.11. If surgery is scheduled after the planned end of study, EOS visit will not be delayed. A follow up contact(s) should be performed around the time of planned surgery to document the surgery date and outcome. Surgery data will be collected until e-CRF closure of the trial.

j Nasal endoscopy: endoscopy (including use of decongestants before the procedure) will be performed after all other efficacy assessments have been completed for each visit. Standard video sequences will be downloaded by the Investigator to the central reader's secured internet site. For eligibility, central reading of V1 will be used. At V2, Investigator will review V1 results from central reader to confirm entry criteria and reconfirm eligibility based on review of Inclusion/Exclusion Criteria and the V2 endoscopy local reading. To confirm eligibility at V2, only the V1 central reading will be made available to the site. In addition at V2 the Investigator will perform the NE to confirm eligibility score and enter the result in the e-CRF. Thus the patient is considered eligible based on a V1 central reading followed by a V2 local reading NPS score of 5 or more and at least 2 each side. The final results of central reading from V2 onward will be made available to the site after the study.

k A CT scan should be performed anytime during the run-in period before the first administration of IMP and at Visit 8 (Week 24). Central reading will be used for comparison baseline (BL) to Week 24 for the primary analysis and at EOT. A Week 48 CT scan may be performed if approved by local ethics committees. Whenever possible, a cone beam CT scan should be utilized. In countries where local EC do not approve a CT scan or for which a specific approval procedure for the CT scan is required by a different committee than the local EC/IRB, patients may be enrolled using a CT available in the previous year or perform an MRI of the sinuses between V1 and V2. These countries will be exempted from all the planned study CT scans until approval from these committees is received. The MRI will be used only for confirmation of exclusion criteria.

l During the study the PROs should be completed by the patient in the e-diary, in the following order: daily symptoms of NC, loss of smell and rhinorrhea; SNOT-22; VAS rhinosinusitis; loss of taste severity, EQ-5D; ACQ-6 (in patients with asthma).

m Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (V1 and V2) and subsequent visit pre-specified in the flow-chart. Height (cm) will be measured at screening (V1) only. Vital signs will be measured prior to receiving investigational product at the clinic visits in the sitting position using preferably the same arm at each visit.

n Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with five-part differential count, and total red blood cell count. Serum chemistry: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Clinical laboratory testing at V1 includes hepatitis screen covering hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) including HBcAb IgM and total, hepatitis C virus antibodies (HCVAb), Human Immunodeficiency Virus (HIV) screen (anti-HIV-1 and HIV-2 antibodies) and antinuclear antibody (ANA). In case of results showing HBsAg (negative), and HBcAb total or HBcAb IgM (positive), an HBV DNA testing must be performed prior to randomization to rule out a false positivity if the Investigator believes the patient is a false positive, or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the patient is a false positive. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer). Tuberculosis local testing at baseline would be performed on a country by country basis according to local guidelines if required by regulatory authorities or ethic committees.

o This is only applicable for patients in countries/regions where there is local regulatory requirement who are HBsAg negative and HBsAb positive at the run-in period visit.

p Serum pregnancy test at V1 and urine pregnancy tests every 4 weeks thereafter. A negative result must be obtained between V1 and V2 prior to randomization visits. Urinary test could be performed at home as part of visit with or without the assistance of a home care provider. In case of positive urinary test the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases.

q Serum dupilumab concentration, immune response assessment (ADA) samples will be collected and archived prior to administration of IMP and during the randomized treatment period. Blood samples for PK and ADA assessment will be collected at any time in case an SAE occurs. In response to AEs of special interest like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgement of the medical Investigator and/or medical monitor. Patients who are ADA positive at their last study visit (early termination or EOS) will be considered for follow-up based on the overall clinical presentation at that time. Patients who are considered for follow-up may be asked to return to the clinic to have additional samples collected for analysis.

[redacted]

Abbreviations: ACQ-6 asthma control questionnaire-6; ADA antidrug antibodies; AE adverse event; AM ante meridiem; CT computed tomography; D day; ECG electrocardiogram; e-CRF electronic case report form; EOS end of study; EOT end of treatment; EQ-5D European quality of life -5D questionnaire; FEF 25-75 forced expiratory flow to 25% to 75% of forced vital capacity; FEV1 forced expiratory volume in one second; FU follow-up; FVC forced vital capacity; HRQoL health-related quality of life; IgE immunoglobulin E; IMP investigational medicinal product; IVRS interactive voice response system; IWRS interactive web response system; LTE4 leukotriene E4; MFNS mometasone furoate nasal spray; MRI magnetic resonance imaging; NC nasal congestion; NERD NSAID exacerbated respiratory disease; NIMP noninvestigational medicinal product; NP nasal polyposis; NPIF nasal peak inspiratory flow; PGDM prostaglandin D2 metabolite; PK pharmacokinetic; RDN randomization; SAE serious adverse event; SCS systemic corticosteroids; SF-36 short form 36; SNOT-22 sino-nasal outcome test; UPSIT University of Pennsylvania smell identification test; VAS visual analog scale; W week; WBC white blood cell; WOCBP women of child bearing potential.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

ACQ-6: asthma control questionnaire-6
AD: atopic dermatitis
ADA: antidrug antibodies
AE: adverse event
AESI: adverse event of special interest
ALT: alanine aminotransferase
AM: ante meridiem
ANA: antinuclear antibody
BID: twice daily administration
CI: confidence interval
CPK: creatine phosphokinase
CRF: case report form
CRSwNP: chronic rhinosinusitis with nasal polyposis
CSR: clinical study report
CT: computed tomography
CYP: cytochrome P450
DMC: data monitoring committee
DNA: deoxyribonucleic acid
DRF: discrepancy resolution form
ECG: electrocardiogram
e-CRF: electronic case report form
e-diary: electronic diary
EOT: end of treatment
EQ-5D: European quality of life 5D scale
FDA: Food and Drug Administration
FEF25-75: forced expiratory flow at 25% to 75% of forced vital capacity
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
GCP: good clinical practice
GSO: Global Safety Officer
HBcAb: hepatitis B core antibody
HBsAb: hepatitis B surface antibody
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HCAb: hepatitis C antibody
HCVAb: hepatitis C virus antibody
HIV: human immunodeficiency virus
HLGT: high level group term
HLT: high level term
HRQoL: health-related quality of life
ICH: International Conference for Harmonization

ID:	Identification
IDMC:	independent data monitoring committee
IEC:	independent ethics committee
IgE:	immunoglobulin E
IL:	interleukin
IL-4Rα:	interleukin-4 receptor alpha
IM:	intramuscular
IMP:	investigational medicinal product
INCS:	intranasal corticosteroid
INN:	international nonproprietary name
IRB:	institutional review board
ITT:	intent-to-treat
IV:	intravenous
IVRS:	interactive voice response system
IWRS:	interactive web response system
K-M:	Kaplan-Meier
LFT:	liver function test
LMK:	Lund Mackay
LS:	least squares
mAB:	monoclonal antibody
MCID:	minimal clinically important difference
MFNS:	mometasone furoate nasal spray
MI:	multiple imputation
MID:	minimal important difference
MRI:	Magnetic Resonance Imaging
NC:	nasal congestion
NERD:	nonsteroidal anti-inflammatory drug exacerbated respiratory disease
NIMP:	noninvestigational medicinal product
NP:	nasal polyposis
NPIF:	nasal peak inspiratory flow
NPS:	nasal polyp score
NSAID:	nonsteroidal anti-inflammatory drug
OC:	osteomeatal complex
OCS:	oral corticosteroid
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PGDM:	prostaglandin D2 metabolite
PK:	pharmacokinetic
POC:	proof of concept
PRO:	patient reported outcome
PT:	preferred term
q2w:	every 2 weeks
q4w:	every 4 weeks
QD:	once daily administration
QoL:	quality of life
qw:	once weekly

RNA:	ribonucleic acid
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SCS:	systemic corticosteroids
SD:	standard deviation
SEM:	standard error of the mean
SF-36:	Short Form 36
SNOT-22:	sino-nasal outcome test
SOC:	system organ class
SUSAR:	suspected unexpected adverse drug reaction
TARC:	thymus and activation regulated chemokine
TEAE:	treatment emergent adverse event
Th2:	T-helper cell-2
TSS:	total symptom score
ULN:	upper limit of normal
UPSIT:	University of Pennsylvania smell identification test
US:	United States
V:	Visit
VAS:	visual analog scale
WOCBP:	women of childbearing potential
WOCF:	worst observation carried forward
β-hCG:	beta human chorionic gonadotrophin

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a clinical condition characterized by the presence of multiple polyps in the upper nasal cavity, originating from the osteomeatal complex (OC) and the spheno-ethmoid recess and characterized by mucosal inflammation of the nasal cavity and paranasal sinuses with symptoms lasting more than 12 weeks. Clinically, CRSwNP is defined by long-term symptoms of nasal obstruction and congestion, reduction in or loss of sense of smell, and anterior and posterior rhinorrhea. These symptoms can impact greatly upon a patient's quality of life (QoL). The presence or absence of polyps is confirmed by performing endoscopy. Coronal computed tomography (CT) scans can confirm the presence and extent of sinus and polyp involvement. With an estimated prevalence of 2% to 4% (in Europe and United States [US]), nasal polyps (NP) has a high burden of symptoms and a high relapse rate after treatment. Despite the high prevalence and significant morbidity associated with CRSwNP, treatment options range from local or systemic corticosteroids (SCS) to functional endoscopic sinus surgery. Patients with CRSwNP and comorbid asthma (~30% of patients with NP) have a characteristically poor therapeutic response and a high recurrence rate, and their disease tends to be more resistant (1, 2).

The pathogenesis of nasal polyps is unknown. Nasal polyps are most commonly thought to be caused by allergy, although a significant number are associated with nonallergic adult asthma or no respiratory or allergic trigger that can be demonstrated. Risk factors include genetic susceptibility, anatomic abnormalities, infection, local immunologic imbalance and eicosanoid dysmetabolism (manifested as aspirin intolerance), some or most of which may play a role in its pathogenesis (3, 4, 5).

Pathophysiologically, CRSwNP is an inflammatory and remodeling process affecting the mucosa of the nose and paranasal sinuses often associated with mucocilliary impairment, bacterial infection, allergic disease, and/or anatomical abnormalities (6, 7, 8). CRSwNP is a T-helper cell-2 (Th2) driven inflammatory process in which eosinophils are the predominant inflammatory cell found in the sinuses and nasal polyps, and is frequently associated with asthma and aspirin sensitivity (9). In European and US populations, more than 80% of patients with CRSwNP have eosinophilic upper airway inflammation. The extent of sinomucosal involvement, the size of the polyps, and the severity of nasal disease correlate with the extent of eosinophilic inflammation (10). The chronic inflammation associated with eosinophilic polyps exhibits elevated levels of interleukin-5 (IL)-5 (promoter of eosinophil survival, differentiation and taxis), eosinophil cationic protein (eosinophil activation product), eotaxins (eosinophil chemoattractants), and immunoglobulin E (IgE) in the nasal polyps and local secretions (11).

The therapeutic armamentarium of clinically proven medical interventions for CRSwNP is limited. First-line treatment is topical corticosteroids. Intranasal corticosteroid (INCS) sprays improve the symptoms of nasal obstruction (12), secretion, and sneezing to some extent. However, their effect in reducing polyp size and on improving the sense of smell (13), a cardinal

symptom of NP (14) is limited. Overall, due to the relatively modest effects on the symptoms of NP, in many instances, INCSs do not address the main QoL issues for patients. Short courses of oral steroids are also prescribed as adjunctive therapy to INCS or in cases of severe disease (15); however, the long-term use of systemic steroids for the treatment of nasal polyps is not recommended as the risk of prolonged systemic steroids use is not outweighed by the benefit (12).

The current US practice guidelines indicate that the duration of clinical benefit of oral corticosteroids (OCS) is variable and may decrease with repeated courses of treatment (16).

The only alternative for most patients that respond inadequately to medical treatment is surgery of the sinuses. However, even after surgical treatment, continued use of at least INCS is needed and disease recurrence requiring repeated surgeries is high.

Recent therapeutic approaches have been focused on trying to control the Th2 response and clinical improvement in CRSwNP and associated symptoms have been observed in other studies of biological therapies, including the anti-IgE monoclonal antibody (mAB) omalizumab (17), or the anti-IL-5 mAB mepolizumab (18).

Dupilumab is a systemic targeted immunomodulatory agent, inhibiting the Th2 pathway. It is a fully human mAB directed against the interleukin-4 receptor alpha (IL-4Rα) subunit, a component of IL-4 receptors Type I and Type II, which mediate signaling by IL-4 (both receptors) and by IL-13 (Type II receptor). Dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 activation of their respective receptors.

For further complete information regarding the preclinical and clinical evaluation of dupilumab to date, refer to the current version of the Investigator Brochure.

Dupilumab is in clinical development for the treatment of CRSwNP worldwide. However in the US, based on Food and Drug Administration (FDA) feedback, this clinical development program will support the indication of nasal polyposis (NP).

Preliminary clinical evidence, based on the proof of concept (POC) data and the mechanism of action, suggests that dupilumab provides an effective treatment and substantial improvement over INCS for patients suffering from CRSwNP. In a POC study (ACT12340), 60 patients with bilateral NP and chronic symptoms of sinusitis refractory to INCS were randomized to dupilumab 300 mg once weekly (qw) SC administration for 16 weeks or placebo, with background intranasal mometasone furoate nasal spray (MFNS; NASONEX). In this study, dupilumab demonstrated a significant improvement in endoscopic, radiographic and clinical measures of NP and sinusitis, as well as improvements in lung function and disease control in patients with comorbid asthma (19).

Dupilumab, therefore, offers promise of significant benefit above and beyond current standard of care in this patient population and may provide an alternative for those patients who respond inadequately to INCS and may obviate the need for repeated surgeries.

4.2 STUDY RATIONALE

This is a phase 3, randomized, placebo-controlled efficacy and safety study of dupilumab in patients with moderate-to-severe signs and symptoms of NP who are not controlled on standard of care.

This study will primarily investigate the efficacy and safety of dupilumab 300 mg every 2 weeks (q2w) compared to placebo on top of the current standard of care background therapy of (daily use of intranasal MFNS [NASONEX]), utilizing multiple objective and subjective outcome measures in patients with NP. By allowing Investigators, at their discretion, to use SCS or surgery as a rescue therapy for worsening of NP, the study will also assess the effect of dupilumab on the need for surgery and SCS use over the randomized treatment period.

4.3 POPULATION

The population of the EFC14146 study is composed of patients with bilateral NP (endoscopic bilateral nasal polyp score [NPS] has to be ≥5 out of a maximum score of 8) that present with chronic symptoms of nasal congestion (NC) (moderate/severe) and another symptom such as loss of smell and/or rhinorrhea despite background treatment with INCS and maximum therapy with standard of care including systemic corticosteroids (in the previous 2 years) and/or surgery in the past (see Section 7.1).

The proposed patient selection criteria will reflect standard of care in this severe uncontrolled patient setting by allowing enrollment of patients that received INCS, SCS prior to the run-in period, and/or patients with previous surgeries.

Approximately 26% to 50% of NP patients suffer from comorbid asthma and it is estimated that asthma is underdiagnosed in up to 25% of these patients (20, 21). NP has also been observed to be associated with chronic bronchitis and, in those with asthma, lower airway obstruction (6, 20).

NP patients also more frequently present with nonsteroidal anti-inflammatory drug (NSAID) intolerance (22) and if they also suffer from asthma they are diagnosed with NSAID-exacerbated respiratory disease (NERD).

These patients have the highest rates of exacerbation and hospital admissions and tend to have a poorer perception of control of disease, due to the persistence and severity of the associated sinonasal symptoms (23). Additionally, asthma symptoms tend to be more severe in these patients.

Taking into account the high prevalence, the high disease burden and unmet need of NP patients that have comorbid asthma and aspirin or NERD, these patients will be allowed to enter the study (unless they present with any of the exclusion criteria described in Section 7.2). In addition, stratification at randomization for asthma and specific subgroup analysis will be performed to specifically assess efficacy in these subgroups.

NP patients who have persistent signs and symptoms or disease relapse after short course treatment with SCS or after a surgery for NP, represent a subgroup of patients with higher burden and unmet

need, and therefore will be also analyzed. In addition, stratification at randomization for patients with prior surgery will be performed.

4.4 STUDY DESIGN

This phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study will evaluate the efficacy of dupilumab 300 mg administered subcutaneously (SC) q2w for 24 weeks followed by 24 weeks off-treatment period on a background of INCS.

The proposed study, allowing daily use of INCS and SCS courses and/or surgery as needed or other treatments considered standard of care, will aim at evaluating a potential role for dupilumab in the existing treatment paradigm, for the treatment of nasal polyps.

The clinical study consists of 3 periods:

- Run-in period where the patients will receive MFNS for 4 weeks +/-3 days.
- Randomized dupilumab/placebo treatment period (24 weeks) where approximately 240 patients will be randomized, 120 p/arm, to one of the following treatments:
  - Arm A: dupilumab 300 mg SC q2w
  - Arm B: placebo matching dupilumab SC q2w.
- Post treatment period - where patients will be followed for 24 weeks to evaluate potential disease recurrence (through objective and subjective efficacy assessments), systemic concentrations of functional dupilumab (PK), immunogenicity, and safety after they are off the investigational medicinal product (IMP).

During the whole study duration, patients will continue MFNS stable dose started at Visit 1 (V1) except if dose is changed due to AE.

In addition, patients may receive rescue medications (including SCS) and/or undergo surgery for NP as deemed necessary by the Investigator and patient. Short courses of oral steroids are often used as adjunctive therapy to INCS or in cases NP patients who fail standard of care with INCS (15). Refer to Section 8.2.2 for additional details.

Overall, this study will evaluate the potential real life benefit that dupilumab may provide for patients that failed currently available treatment options.

4.4.1 Endpoints rationale and description

Clinically, NP is defined by long-term symptoms of nasal obstruction and congestion, reduction in or loss of sense of smell, and anterior and posterior rhinorrhea. The presence or absence of polyps is confirmed by performing endoscopy. These symptoms can greatly impact patient's QoL.

Medical and surgical intervention decisions are mainly driven by the nasal polyp symptom burden and response to standard therapy with topical and SCS. Therefore, in this study severity of symptoms will be scored daily by the patient (0-3). For NC which is a major clinical symptom,

the monthly average of the daily recorded symptom score will be assessed as coprimary endpoint along with the objective endoscopic assessment of NP score.

Thus, the coprimary endpoints of this study are the change from baseline at Week 24 in:

- ***Nasal congestion/obstruction severity score*** consisting of the monthly average of the daily morning ante meridiem (AM) patient-assessed daily symptom severity (using a 0 to 3 categorical scale). The NC is assessed by the patient on a daily basis from V1 and throughout the study, using an electronic diary (e-diary) using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms).
- ***The bilateral endoscopic NPS*** ranges from 0 to 8 points and is the sum of the right and left scores (from 0 = no polyps; 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the lower border of the middle turbinate; 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4 = large polyps causing complete obstruction of the inferior nasal cavity) (17, 18, 24). For further detail, see Section 9.1.
- ***In addition, for Japan: Lund-Mackay score.*** The Lund-Mackay (LMK) system is based on localization with points given for degree of opacification on CT scan: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The OC is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side. For further detail, see Section 9.1.

Key secondary endpoints of the study include:

- Change from baseline in the severity of total symptoms score (TSS) at Week 24.
- Change from baseline in University of Pennsylvania smell identification test (UPSIT) at Week 24.
- Change from baseline in the severity of decreased/loss of smell daily assessed by the patient at Week 24.
- Change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 24. (Note for Japan: this is considered as primary endpoint)
- Change from baseline in 22-item sino-nasal outcome test (SNOT-22) at Week 24.
- Proportion of patients receiving SCS and/or undergoing surgery (actual or planned) for nasal polyps during the study treatment.

The proposed study design and endpoints will answer important clinical questions about the efficacy on symptoms and objective signs of the disease and the effect of dupilumab on reduction of SCS rescue therapy and surgery, which are the most relevant clinical practice assessments and reflect current standard of care.

Other efficacy, safety and exploratory assessments in patient reported outcomes (PROs), health-related quality of life (HRQoL) and condition-specific and general medical questionnaires to evaluate the potential real life benefit will be evaluated too.

These treatment approaches and endpoints reflect real-life clinical assessment and are in line with increasing focus in the medical field on the effects of medical conditions and treatments on the QoL of, and functioning of, patients (1).

4.4.2 Dupilumab dose and regimen rationale

The dose regimens are selected based on the totality of clinical evidence in the dupilumab program including data from Phase 2 efficacy and safety study (ACT12340) in patients with nasal polyps and symptoms of chronic sinusitis, the result of Phase 2b dose ranging study in patients with moderate to severe asthma (DRI12544), the Phase 2b dose ranging study (R668-AD-1021) and Phase 3 studies (R668-AD-1334 and R668-AD-1416) in patients with moderate to severe atopic dermatitis (AD), as well as the supportive pharmacokinetic (PK)/pharmacodynamic (PD) analysis.

While the clinical manifestations may be distinct across NP, asthma and AD indications, Th2 mediated inflammation is implicated in the disease etiology and pathophysiology of all 3 conditions. Dupilumab has demonstrated marked concentration dependent inhibition of the upstream and downstream Th2 inflammatory biomarkers including thymus and activation-regulated chemokine (TARC) and IgE with a very similar PD profile and exposure-response relationship in AD, asthma and NP patients. In asthma dose ranging study (DRI12544), 300 mg q2w regimen demonstrated a robust treatment effect across all relevant indices of drug action, while less frequent dose regimens 200 mg q2w and 300 mg once every 4 weeks (q4w) showed less effect in some endpoints including SNOT-22. Both dose-response and exposure-response analyses indicated that therapeutic responses (eg, improvement in forced expiratory volume in 1 second [FEV1] at Week 12) and biomarker responses (including fractional exhaled nitric oxide and TARC) plateaued by 300 mg q2w. Thus, a further increase in dose above 300 mg q2w is unlikely to achieve additional clinical benefit. The 300 mg q2w regimen is being currently evaluated as the higher dose regimen in the asthma phase 3 pivotal study.

In the AD dose ranging study (R668-AD-1021), a similar treatment effect between 300 mg qw and 300 mg q2w was also observed for most efficacy endpoints (eg, IGA [Immunoglobulin A] and EASI [Eczema Area and Severity Index]). Consistently, results from the Phase 3 efficacy and safety studies in AD patients (R668-AD-1334 and R668-AD-1416) confirmed the highly similar clinical efficacy for the 300 mg qw and 300 mg q2w regimens across all endpoints.

In the phase 2 POC study in NP patients with chronic symptoms of sinusitis (ACT12340), the 300 mg qw regimen demonstrated a robust, clinically and statistically significant treatment response on the primary and secondary efficacy endpoints for NP and chronic sinusitis at the end of the 16-week treatment period. Pharmacokinetic/PD analysis of ACT12340 efficacy endpoints predicted a superior therapeutic benefit at both 300 mg q2w and 300 mg qw regimens, including clinical significant reduction in bilateral NPS (>1 point from baseline) and significant improvement in symptoms of NC and decrease/loss of smell. The exposure-response analysis of SNOT-22 by leveraging both ACT12340 and the dose ranging data from DRI12544 NP patients consistently supports significant clinical benefits of 300 mg q2w regimen in improving SNOT-22 outcome (total score and selected nasal components of loss of smell and nasal blockage) and limited additional benefit with further increase in dose beyond 300 mg q2w. Thus, the available

efficacy data from asthma, AD and NP trials collectively indicate a high potential for achieving an optimal treatment effect at 300 mg q2w in NP patients.

Nasal polyposis is an inflammatory disorder of upper airways of chronic and recurring nature requiring the use of long-term anti-inflammatory treatment to achieve a maintenance state (25).

In the ACT12340 study, a gradual development of treatment response was observed for bilateral NPS and NP symptoms of NC and sense of smell. The PD steady-state for the above endpoints was not reached at the end of treatment (EOT) at Week 16, suggesting additional therapeutic benefit with longer treatment duration. The time-course PK/PD analysis predicts 24 weeks to be the optimal treatment duration to assess the maximal symptomatic effect for NPS, NC and other key secondary efficacy endpoints.

In ACT12340 study, a single loading dose of 600 mg was used on Day 1 to rapidly achieve an efficacious concentration range for a potentially earlier onset of significant response. Consistent with the observed PK and PD profile of NP response (gradual development of response as well as slow offset of response during off-treatment), PK/PD simulation of coprimary endpoints of NPS and NC showed minimal difference in the development of treatment effect and steady-state response of NPS and NC in the presence and absence of the loading dose of 600 mg on Day 1. Therefore, no loading dose is included in the present study.

In summary, the present clinical evidence from the 3 related Th2 disease populations of NP, AD, and asthma supports selection of 300 mg q2w as the potential efficacious dose regimen to be evaluated for benefit risk in the Phase 3 study.

4.5 OVERALL BENEFITS AND RISKS ASSESSMENT

Polyps are generally comprised of eosinophilic infiltrate and associated with a Th2 orchestrated inflammatory state characterized by high IgE, increased Th2 cytokines such as IL-5 and IL-13, and decreased T-regulatory function.

Dupilumab prevents IL-4 and IL-13 binding and activation of their respective receptors involved in signaling pathways that play key roles in the pathophysiology of NP. A Phase 2a study in patients with NP and symptoms of sinusitis, demonstrated efficacy of dupilumab with improvements in endoscopic, radiographic and clinical measures of disease as well as improvements in lung function and disease control in patients with comorbid asthma. Based on the POC data and the mechanism of action, dupilumab may provide an effective treatment for patients suffering from NP despite maximal treatment with available therapy.

Overall, 7408 subjects have been enrolled into the dupilumab development program (completed and ongoing studies) as of 30 September 2016.

Based upon the currently available data for dupilumab and the review of the data by an independent data monitoring committee (IDMC), systemic hypersensitivity has been identified as an important potential risk. Use in patients with helminthic infections is considered missing information based on mechanism of action and evidence of the role of IL-4 in helminth repulsion

in animal studies published in literature. Other theoretical risks based on immune-modulating properties of IL-4 are being managed conservatively through:

- Exclusion of patients with immunosuppressed status or receiving systemic immunosuppressants, and/or having active bacterial, viral or parasitic infection, or at high risk for developing or reactivating infections.
- Monitoring of safety data, including periodic blinded safety monitoring team review and unblinded IDMC review.

The total number of patients exposed to dupilumab is over 5,000. Data from these patients showed that dupilumab is well tolerated and has a favorable safety profile. This, together with the efficacy demonstrated in ACT12340 study in patients with NP, show a favorable benefit risk balance, and support continued development of dupilumab in NP.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of the study is to evaluate the efficacy of dupilumab 300 mg q2w compared to placebo on a background of MFNS in reducing NC/obstruction severity and endoscopic NPS in patients with bilateral NP.

5.2 SECONDARY

- To evaluate the efficacy of dupilumab in improving total symptoms score (TSS).
- To evaluate the efficacy of dupilumab in improving sense of smell.
- To evaluate the efficacy of dupilumab in reducing CT scan opacification of the sinuses (for Japan, this is part of the primary objective)
- To evaluate the ability of dupilumab to reduce the proportion of patients who require treatment with SCS or surgery for NP.
- To evaluate the effect of dupilumab on PROs and HRQoL.
- To evaluate the effect of dupilumab in the subgroups of patients with prior surgery and comorbid asthma (including NERD).
- To evaluate the residual effect of dupilumab through the 24-week follow-up period.
- To evaluate the safety of dupilumab in patients with bilateral NP.
- To evaluate functional dupilumab concentrations (systemic exposure) and incidence of treatment-emergent antidrug antibodies (ADA).

5.3 EXPLORATORY

- To explore the effects of dupilumab on nasal microbiome, total and allergen-specific IgEs in blood, and urinary leukotriene E4 and a metabolite of prostaglandin D2 (PGDM).
- To evaluate the effect of dupilumab on healthcare resource utilization.
- To evaluate the effect of dupilumab on SNOT-22 items: ‘decreased sense of smell/taste’, 'difficulty falling asleep,' 'wake up at night,' 'lack of a good night's sleep,' 'wake up tired,' 'fatigue,' and 'reduced productivity’.
- To assess the effect of dupilumab in improving sense of taste.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

EFC14146 is a multinational, multicenter, randomized, double-blind, Phase 3, placebo-controlled, parallel group study to evaluate dupilumab in patients with bilateral NP. All patients will enter a run-in period of 4 weeks +/-3 days receiving MFNS of 2 actuations (50 µg/actuation) in each nostril twice daily (BID), total daily dose of 400 µg, starting at V1, unless they are unable to tolerate or there is a specific regulatory requirement preventing use of this dose, in which case they can stay on a lower dose regimen (200 µg) of MFNS.

Approximately 240 patients with bilateral NP will be randomized 1:1 (120 patients/arm) into 2 treatment groups as follows:

- Arm A: dupilumab 300 mg SC q2w until Week 24.
- Arm B: placebo matching dupilumab SC q2w until Week 24.

The 240 patients will be included in approximately 80 sites. Patients will be randomized according to asthma status (history of asthma or not), prior NP surgery (yes or no), and country.

In order to have adequate number of patients for the subgroup analysis of patients with asthma/NERD and prior surgery enrollment of the following categories of patients will be limited as follows (see rationale Section 4.2):

- Patients without asthma and/or NERD history will be limited to 120 patients (out of the total 240 randomized patients).
- Patients without prior surgery will be limited to 120 patients (out of the total 240 randomized patients).

Patients may fall into more than one category without limitation in numbers.

During the randomized treatment period, patients will continue the stable dose of intranasal MFNS stabilized during the run-in period except if dose is changed due to AE. For a schematic study design refer to Section 1.1.

During the study, patients who report deterioration requiring medical/surgical intervention may come to the site for an endoscopy and clinical evaluation. An unscheduled visit may be used for this purpose and if necessary the Investigator may consider one of the treatment alternatives described in Section 8.2.2.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The clinical trial will consist of 3 periods:

- Run-in period (4 weeks, +/-3 days): to determine a patient's eligibility and for run-in/standardization of background INCS (MFNS) prior to randomization.
- Randomized dupilumab/placebo treatment period (24 weeks +/-3 days): to randomize the patient into a treatment arm and treat with dupilumab or placebo dose regimen.
- Post treatment period (24 weeks +/-3 days): to continue to collect data for PK, immunogenicity, safety, and efficacy after the patient has completed the study drug treatment period.

If surgery is scheduled after the planned end of study, EOS visit will not be delayed. A follow up contact(s) should be performed around the time of planned surgery to document the surgery date and outcome (see Section 9.2.1.5). Surgery data will be collected until e-CRF closure of the trial.

The total duration of study participation for patients that complete the randomized treatment period and post treatment follow up is approximately 52 weeks. The schedule of the visits is described in the study flow chart in Section 1.2.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur when the last randomized patient has completed the end of his or her 24-week follow-up period or prematurely discontinues from the study. The end of the clinical trial is defined as the last patient's last visit.

6.3 FIRST STEP ANALYSIS

A first step analysis may be performed when all patients complete the Week 24 visit, including early dropouts. Since this analysis is the final analysis of the coprimary endpoints and other 24-week endpoints, and no decision on the conduct of the study will be made based on the first step analysis (in particular, no decision to prematurely stop the study), there will be no alpha adjustment due to the interim analysis. Specific steps will be taken to maintain the blind of the study to all individuals involved in the conduct of the study and/or analysis, if we perform this first step analysis, and to protect the overall blinding of, and integrity of, the study data given the first step analysis as further described in Section 11.5.

Individuals involved in the first step analysis of the study will not be involved in the conduct of the study afterwards; individual patient identification (ID) will not be released to anyone who is directly involved in the conduct of the study.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

A data monitoring committee (DMC) with members independent from Sponsor and Investigators is commissioned for the dupilumab clinical development program. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC will monitor the safety data of patients (serious adverse events [SAE], treatment emergent adverse events [TEAE] and/or adverse events of special interest [AESI]) at regular intervals and is responsible for providing recommendations for protecting the safety and ensuring the welfare of these patients and provide sanofi with appropriate recommendations in a timely manner to ensure the welfare and safety of the study patients. The DMC review is blinded with the ability to be unblinded at DMC request.

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

6.4.2 Clinical advisory committee

Not applicable.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Patients with bilateral sino-nasal polyposis that despite prior treatment with SCS anytime within the past 2 years; and/or have a medical contraindication/intolerance to SCS; and/or had prior surgery for NP at the screening visit, have:

I 01. An endoscopic bilateral NPS at V1 of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity).

I 02. Ongoing symptoms (for at least 8 weeks before V1) of:

- Nasal congestion/blockade/obstruction with moderate or severe symptom severity (score 2 or 3) at V1 and a weekly average severity of greater than 1 at time of randomization (V2).

and

- Another symptom such as loss of smell, rhinorrhea (anterior/posterior).

I 03. 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 <18 years of age.

E 02. Patient who has previously been treated in dupilumab studies.

E 03. Patient who has taken:

- Biologic therapy/systemic immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) within 2 months before V1 or 5 half-lives, whichever is longer.
- Any experimental mAB within 5 half-lives or within 6 months before V1 if the half-life is unknown.
- Anti-IgE therapy (omalizumab) within 130 days prior to V1.
- Patients who are receiving leukotriene antagonists/modifiers at V1 unless they are on a continuous treatment for at least 30 days prior to V1.

E 04. Initiation of allergen immunotherapy within 3 months prior to V1 or a plan to begin therapy or change its dose during the run-in period or the randomized treatment period.

E 05. Patients who have undergone any intranasal and/or sinus surgery (including polypectomy) within 6 months prior to V1.

E 06. Patients who have had a sino-nasal or sinus surgery changing the lateral wall structure of the nose making impossible the evaluation of NPS.

E 07. Patients with conditions/concomitant diseases making them nonevaluable at V1 or for the primary efficacy endpoint such as:

- Antrochoanal polyps.
- Nasal septal deviation that would occlude at least one nostril.
- Acute sinusitis, nasal infection or upper respiratory infection.
- Ongoing rhinitis medicamentosa.
- Allergic granulomatous angiitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, concomitant cystic fibrosis.
- Radiologic suspicion, or confirmed invasive or expansive fungal rhinosinusitis.

E 08. Patients with nasal cavity malignant tumor and benign tumors (eg, papilloma, blood boil etc).

E 09. Patients with forced expiratory volume (FEV1) 50% or less of predicted normal.

E 10. Patients receiving concomitant treatment prohibited in the study (see Section 8.8.1).

E 11. Patient is the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

E 12. NIMP noncompliance at V2 (<80%) or any condition that could make the patient noncompliant with the study procedures and daily assessment in the e-diary.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

E 13. Patients meet any contraindications or warning on National Product labeling for MFNS.

7.2.3 Exclusion criteria related to the current knowledge of sanofi compound

E 14. Pregnant or intent to become pregnant during the study, or breast-feeding women.

E 15. Women of childbearing potential (WOCBP) (premenopausal female biologically capable of becoming pregnant) who do not fulfill:

- A confirmed negative serum beta-human chorionic gonadotrophin (β-hCG) test at V1.

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), if allowed by local regulation.

OR

- Female sterilization (eg, tubal occlusion, hysterectomy or bilateral salpingectomy).
- True abstinence in keeping with the preferred and usual lifestyle and if allowed by local regulation; periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) is not an acceptable method of contraception.
- Postmenopausal women (defined as at least 12 consecutive months with no menses without an alternative medical cause) are not required to use additional contraception.

E 16. Diagnosed active parasitic infection (helminths); suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.

E 17. History of human immunodeficiency virus (HIV) infection or positive HIV screen (anti HIV-1 and HIV-2 antibodies) at V1.

E 18. A subject with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to uncontrolled diabetes, uncontrolled hypertension, and active hepatitis.

E 19. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per Investigator's judgment.

E 20. Active tuberculosis, latent untreated tuberculosis or a history of incompletely treated tuberculosis or non-tuberculous mycobacterial infection will be excluded from the study unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing would be performed on a country by country basis according to local guidelines if required by regulatory authorities or ethics committees.

E 21. Evidence of acute or chronic infection requiring treatment with systemic antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before V1 or during the run-in period, or significant viral infections within 4 weeks prior to V1 that may not have received antiviral treatment.

E 22. Live, attenuated vaccinations within 4 weeks prior to V1 or planned live attenuated vaccinations and during the study (refer to Appendix A).

E 23. Patients with active autoimmune disease and/or patients using immunosuppressive therapy for autoimmune disease (eg, Hashimoto's thyroiditis, Graves' disease, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematous, multiple sclerosis, and other neuro-inflammatory disease, psoriasis vulgaris, rheumatoid arthritis), or patients with high titer autoantibodies at V1 who are suspected of having high risk for developing autoimmune disease at the discretion of the Investigator or the Sponsor.

E 24. History of malignancy within 5 years before V1, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

E 25. Known or suspected alcohol and/or drug abuse.

E 26. Patients with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

E 27. Active hepatitis or patients with positive or indeterminate hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) [confirmed with presence of hepatitis B virus (HBV) deoxyribonucleic acid (DNA)], or positive hepatitis C virus antibody (HCVAb) [confirmed with presence of HCV ribonucleic acid (RNA)] at V1.

E 28. Patient with the following liver injury related criteria at V1:

- Clinically significant/active underlying hepatobiliary disease

OR,

- Alanine aminotransferase (ALT) >3 upper limit of normal (ULN).

E 29. Abnormal laboratory values at V1:

- Creatine phosphokinase (CPK) >10 ULN

OR,

- Platelets <100 000 cells/mm^3

OR,

- Eosinophils >1500 cells/mm^3.

E 30. Conditions/situations such as: Patients considered by the Investigator or any Subinvestigator as inappropriate for this study for any reason, eg,:

- Those deemed unable to meet specific protocol requirements, such as scheduled visits.
- Those deemed unable to administer or tolerate long-term injections as per the patient or the Investigator.
- Presence of any other conditions (eg, geographic, social…) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study.

7.2.4 Additional exclusion criteria during or at the end of the run-in period

E 31. Patient who has withdrawn consent before enrollment/randomization.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Dupilumab

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

8.1.2 Placebo for dupilumab

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

8.1.3 Preparation of investigational medicinal product

Dupilumab in prefilled syringes will be dispensed to the patients, if required for home administration.

8.1.4 Dosing schedule

Regardless of the treatment arm, all randomized patients will receive q2w SC administrations of either dupilumab or placebo on Day 1 (V2). Every other week IMP administrations must be separated by at least 11 days (See Section 1.2).

At V2, the Investigator (or delegate) will perform the injection. After V2, q2w administration of IMP will be performed at the investigational site up to at least Week 8 (V6). The IMP will be administered following clinic procedures and blood collection. Patients will be monitored at the study site for at least 30 minutes (or minimum time approved by the local regulator) after injections for signs of a hypersensitivity reaction.

From Week 10, q2w home administration of IMP (by patient, caregiver, or health care professional) is possible if the patient (or caregiver) has been trained for 4 injections. Training must be documented when completed successfully and training injections must be recorded in the source documents. When IMP is administered at home, the patients must be advised by the site staff to self-monitor for potential signs and symptoms that may suggest a hypersensitivity reaction for at least 30 minutes after administration (or minimum time approved by the local regulator). If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or healthcare professionals to administer IMP for the doses not scheduled to be given at the study site. If the patient, or caregiver(s) do not develop the comfort to inject the IMP 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 (caregiver trained by Investigator or Delegate) or healthcare professional but not the patient themselves.

Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the patient. For doses not given at the study site patients will complete a paper dosing diary to document compliance with self-injection (or caregiver) of IMP, location of injection, and any symptoms. The diary will be kept as source data in the patient's study file.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Intranasal corticosteroid background therapy

On a daily basis throughout the study, the patient will use an e-diary to record daily use of mometasone furoate nasal spray (MFNS) (NASONEX) 50 µg/actuation nasal spray suspension, (refer to the package insert & SmPC for a description, administration details and precautions for use). MFNS is provided in a bottle that contains 18 g (140 actuations) of product formulation. The Sponsor will provide the MFNS to the Investigator sites for dispensing to the patients. If patient is unable to tolerate 200 micrograms twice a day (total dose 400 micrograms) due to experiencing AE, patient may reduce dose to 200 micrograms once per day.

Detailed instructions for transport, storage, preparation, and administration of noninvestigational medicinal product (NIMP) are provided to the patient. Patients will complete the e-diary to document compliance. The e-diary will be considered as source data.

8.2.1.1 Run-In Period

After V1, once patient eligibility for study entry has been confirmed, all patients will enter a run-in period of 4 weeks during which they will receive starting at V1 MFNS:

- Two actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg), unless they are unable to tolerate the BID regimen or this dose is not approved in specific countries, in which case, they will follow a once daily (QD) regimen.

MFNS will be self-administered by the patient, and at each visit the Investigator must ensure that the patient has the necessary doses up to the next visit, knowing that one MFNS device (1 bottle) contains sufficient doses for either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen.

Patients who receive rescue medication including INCS drops or systemic (oral, intravenous [IV], intramuscular [IM]) steroids between V1 and V2 will not be randomized. They can be rescreened as described in Section 10.1.

8.2.1.2 Randomized treatment period

During the randomized treatment period, all patients will continue on the MFNS stable dose initiated at V1. If they experience an AE during the treatment period, patients can reduce the frequency of MFNS administration.

8.2.1.3 Post treatment period

Upon completing the randomized treatment period (or following early discontinuation of IMP or discontinuation from the study), patients can continue treatment with the stable dose of MFNS that was maintained throughout the randomized treatment period until the EOS visit, or modify treatment based on medical judgment.

If surgery is scheduled after the planned end of study, EOS visit will not be delayed. A follow up contact(s) should be performed around the time of planned surgery to document the surgery date and outcome (see Section 9.2.1.5). Surgery data will be collected until e-CRF closure of the trial.

8.2.2 Rescue treatment

During the study treatment period and off-treatment follow-up, based on clinical evaluation, in case of worsening of endoscopic/radiological signs and/or clinical symptoms requiring medical intervention, the Investigator may consider rescue treatment with:

- Nasal lavage with saline and/or systemic antibiotics (up to 2 weeks in case of acute infection).
- Short course OCS (prednisone or prednisolone up to 2 weeks).
- Sino-nasal surgery for nasal polyps. Based on previous observations from the POC study, 8 weeks of IMP treatment is recommended prior to surgery to allow onset of treatment effect.

Patients receiving rescue medication during the study should continue on study drug unless the Investigator decides to withdraw the study treatment. Before starting treatment with SCS, patients should come to the study site for clinical assessments including endoscopy and PROs.

Patients scheduled for sino-nasal surgery may continue IMP up to the time of surgery or EOT whichever date comes first and at time of surgery will be permanently discontinued from study treatment and perform the efficacy and safety assessments planned at the EOT visit and return to the site for additional visits as described in Section 10.3.1.

In any case, patients who prematurely discontinue the treatment will be encouraged to return to the study site for the efficacy and safety assessments planned at EOT visit and for additional visits as described in Section 10.3.1.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matching 2 mL prefilled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab/placebo) glass prefilled syringes will be prepared such that the treatments (dupilumab and its matching placebo according to its dose) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by sanofi. Both the patient and Investigator will be blinded to assigned active drug or placebo for the whole study period. For further details, see Section 8.5, Packaging and Labeling.

Study patients, Investigators, and study site personnel will not have access to the randomization code list except under circumstances described in Section 8.3.2.

Refer to Section 10.5 for suspected unexpected adverse drug reaction (SUSAR) unblinding by the Sponsor.

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.

If possible, a contact should be initiated with the Monitoring Team before breaking the code. 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), it is not required to withdraw the patient from treatment.

At the facilities where the PK measurements, ADA and selected biomarkers are determined, the samples will be analyzed prior to database lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

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

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

A randomized treatment kit number list will be generated centrally by sanofi. The IMP (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 one of the following treatment arms using a 1:1 randomization ratio:

- Arm A: dupilumab 300 mg SC q2w until Week 24.
- Arm B: placebo matching dupilumab SC q2w until Week 24.

Approximately 240 (120 patients/arm) patients shall be randomized. Randomization will be stratified based on asthma status (history of asthma or not), prior NP surgery (yes or no) and country.

In order to have adequate number of patients for the subgroup analysis of patients with asthma/NERD and prior surgery enrollment of the following categories of patients will be limited as follows (see rationale Section 4.2):

- Patients without asthma and/or NERD history will be limited to 120 patients (out of the total 240 randomized patients).
- Patients without prior surgery will be limited to 120 patients (out of the total 240 randomized patients).

At randomization, IVRS will allocate to a patient a treatment number for dupilumab or placebo. A patient cannot be randomized more than once in the study.

Patients who meet exclusion criteria may be rescreened and a different patient identification will be issued. 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 who are rescreened must sign a new consent form and all V1 procedures must be repeated. The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via the IVRS/IWRS which will be available 24 hours a day.

8.5 PACKAGING AND LABELING

From randomization (V2) up to Week 22, dupilumab 300 mg or placebo will be supplied as one glass prefilled syringe packed in one patient kit box. The kit boxes for Arm A (300 mg q2w administration) will contain only dupilumab 300 mg syringes and the kit boxes for Arm B (placebo q2w administration) will contain only placebo syringes.

Mometasone furoate nasal spray will be supplied as commercial product of a box containing a bottle. Both bottle and box will be relabeled.

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

Dupilumab and placebo IMPs should be stored at a temperature between 2°C and 8°C. Mometasone furoate nasal spray storage conditions are specified on the bottle and its box.

All IMP and NIMP should be stored 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. NASONEX should be stored at room temperature.

Control of storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the sanofi compound should be managed according to the rules provided by the Sponsor. It is the responsibility of the Investigators to inform the patients regarding the mandatory storage requirements for the IMP. No temperature monitoring will be performed at the patients' homes.

8.7 RESPONSIBILITIES

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

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

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

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

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

8.7.1 Treatment accountability and compliance

The Investigator or delegate will keep accurate records of the quantities of the IMP dispensed and returned, used and unused and NIMP dispensed and returned, used and unused by each patient.

- Proper recording of treatment kit numbers as required on appropriate electronic case report form (e-CRF) page for accounting purposes.
- All medication treatment kits (whether empty or unused) will be returned by the patient at each visit when a treatment dispensing is planned, and at the EOT visit.
- The completed patient diary (returned to the site at each visit), returned IMP treatment and NIMP kit boxes (used and unused) along with any unused prefilled syringes will be used for drug accountability purposes. Patients will also return used prefilled syringes to the site in a sharps container.
- The Investigator (or designee) will track treatment accountability/compliance, by diary, and by counting the number of used and unused treatment kits and syringes and will complete the appropriate page of the patient treatment log.
- The monitor in charge of the study will check the data entered on the IMP and NIMP administration page by comparing them with the IMP and NIMP that have been retrieved and the patient treatment log forms. Reconciliation will occur with paper and electronic diary as appropriate depending on study visit/period.

8.7.2 Return and/or destruction of treatments

Whenever possible all partially used, used or unused IMP and NIMP provided by the Sponsor will be destroyed on site according to the standard practices of the site. A detailed treatment log of the destroyed IMP and NIMP supplied by the Sponsor will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy any IMP and NIMP supplied by the Sponsor unless the Sponsor provides written authorization. When destruction at site cannot be performed, all IMP and NIMP supplied by the Sponsor will be retrieved by the Sponsor. A detailed treatment log of the returned IMP and NIMP supplied by the Sponsor will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

8.8 CONCOMITANT MEDICATION

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

8.8.1 Prohibited concomitant medication

The following concomitant treatments are not permitted during the run-in period and/or the randomized treatment period:

- Any systemic immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrilomus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, and cyclophosphamide.
- Anti-IgE therapy (omalizumab)
- Mepolizumab or Reslizumab
- Allergen immunotherapy (except if initiated more than 3 months prior to V1 and dose stable 1 month prior to V1).
- Intranasal corticosteroid drops.
- Long term use of intranasal decongestants
- Long term courses (>2 weeks) of systemic steroids.
- Short term courses (≤2 weeks) of IV, IM, SCS except as indicated treatment of NP or to treat other serious coexisting disease (such as asthma).
- Short course use (≤2 weeks) of SCS between V1 and V2.
- Live, attenuated vaccines (Appendix A).
- Monoclonal antibodies.

Patients who between V1 and V2, receive any of the prohibited treatments, or treatment with INCS drops or systemic (oral, IV, IM) steroids, or undergo surgery will not be randomized. They may, however, be rescreened following the procedures described in Section 10.1.

8.8.2 Permitted concomitant medication

The following treatments are allowed:

- MFNS during the run-in period and throughout the whole study.
- Nasal normal saline lavage (only considered rescue if initiated after V2).
- Single topical decongestants administration for example oxymetazoline hydrochloride (to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic for example lidocaine are allowed before endoscopy.
- Short term use of antibiotics (<2 weeks) are allowed during the study.
- Short-acting β_2-adrenoceptor agonist, long-acting β_2-adrenoceptor agonist and long-acting muscarinic antagonist.
- Methylxanthines (for example theophylline, aminophyllines).
- Inhaled corticosteroids.
- Systemic antihistamines.
- Leukotriene antagonists/modifiers are permitted during the study, only for patients who were on a continuous treatment for ≥30 days prior to V1.

- Allergen immunotherapy in place for ≥3 months prior to V1 is permitted.
- Rescue medication including short courses of SCS for treatment of NP as described in Section 8.2.2 or short courses of SCS to treat other serious coexisting diseases (such as asthma exacerbation) are allowed.

Cytochrome P450 (CYP) substrates

The impact of dupilumab on cytochrome P450 (CYP450) enzymes activity has not been studied and the effect on dupilumab on the levels of IL-4 and IL-13 cytokines has not been fully characterized.

However, literature data of studies in human hepatocytes indicate that the IL-4 was able to upregulate CYP450 2E1, 2B6, 3A4 mRNA expression or down regulate CYP1A2 mRNA (26, 27). Another study in human peripheral blood mononuclear cells incubated with various Th2 cytokines, reports that Th2 cytokines IL-4 and IL-13 generally increased the protein expression of CYP2B6 and CYP3A4 (28).

A drug-drug interaction study (R668-AD-1433) designed to examine the effects of dupilumab on the PK of selected CYP450 substrates in adult patients with moderate to severe AD was completed recently. The data indicated no clinically meaningful effect of dupilumab on CYP1A2, CYP3A4, CYP2C19 or CYP2C9 activity.

During the study medication and at least up to the end of follow-up, caution should be used for drugs with narrow therapeutic index that are metabolized via these CYP450 isoforms.

This means that unless the drug is prohibited in the study Section 8.8.1, 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.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

Investigators must make their best efforts educating their patients on the importance of sticking to visit schedules, study required procedures and assessments up to the end of the study. Investigators must make best efforts to prevent missing data, in order that a high level of quality can be achieved for the study.

9.1 COPRIMARY ENDPOINTS

There are 2 coprimary endpoints for this study for countries other than Japan:

1. **Change from baseline in nasal congestion/obstruction (NC) at Week 24:** NC is assessed by the patient on a daily basis from V1 and throughout the study, using an e-diary using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms) (2).

Nasal congestion/obstruction will be scored as a reflective score (evaluation of symptom severity over the past 24 hours) by the patient (see Table 1).

Table 1 – Symptom severity score

Scale	Symptoms
0	No symptoms
1	Mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated)
2	Moderate symptoms (definite awareness of symptoms that is bothersome but tolerable)
3	Severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living)

The e-diary is dispensed at V1 and information is downloaded from this device on the other indicated days.

A severity ≥2 on the day of V1 and a weekly average severity greater than 1 at time of randomization (V2) is required and will be provided to the site to determine patient eligibility. If there are 4 or more measurements collected within 7 days prior to randomization, the baseline will be the average of these measurements; if less than 4 measurements are collected, the baseline will be the average of the most recent 4 prior to randomization.

For the baseline to EOT analysis, 4 weeks average of the symptom scores will be used.

2. **Change from baseline in NPS at Week 24:** NPS (17, 18, 24) is assessed by central video recordings of nasal endoscopy. The score (NPS) is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. NPS is graded based on polyp size described in Table 2.

Table 2 - Endoscopic nasal polyp score

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

Nasal endoscopy should be performed at the end of the scheduled visits before the administration of IMP and preceded by local administration of anesthetic drugs in combination with a decongestant.

Standard video sequences will be downloaded or sent to centralized reader. Centralized imaging data assessments and scoring by independent physician reviewer(s) for the imaging data will be performed for all endoscopies. To confirm eligibility at V2, only the V1 central reading will be made available to the site. In addition at V2 the Investigator will perform the nasal endoscopy to confirm eligibility score and enter the result in the e-CRF. Thus the patient is considered eligible based on a V1 central reading followed by a V2 local reading NPS score of 5 or more and at least 2 each side. The final results of central reading from V2 onward will be made available after the study.

For the analysis of primary endpoint, central reading of V2 will be used for comparison with the Week 24 reading. The sites will remove patient-identifying information from the imaging data header prior to sending the imaging data to the central reader.

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

3. **Lund-Mackay score**
   For Japan, in addition to the two coprimary endpoints above, the following will also be a coprimary endpoint:

The LMK system is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The OC is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side. This scoring system has been validated in several studies (29, 30, 31).

For patients in whom the OC is missing (because of a previous surgery) the reader should consider the location of the former OC and provide a scoring (as if the OC was there).

CT scan should be performed anytime during the run-in period before first administration of IMP, and at V8 (Week 24). Whenever possible a cone beam CT scan should be utilized. In countries for which a specific approval procedure for the CT scan is required by a different committee than the

local independent ethics committee (IEC)/institutional review board (IRB), patients may be enrolled using a CT available in the previous year or perform an MRI of the sinuses between V1 and V2. These countries will be exempted from all the planned study CT scans until approval from these committees is received. The MRI will be used only for confirmation of exclusion criteria.

Details for CT will be available in a separate operational manual provided to the sites.

CT scans central reading for LMK scoring will be used for the analysis.

9.2 SECONDARY ENDPOINTS

9.2.1 Key secondary efficacy endpoints

For the analysis of key secondary endpoints see Section 11.4.2.2.

9.2.1.1 Disease specific daily symptom assessment and total symptom score (TSS)

On a daily basis from V1 and throughout the study, the patient will use an e-diary to:

- Respond to the morning individual rhinosinusitis symptom questions using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms) (2):
  - Congestion and/or obstruction.
  - Loss of sense of smell.
  - Anterior rhinorrhea (runny nose).
  - Posterior rhinorrhea (postnasal drip).

The total symptom score is a composite score (ranging between 0 and 9) consisting of the sum of the following symptoms assessed daily in the morning: NC, decreased/loss of sense of smell, rhinorrhea (average of anterior/posterior nasal discharge).

9.2.1.2 Smell test: University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT (UPSIT 40-odorant test) is a rapid and easy-to-administer method to quantitatively assess human olfactory function. The UPSIT shows a high test-retest reliability (r: 0.981) and scores on this test are strongly correlated with the detection threshold for phenyl ethyl alcohol in the same individuals. When the UPSIT is administered in the standardized manner, clinical subjects show a high degree of uniformity in UPSIT performance when tested in different laboratories.

The test will be dispensed to the patient by the study site personnel and consists of 4 booklets, each containing 10 odorants with one odorant per page. The test-time is about 15 minutes. The stimuli are embedded in 10 to 50 (mu) diameter plastic microcapsules on brown strips at the bottom of each page. Above each odorant strip is a multiple choice question with 4 alternative words to describe the odor. The subject is asked to release the odorant by rubbing the brown-strip

with the tip of a pencil and to indicate which of 4 words best describes the odor. Thus each subject receives a score out of 40 possible correct answers. The final score will be recorded in the e-CRF. The odorants of the UPSIT test utilized in this study will take into account cultural differences.

The 40-odorant UPSIT is used in over 1500 clinics and laboratories throughout the US, Canada, South America, and Europe, and has been administered to nearly 200 000 people since its development in the early 1980s. A particular strength of this test is that it provides an olfactory diagnosis based on comparing the patient's test score with normative data, providing a percentile score of an individual relative to his or her age-matched normal group. Furthermore, a clinician can distinguish patients with a normal sense of smell ("normosmia") from those with different levels of reduction ("mild, moderate and severe microsmia") or loss ("anosmia") (32).

9.2.1.3 Decreased/loss of sense of smell

The decreased/loss of sense of smell severity is assessed by the patient on a daily basis from V1 and throughout the study, using an e-diary to using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms).

9.2.1.4 Lund-Mackay score

Lund-Mackay score is a secondary efficacy endpoint in countries other than Japan. Details of this endpoint are presented in Section 9.1.

9.2.1.5 Proportion of patients during the treatment period who receive SCS rescue or are planned to undergo surgery for NP

SCS rescue

Oral steroids for rescue treatment of nasal polyps or for another reason will be prescribed to the patient by the site depending on local legislation/regulation. PROs and a nasal endoscopy should be performed before starting treatment with SCS. The Investigator (or designee) records the date and dosing information (daily dose, duration, INN) on the appropriate page(s) of the e-CRF. Indication for SCS use will also be captured by selecting one or more of the following categories:

1. Nasal polyposis
2. Asthma
3. Other respiratory disease (specify)
4. Other ear, nose or throat disease (specify)
5. Other reason (specify).

Surgery (actual or planned) for NP

For patients who have a surgery or have a scheduled date for sino-nasal surgery for NP, the reason (worsening signs and/or symptoms during the study), the expected or actual surgery date, the type and outcome of surgery will be recorded in a specific CRF page. If surgery:

- Is performed during the study treatment period, patient and Investigator may decide to continue IMP up to the time of surgery or EOT whichever date comes first. At the time of surgery patients will be permanently discontinued from study treatment and assessed as soon as possible using the procedures normally planned for the EOT Visit and will be instructed to return to the study site as described in Section 10.3.1. An AE or SAE page will be completed.
- Is performed during the follow-up the patients will be assessed according to the procedures normally planned for the EOS Visit and will be instructed to return to the study site as described in Section 10.3.1 An AE or SAE page will be completed.
- If surgery is scheduled after the planned end of study, EOS visit will not be delayed. A follow up contact(s) should be performed around the time of planned surgery to document the surgery date and outcome. Surgery data will be collected until e-CRF closure of the trial.

9.2.1.6 22-Item Sino-nasal Outcome Test (SNOT-22)

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on HRQoL (Appendix B). The SNOT-22 has 22 items on a 5-category scale applicable to sino-nasal conditions and surgical treatments. The range of the global score is 0 to 110 and a minimal important difference (MID), the smallest difference between clinical trial arms mean change from baseline (point estimates) that will be interpreted as important, of 8.9 (33). Lower scores indicate less impact and the recall period is the past 2 weeks. There are 5 domains that can be described within SNOT-22, including nasal, ear, sleep, general and practical, and emotional.

9.2.2 Other secondary endpoints

For the assessment of other secondary endpoints, see analyses of efficacy endpoints, Section 11.4.2.4.

9.2.2.1 SCS dose and number of courses

Total SCS rescue dose prescribed (in mg/year) during the study period and total SCS rescue intake in days and courses during the study period could be derived based on SCS dose prescribed and intake days of SCS during the study, recorded in e-CRF pages.

A course of SCS is considered continuous if treatment is separated by less than 7 days. Various doses of systemic corticosteroids will be converted to prednisone-equivalent OCS.

9.2.2.2 Visual analog scales (VAS)

The visual analog scale (VAS) for rhinosinusitis is used to evaluate total severity (2). Rhinosinusitis disease can be divided into MILD, MODERATE and SEVERE based on total severity VAS score (0 to 10 cm):

- MILD = VAS 0 to 3
- MODERATE = VAS >3 to 7
- SEVERE = VAS >7 to 10.

The patient is asked to indicate on a VAS the answer to the question: "How troublesome are your symptoms of rhinosinusitis?"

The VAS ranks from 0 (Not troublesome) to 10 (Worst thinkable troublesome) (Appendix D).

9.2.2.3 Nasal peak inspiratory flow

Nasal peak inspiratory flow (NPIF) evaluation represents a physiologic measure of the air flow through both nasal cavities during forced inspiration expressed in liters per minute. The NPIF is the best validated technique for the evaluation of nasal flow through the nose. Nasal inspiration correlates most with the subjective feeling of obstruction and is the best validated technique for monitoring nasal flow in clinical trials.

On V1, patients will be issued an NPIF meter for recording morning NPIF. Patients will be instructed on the use of the device, and written instructions on the use of the NPIF meter will be provided to the patients. In addition, the Investigator will instruct the patients on how to record the following variables in the e-diary on a daily basis.

- AM NPIF performed within 15 minutes after arising (before 12 noon) prior to taking MFNS.

Three NPIF efforts will be performed by the patient; all 3 values will be recorded by the patient in the e-diary, and the highest value will be used for evaluation. The procedure takes about 5 minutes.

Baseline AM NPIF will be the mean AM measurement recorded for the 7 days prior to the first dose of IMP. If fewer than 4 measurements are collected during the 7 days, the average of the most recent 4 prior to randomization during the run-in period will serve as the baseline.

The NPIF will be performed daily from V1 to Week 24 (V8). After V8 the NPIF will be performed every 4 weeks.

The nasal flow is expressed in liters per minute, and consecutive measurements are performed. Taking the best of 3 outcomes with less than 10% variation is considered to be the best means of expression of the result (32).

9.2.2.4 Asthma Control Questionnaire, 6-question version (ACQ-6) in those patients comorbid with asthma

The asthma control questionnaire-6 (ACQ-6) 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. Only patients with comorbid asthma will be asked to complete the questionnaire in the e-diary during clinic visits. Patients should complete the questionnaire before the spirometry test.

The ACQ-6 has 6 questions which assess the most common asthma symptoms:

- Frequency in past week awoken by asthma during the night.
- Severity of asthma symptoms in the morning.
- Limitation of daily activities due to asthma.
- Shortness of breath due to asthma.
- Frequency of wheezing.
- Short-acting bronchodilator use.

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

A global score is calculated: the questions are equally weighted and the ACQ-6 score is the mean of the 6 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-6, 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, ability to detect change have been documented in the literature (34).

9.2.2.5 Health related quality of life (HRQoL)

9.2.2.5.1 Euro-QOL-5D

The European quality of life-5D scale (EQ-5D) (Appendix C) is a standardized HRQoL questionnaire developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal (35). EQ-5D is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ VAS. 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 VAS. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

9.2.2.5.2 Short Form 36 (SF-36) Version 2

The SF-36 (Short-Form-36 (SF-36)-Version 2.0) (Appendix G) is a generic questionnaire measuring general health status (QoL) in the last 4 weeks before completing the questionnaire. The SF-36 is a 36-item questionnaire that measures eight multi-item dimensions of health: physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items).

For each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardized summary scores can also be calculated from the SF-36; the physical component summary (PCS) and the mental health component summary (MCS).

In this study SF-36 will be assessed only at V2 to evaluate the baseline QoL impact in the defined phase 3 population.

9.3 EXPLORATORY ENDPOINTS

- Healthcare resource utilization.
- Proportion and time-to-event of patients with SCS rescue for nasal polyps.
- Proportion and time-to-event of patients who have or are planned for surgery for nasal polyps.
- Change from baseline in decreased/loss of sense of taste symptom severity.
- SNOT-22 items: 'decreased sense of smell/taste', 'difficulty falling asleep,' 'wake up at night,' 'lack of a good night's sleep,' 'wake up tired,' 'fatigue,' and 'reduced productivity'.
- Patient reported outcomes including HRQoL scale (Index Score of EQ5D-5L)
- Pharmacodynamic biomarkers in blood and urine.
- Microbiome in nasal mucus swab.
- [redacted]
- FEV1, FVC and FEF 25-75 in patients with asthma.
- Efficacy endpoints for the subgroup of patients with systemic corticosteroid use in the year prior to study (V1).

9.3.1 Spirometry

Spirometry will be performed at local level (study site or another facility) in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours. FEV1, forced vital capacity (FVC), and forced expiratory flow at 25% to 75% of forced

vital capacity (FEF 25-75) will be determined at the designated treatment visits. The result of FEV1 (% of predicted normal), FVC, and FEF 25-75 should be recorded in the e-CRF anytime during run-in period (before V2) for all patients, and in patients with asthma for the other scheduled visits during the randomized treatment period and follow-up.

Whenever possible the same spirometer and standard spirometric techniques, including calibration, must be used to perform spirometry at all visits and the same person should perform the measurements.

9.4 SAFETY ENDPOINTS

9.4.1 Adverse events

Refer to Section 10.4 to Section 10.6 for details.

9.4.2 Laboratory safety variables

The clinical laboratory data consist of blood and urine analysis (including serum hematology and clinical chemistry). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

- Hematology includes: hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.
- Serum chemistry includes: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), ALT, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and CPK.
- HIV screening (anti-HIV-1 and HIV-2 antibodies)
- Anti-nuclear antibody (ANA). Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

9.4.3 Hepatitis screening

Clinical laboratory testing at V1 includes hepatitis screen covering HBsAg, hepatitis B surface antibody (HBsAb), HBcAb including HBcAb IgM and total, and HCVAb. In case of results showing HBsAg (negative), and HBcAb total or HBcAb IgM (positive), an HBV DNA testing must be performed prior to randomization to rule out a false positivity if the Investigator believes the patient is a false positive, or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the patient is a false positive.

In countries where there is local regulatory requirement, for patients who are HBsAg negative and HBsAb positive at V1, hepatitis B viral load will be tested at V2 and V8.

9.4.4 Pregnancy test

A serum pregnancy test (β-hCG) will be performed at run-in (V1) in WOCBP, and a urine dipstick pregnancy test will be performed at V2 prior to randomization and every 4 weeks during the study. A negative result must be obtained at V1 and V2 prior to randomization.

In case of positive urinary test the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases.

9.4.5 Vital signs

Vital signs include: blood pressure (mmHg), heart rate (beats per minute), respiration rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg). Height (cm) will be measured at V1 only. Vital signs will be measured in the sitting position using the same arm (preferably) at each visit, and will be measured prior to receiving IMP at the clinic visits.

9.4.6 Physical examination

Physical examinations will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient's disease.

9.4.7 Electrocardiogram variables

A standard 12-lead electrocardiogram (ECG) will be performed at the sites at the time points noted in the study flow chart (see Section 1.2) to monitor any potential abnormality. In case of an abnormal ECG finding, the Investigator should enter details into the e-CRF. At V2, the Investigator should use their medical judgment to consider whether the patient is eligible for the study.

9.5 OTHER ENDPOINTS

9.5.1 Functional dupilumab concentration and antidrug antibodies in serum

9.5.1.1 Sampling time

Predose blood samples will be collected for determination of functional dupilumab (PK) in serum and antidupilumab antibodies at timepoints designated in the study flow chart (see Section 1.2). The date of collection should be recorded in the patient e-CRF. The date and time will also be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

In the event of any serious adverse event (SAE) or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe injection site reaction

lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes. An unscheduled systemic drug concentration page in the e-CRF must be completed as well.

Patients who are ADA positive at their last study visit (early termination or planned EOS), may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall clinical presentation at the time of discontinuation.

9.5.1.2 Handling procedure

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedures for samples used in the determination of functional dupilumab serum concentration and ADAs is provided in Table 3.

Table 3 - Summary of handling procedures for SAR231893 (dupilumab)

Sample type	Functional dupilumab serum concentration	Antidupilumab 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	Two aliquots	Two aliquots
Storage conditions	<6 months: below -20°C	<6 months: below -20°C
Serum shipment condition	≥6 months: below -80°C (preferred)	≥6 months: below -80°C (preferred)
	In dry ice	In dry ice

9.5.1.3 Bioanalytical methods

Serum 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 concentration	Anti-dupilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	ECL bridging

ECL electrochemiluminescence; ELISA enzyme-linked immunosorbent assay

9.5.1.4 Functional dupilumab concentration and antidrug antibody measurement and samples

Predose functional dupilumab concentrations in serum at V2 (Day 1), dupilumab trough concentrations at Week 4, Week 8, Week 16, Week 24 (EOT), and post treatment at Week 36 and Week 48 (EOS) will be provided.

Antidupilumab antibody status (negative or titer value) will be provided for samples collected at timepoints as specified in the study flow chart.

Patients who are ADA positive at their last study visit (early termination or planned EOS), will be considered for follow-up based on the overall clinical presentation at that time.

Unused samples collected for drug concentration or ADA analyses may be used for exploratory analyses if the specific Future Use of Samples Informed Consent is signed (see Section 9.6).

9.5.2 Pharmacodynamics

Several biomarkers related to CRSwNP and Th2 polarization will be assessed for their value in predicting therapeutic response and/or in documenting the time course of drug response.

Patients, Investigators and site personnel will not have access to assay results for total IgE, allergen-specific IgE (including aeroallergen and Staphylococcal aureus enterotoxin-specific IgEs), while the study is ongoing, as the related data are not essential for patient care and have the potential for unblinding the study treatments.

Sample collection will be performed as per the study flow chart (Section 1.2) and assay methodologies are briefly summarized below. In general, duplicate aliquots of each sample for PD biomarkers should be stored to assure generation of a complete set of assay results. 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.

9.5.2.1 Serum biomarkers

Total IgE, allergen-specific IgE for aeroallergens (regional panels) and Staphylococcus aureus enterotoxins A and B IgE will be measured using quantitative methods (eg, ImmunoCAP® FEIA), approved for diagnostic testing.

Thymus and activation-regulated chemokine will be assayed with a validated enzyme immunoassay (eg, Human TARC Quantikine ELISA kit; R&D Systems).

Concentrations of periostin will be assayed with a validated immunoassay.

9.5.2.2 Plasma biomarkers

Eotaxin-3 will be measured in heparinized plasma with a validated enzyme immunoassay.

9.5.2.3 Urine biomarkers

Leukotriene E4 and a metabolite of prostaglandin D2 (PGDM) will be measured in morning spot urine samples using validated quantitative assays. Assay results will be reported per mg of creatinine.

9.5.2.4 Microbiome in nasal mucus

Using a nasal swab, mucus will be collected from the middle meatus of each nostril and assessed for relative abundance of microbes, in all patients prior to MFNS administration. A minimum of 2 hours should be allowed following MFNS administration in all patients prior to collection.

9.5.3 [redacted]

[redacted]

[redacted]

9.6 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 [redacted] For patients who have consented to it, archival blood samples will be collected at the visit specified in the study flow chart, 10 mL each, will be collected into a dry, red topped tube with clotting activator (or into smaller tubes of equivalent total volume) kept at room temperature for 30 minutes and then centrifuged at approximately 1500 g for 10 minutes at room temperature. The serum will then be transferred, in equal portions, into 3 storage tubes, which will be immediately capped and frozen in an upright position at -20°C or colder.

These archived serum samples, and any residual or leftover serum, plasma or blood remaining from planned laboratory work, may be used for research purposes related to airway disease, response to dupilumab treatment, additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol.

These samples will remain labelled with the same identifiers as the ones used during the study (ie, Subject ID, Sample ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see Section 14.3 and Section 14.5).

9.7 APPROPRIATENESS OF MEASUREMENTS

Refer to Section 4.4.1 for rationale on the coprimary and secondary endpoints. The proposed study design and endpoints will answer important clinical questions about the efficacy on symptoms and objective signs of the disease and the effect of dupilumab on reduction of SCS rescue therapy and surgery, which are the most relevant clinical practice assessments and reflect current standard of care.

10 STUDY PROCEDURES

Medical history should be recorded consistent with Good Clinical and local practice. This would typically include atopic medical history (including asthma history, hypersensitivity to aspirin or NSAIDs, NERD, allergy/atopy history), history of surgeries, concomitant medications, etc.

10.1 VISIT SCHEDULE

This section describes how the visits are carried out, in chronological order (according to the flow chart Section 1.2 and identical to the order shown in the e-CRF):

The clinical trial consists of 3 periods, using an add-on therapy approach to INCS:

- Run-in period (28 days +/-3 days; V1).
- Randomized treatment period (up to 24 weeks +/-3 days; V2 to V8).
- Post treatment period (24 weeks +/-3 days; V9 and V10).

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

If a patient is prematurely discontinued from treatment, every attempt should be made for the patients to return to the study site as soon as possible after last IMP administration to perform all assessments planned at the EOT visit, and patients will be asked and encouraged to return to the study site for the visit scheduled as described in Section 10.3.1 (early treatment discontinuation) for a 24-week follow-up.

Prior to all screening assessments, after discussion of participation in the study, the written consent form including HIV as required by local regulations, [redacted] must be signed and dated (see Section 12.2).

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the visit window prior to Day 1 (V2) is respected. These patients do not need to sign a new consent form and be allocated a new patient number within this same window.

Rescreening

Patients that fail screening between V1 and V2 may be rescreened for study eligibility only once for the following criteria:

- They do not meet the inclusion criteria for a weekly average NC >1 at V2.
- They had an acute illness such as acute sinusitis, nasal infection or upper respiratory infection (E 07). These patients can be rescreened only after complete resolution of symptoms.
- They took one of the prohibited treatments listed in Section 8.8.1 below between V1 and V2.

Patients that are rescreened must sign a new consent form and all of the V1 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 or the V1 baseline CT scan of sinuses and spot urine for biomarker sampling were performed.

Note, no waivers will be approved for randomization; all patients must fulfil all eligibility criteria before randomization into the study.

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.

For patients who do not fulfil other exclusion criteria, rescreening should be discussed with the Sponsor. In all cases, a given patient can only be re-screened once.

Order of assessments

During the treatment and post treatment period if necessary, it is possible to perform the study procedures within a 3 day period as long as these days are within the scheduled visit window and the order of procedures is maintained.

It is recommended that assessments/procedures at a site visit are performed in the following order if applicable:

1. Patient-reported outcomes and other questionnaires:
    - Daily symptoms of NC, loss of smell and anterior and posterior rhinorrhoea
    - SNOT-22
    - VAS rhinosinusitis
    - Reduced sense of taste severity
    - EQ-5D
    - ACQ-6 (in patients with asthma)
    - Other questionnaires.
2. Procedures.
3. Safety and laboratory assessments.
4. IMP administration.
5. NIMP boxes should be collected at all visits following provision during all study periods.
6. IMP boxes should be collected at all visits following provision for home dosing during treatment period.

10.1.1 Visit 1 (Week -4/Day -28 +/- 3 days): Run-in period

Following a discussion of participation in the clinical trial, signed informed consent must be obtained and documented.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number, register V1, and obtain first NIMP (NASONEX) box(es).
- Interview to collect patient demographic information, NP information, other medical history (including asthma history, hypersensitivity to aspirin or NSAIDs, NERD, allergy/atopy history), surgical history (including number, type and dates of previous surgery for nasal polyps in the past), and prior and concomitant medications (including background therapy for NP and asthma), courses of SCS in the previous 2 years (number of SCS courses, doses, route of administration and duration in the previous year will be entered in the e-CRF. Long term antibiotics use [> 2 weeks] in the previous year will be also entered in the e-CRF).
- Review entry criteria to assess eligibility, with special attention to verify and document the following:
  - Use of SCS for NP within 2 years prior to V1; and/or contraindication/intolerance to SCS; and or prior surgery for NP (whenever in the past)
  - Nasal polyp score of 5 or greater (and at least 2 in each side).
  - Presence of NC (blockade/obstruction) severity ≥2 on the day of V1 and loss of smell, rhinorrhea (anterior/posterior).
  - Patients have not received any of the prohibited medications described in E 03 and/or Section 8.8.1.
- Measure vital signs: blood pressure, heart rate, respiration rate, body temperature, weight, height.
- Perform physical examination.
- Perform CT scan (within the time period between V1 and V2, prior to first administration of IMP). In countries for which a specific approval procedure for the CT scan is required by a different committee than the local IEC/IRB, patients may be enrolled using a CT available in the previous year or perform an MRI of the sinuses between V1 and V2.
- Perform spirometry within the time period between V1 and V2, for all patients and ensure that patients with co-morbid asthma have FEV1>50%. Spirometry will be performed after the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol has been withheld for at least 6 hours.
- Obtain blood samples for screening clinical laboratory determinations: Hematology and serum chemistry (see Section 9.4.2 for details)
- Obtain blood samples for hepatitis screen (HBsAg, HBsAb, HBcAb, HCVAb, HIV screen (anti-HIV-1 and HIV-2 antibodies) and antinuclear antibody (ANA). In case of results showing HBsAg (negative), and HBcAb total or HBcAb IgM (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the

Investigator believes the patient is a false positive, or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCVAb (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the patient is a false positive.

  - Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

- Obtain serum β-hCG pregnancy test if WOCBP.
- Perform chest X-ray if no chest imaging (X-ray, CT, magnetic resonance imaging) available within the previous year as per local standard of care, or if there is local requirement. In countries for which specific approval procedure for the X-ray or CT scan is required by a different committee than the IEC/IRB, a chest MRI between V1 and V2 can be performed).
- Perform nasal endoscopy and send to central reader.
- Dispense e-diary/NPIF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- NIMP: Dispense MFNS for use as mandatory background therapy throughout the study. Ensure that the patient has sufficient quantity for dosing up until the next visit, knowing that one MFNS bottle contains sufficient doses for either 2 weeks of BID treatment or 4 weeks of QD treatment. Instruct patient to record usage in the e-diary.
- Start AE reporting.
- Review and record all medication use with start date and dose in e-CRF.
  - Check for use of prohibited medications.
- Advise patients with comorbid atopic conditions (such as asthma) not to adjust their treatment without consultation with their physicians.
- Schedule appointment for the next visit.

10.1.2 Visit 2 (Week 0): Randomization

- PRO patient administration in the e-diary before seeing the physician:
  - Daily symptoms of NC, loss of smell and anterior and posterior rhinorrhoea
- Inquire about AEs/SAEs and background therapy tolerability.
- Review and record all medication use with start date and dose in e-CRF.
  - Check for use of prohibited medications.
- Download data from e-diary/NPIF meter and check compliance with use of the mandatory background therapy (MFNS), as defined as:
  - ≥80% of total number of prescribed “stable dose” sprays taken during the run-in period. Compliance is verified based on MFNS use recorded in the patient e-diary.
  - Remind patient to bring the device to the next visit.

- Confirm patient eligibility:
  - Review V1 nasal endoscopy results from central reader to confirm that patient has a score of 5 or more and at least 2 each side.
  - Perform and review local nasal endoscopy to confirm that patient still has a score of 5 or more and at least 2 on each side and record result in e-CRF. If the patient does not have the required scores at the V2 nasal endoscopy, the inclusion criteria are not fulfilled and the patient should not be randomized.
  - Record symptoms of sinusitis, and check the severity average of the last week before V2 is >1 for NC.
  - Record spirometry result from V1 and FEV1(liters and predicted), FVC and FEF 25-75 result in the e-CRF. Confirm eligibility for patients with FEV1 >50%.
  - Check patient compliance with daily diary.
- Investigator to assess eligibility for nasal polyp surgery.
- Perform ECG.
- Obtain urine β-hCG pregnancy test if WOCBP. In case of a positive urinary test, a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to a definitive screen failure in all cases.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Review all inclusion/exclusion criteria to reconfirm eligibility.
  - Reminder that patients receiving prohibited medications described in Section 8.8.1, including rescue with INCS drops, SCS, or surgery for NP during the run-in period, are NOT eligible for randomization.

If entry criteria are not met, call IVRS/IWRS to register the visit and screen-fail the patient. Refer to Section 8.4 for details regarding rescreening.

If the patient meets all eligibility criteria:

- Call IVRS/IWRS to register visit to randomize the patient and receive the first IMP kit number assignment and NIMP (NASONEX) boxes, if needed.
- Administer SNOT-22, VAS (for rhinosinusitis), reduced sense of taste severity, QoL (EQ-5D), ACQ-6 (for patients with asthma), and SF-36.
- Healthcare resource utilization via e-CRF.
- Administer smell test (UPSIT).
- Obtain blood samples (prior to IMP) for:
  - Hematology and serum chemistry laboratories (see Section 9.4.2 for details),
    - Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).
  - Serum dupilumab concentration and ADA.
  - Hepatitis B viral load for patients in countries/regions if there is local regulatory requirement who are HBsAg negative and HBsAb positive at V1.

  - Tuberculosis test if required by local regulation.
  - Serum and plasma biomarkers (TARC, eotaxin, and periostin).
  - Serum for total IgE, allergen-specific IgE including Staphylococcal enterotoxins IgE.
  - Stored DNA sampling, stored serum, and stored whole blood RNA, for those patients who have signed a specific informed consent form.
- Perform urine sampling for biomarkers and creatinine.
- Obtain nasal swabs for microbiome prior to MFNS administration.
- Remind patient to bring the e-diary/NPIF meter to the next visit.
- Reminder: sexually active female patients of reproductive potential are required to practice an acceptable contraception (as defined in E 15 or local protocol amendment in case of specific local requirement) during the entire study duration, while taking dupilumab and for 12 weeks after the last IMP dose. Sexually active male patients should be reminded that if their partner is a woman of childbearing potential, their partner should consider protection by acceptable method(s) of birth control.
- Administer IMP:
  - Patients will be monitored for at least 30 minutes (or minimum time required by your local regulator) after the end of administration of IMP for any signs or symptoms of a hypersensitivity reaction.
  - Throughout the study, SC injection sites will be alternated between the 4 quadrants of the abdomen (avoiding navel and waist areas) or upper thighs or upper arms, so that the same site is not injected twice consecutively. Injection in the upper arms can only be performed by a person trained for 4 injections (caregiver trained by Investigator or delegate) or health care professional, but not the patient themselves. This instruction pertains to the day the first dose is injected as well as the administration of q2w injections. Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the patient.
- NIMP:
  - Ensure that the patient has sufficient quantity for dosing up until the next visit, knowing that one MFNS bottle contains sufficient doses for either 2 weeks of BID treatment or 4 weeks of QD treatment. Dispense MFNS if needed. Instruct patient to record usage in the e-diary.
- Advise patients with comorbid atopic conditions (such as asthma) not to adjust their treatment without consultation with their physicians.
- Schedule appointment for next visit.

10.1.3 Visit 3 (Week 2 +/- 3 days)

- PRO patient administration in the e-diary:
  - Daily symptoms of NC, loss of smell and anterior and posterior rhinorrhoea
  - VAS for rhinosinusitis and

  - Reduced sense of taste severity score.
- Administer smell test (UPSIT)
- Inquire about AEs/SAEs and background therapy tolerability.
- Collect NIMP boxes
- Record all medication use with start date and dose in the e-CRF.
  - Check for use of prohibited medications.
  - Complete rescue medication/surgery page(s) of e-CRF. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.
- Call IVRS/IWRS to register visit, and obtain next IMP kit number assignment and NIMP (NASONEX) box(es), if needed, or report potential definitive IMP stop.
- Download e-diary/NPIF meter and review the data; remind patient to bring the device to the next visit.
- Administer IMP (one SC injection).
  - Patients will be monitored at the study site for at least 30 minutes (or minimum time required by your local regulator) after the injection.
- NIMP:
  - Ensure that the patient has sufficient quantity for dosing up until the next visit, knowing that one MFNS bottle contains sufficient doses for either 2 weeks of BID treatment or 4 weeks of QD treatment. Dispense MFNS if needed. Instruct patient to record usage in the e-diary.
- Schedule appointment for next visit.

10.1.4 Visit 4 (Week 4 +/- 3 days)

- PRO patient administration in the e-diary:
  - Daily symptoms of NC, loss of smell, and anterior and posterior rhinorrhea.
  - VAS for rhinosinusitis.
  - Reduced sense of taste severity score.
- Inquire about AEs/SAEs and background therapy tolerability.
- Collect NIMP boxes
- Record all medication use with start date and dose in the e-CRF.
  - Check for use of prohibited medications.
  - Complete rescue medication/surgery page(s) of e-CRF. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the

Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.

- Call IVRS/IWRS to register visit and obtain next IMP kit number assignment and NIMP (NASONEX) box(es), if needed or report potential definitive IMP stop.
- Download e-diary/NPIF meter and review the data; remind patient to bring the device to the next visit.
- Perform blood sampling for serum dupilumab concentration.
- Obtain urine β-hCG pregnancy test if WOCBP. In case of a positive urinary test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to a definitive treatment discontinuation in all cases.
- Administer IMP (one SC injection).
  - IMP can be administered by the patient or caregiver under supervision of the Investigator or the designee.
  - Patients will be monitored at the study site for a minimum of 30 minutes (or minimum time required by your local regulator) after the injection.
- NIMP:
  - Ensure that the patient has sufficient quantity for dosing up until the next visit, knowing that one MFNS bottle contains sufficient doses for either 2 weeks of BID treatment or 4 weeks of QD treatment. Dispense MFNS if needed. Instruct patient to record usage in the e-diary.
- Schedule appointment for next visit.

10.1.5 Visit 5 (Week 6 +/- 3 days)

- Inquire about AEs/SAEs and background therapy tolerability.
- Collect NIMP boxes
- Record all medication use with start date and dose in the e-CRF.
  - Check for use of prohibited medications.
  - Complete rescue medication/surgery page(s) of e-CRF. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.
- Call IVRS/IWRS to register visit and obtain next IMP kit number assignment and NIMP (NASONEX) box(es), if needed or report potential definitive IMP stop.

- Download e-diary/NPIF meter and review the data; remind patient to bring the device to the next visit.
- Administer IMP (one SC injection).
  - IMP can be administered by the patient or caregiver under supervision of the Investigator or the designee.
  - Patients will be are monitored for a minimum of 30 minutes (or minimum time required by your local regulator) after the injection.
- NIMP:
  - Ensure that the patient has sufficient quantity for dosing up until the next visit, knowing that one MFNS bottle contains sufficient doses for either 2 weeks of BID treatment or 4 weeks of QD treatment. Dispense MFNS if needed. Instruct patient to record usage in the e-diary.
- Schedule appointment for next visit.
- Remind patients with asthma to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours prior to arriving at V6.

10.1.6 Visit 6 (Week 8 +/- 3 days)

- PRO patient administration in the e-diary:
  - Daily symptoms of NC, loss of smell, and anterior and posterior rhinorrhea.
  - SNOT-22.
  - VAS for rhinosinusitis.
  - Reduced sense of taste severity score.
  - ACQ-6 (for patients with asthma)
- Health care resource utilization via e-CRF.
- Inquire about AEs/SAEs and background therapy tolerability.
- Collect NIMP boxes
- Review and record all medication use with start date and dose in e-CRF.
  - Check for use of prohibited medications.
  - Complete rescue medication/surgery page(s) of e-CRF. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.
- Call IVRS/IWRS to register visit and obtain next IMP kit number assignment and NIMP (NASONEX) box(es), if needed or report potential definitive IMP stop.

- Download e-diary/NPIF meter and review the data; remind patient to bring the device to the next visit.
- Perform spirometry (for patients with asthma) and record FEV1, FVC and FEF 25-75 result in the e-CRF.
- Administer smell test (UPSIT).
- Perform nasal endoscopy and send to central reader.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform blood sampling for serum dupilumab concentration and ADA.
- Obtain urine β-hCG pregnancy test if WOCBP. In case of a positive urinary test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to a definitive treatment discontinuation in all cases.
- Administer IMP:
  - IMP can be administered by the patient or caregiver under supervision of the Investigator or the designee.
  - Patients will be monitored for a minimum of 30 minutes (or minimum time required by your local regulator) after injection.
- NIMP:
  - Ensure that the patient has sufficient quantity for dosing up until the next visit, knowing that one MFNS bottle contains sufficient doses for either 2 weeks of BID treatment or 4 weeks of QD treatment. Dispense MFNS if needed. Instruct patient to record usage in the e-diary.
- In case of home administration for next IMP injection remind the patient to return IMP treatment and NIMP kit boxes along with any unused prefilled syringes that will be used for drug accountability purposes. Patients will also return used prefilled syringes to the site in a sharps container.
- WOCBP are reminded to perform at Week 12 a urinary pregnancy test and bring the test back for the next visit. In case of a positive urinary test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to a definitive treatment discontinuation in all cases. In case of positive test at home, patient should contact the site immediately.
- Remind the patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours prior to arriving at V7.
- Supply IMP for patients who will have off-site visits on Weeks 10, 12 and 14.
- Schedule appointment for next visit.

10.1.7 Optional visits (Weeks 10, 12, 14)

Optional visits can be scheduled at Weeks 10, 12 and 14 for IMP/NIMP supply or IMP administration.

From Week 10, q2w home administration of IMP (by patient, caregiver, or health care professional) is possible if the patient (or caregiver) has been trained. When IMP is administered at home, the patients must be advised by the site staff to self-monitor for potential signs and symptoms that may suggest a hypersensitivity reaction for at least 30 minutes (or minimum time required by your local regulator) after administration. Patients will complete a dosing diary to document compliance with self-injection of IMP (or injection by a caregiver), including anatomic site of administration and any adverse reactions).

If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or healthcare professionals to administer IMP for the doses not scheduled to be given at the study site.

- Urinary pregnancy test for WOCBP performed at home at Week 12. In case of positive test at home, patient should contact the site immediately.
- Patient should be informed to record home administration of the IMP in the diary.

10.1.8 Visit 7 (Week 16 +/- 3 days)

- PRO patient administration in the e-diary:
  - Daily symptoms of NC, loss of smell, and anterior and posterior rhinorrhea.
  - SNOT-22.
  - VAS for rhinosinusitis.
  - Reduced sense of taste severity score.
  - ACQ-6 (for patients with asthma)
- Health care resource utilization via e-CRF.
- Inquire about AEs/SAEs and background therapy tolerability.
- Collect IMP and NIMP boxes
- Record all medication use with start date and dose in the e-CRF.
  - Check for use of prohibited medications.
  - Complete rescue medication/surgery page(s) of e-CRF. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.
- Call IVRS/IWRS to register visit and obtain next IMP kit number assignment and NIMP (NASONEX) box(es), if needed or report potential definitive IMP stop.
- Download e-diary/NPIF meter and review the data; remind patient to bring the device to the next visit.

- Perform spirometry (for patients with asthma) and record FEV1, FVC and FEF 25-75 results in the e-CRF.
- Perform nasal endoscopy and send to central reader.
- Administer smell test (UPSIT).
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Obtain blood samples (prior to IMP) for:
  - Hematology and serum chemistry (see Section 9.4.2 for details)
  - Serum dupilumab concentration and ADA.
- Obtain urine β-hCG pregnancy test if WOCBP and record the Week 12 result. In case of a positive urinary test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to a definitive treatment discontinuation in all cases.
- Administer IMP (one SC injection).
  - IMP can be administered by the patient or caregiver under the supervision of the Investigator or the designee
  - Patients will be monitored for a minimum of 30 minutes (or minimum time required by your local regulator) after the injection.
- NIMP:
  - Ensure that the patient has sufficient quantity for dosing up until the next visit, knowing that one MFNS bottle contains sufficient doses for either 2 weeks of BID treatment or 4 weeks of QD treatment. Dispense MFNS if needed. Instruct patient to record usage in the e-diary.
- Schedule appointment for next visit.
- Remind the patient to withhold the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours prior to arriving at V8.
- Remind the patient to return IMP treatment and NIMP kit boxes along with any unused prefilled syringes that will be used for drug accountability purposes. Patients will also return used prefilled syringes to the site in a sharps container.
- WOCBP are reminded to perform the urinary pregnancy test at Week 20 and bring the test back for the next visit. In case of a positive urinary test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to a definitive treatment discontinuation in all cases. In case of positive test at home, patient should contact the site immediately.
- Supply IMP for optional visits can be scheduled at Weeks 18, 20, and 22.

10.1.9 Optional visits (Weeks 18, 20, 22)

Optional visits can be scheduled at Weeks 18, 20, and 22 for IP/NIMP supply or IMP administration.

- Urinary pregnancy test for WOCBP performed at home at Week 20. In case of positive test at home, patient should contact the site immediately.

- Patient should be informed to record home administration of the IMP in the diary.

10.1.10 Visit 8 (Week 24 +/- 3 days): End of treatment

- PRO patient administration in the e-diary:
  - Daily symptoms of NC, loss of smell, and anterior and posterior rhinorrhea.
  - SNOT-22.
  - VAS for rhinosinusitis.
  - Reduced sense of taste severity score.
  - EQ-5D
  - ACQ-6 (for patients with asthma)
- Health care resource utilization via e-CRF.
- Inquire about AEs/SAEs and background therapy tolerability.
- Collect IMP and NIMP boxes
- Record all medication use with start date and dose in the e-CRF.
  - Check for use of prohibited medications.
  - Complete rescue medication/surgery page(s) of e-CRF. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.
- Call IVRS/IWRS to register visit and obtain next NIMP (NASONEX) box(es), if needed.
- Download e-diary/NPIF meter and review the data; remind patient to bring the device to the next visit.
- Perform spirometry (for patients with asthma) and record FEV1, FVC and FEF 25-75 results in the e-CRF.
- Perform nasal endoscopy and send to central reader.
- Administer smell test (UPSIT).
- Perform ECG.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Perform CT scan.
- Obtain blood samples for:
  - Hematology and serum chemistry (see Section 9.4.2 for details).

- Hepatitis B viral load (for patients in countries/regions if there is local regulatory requirement) who are HBsAg negative and HBsAb positive at V1.
- Serum dupilumab concentration and ADA.
- Serum for total IgE, allergen-specific IgE including Staphylococcal enterotoxins IgE
- Stored serum for those patients who have signed a specific informed consent form.

- Obtain urine for:
  - β-hCG pregnancy test if WOCBP and record the Week 20 result. In case of a positive urinary test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to a definitive treatment discontinuation in all cases
  - Urine biomarkers and creatinine.
- Obtain nasal swabs for microbiome prior to MFNS administration.
- NIMP:
  - Ensure that the patient has sufficient quantity for dosing up until the next visit, knowing that one MFNS bottle contains sufficient doses for either 2 weeks of BID treatment or 4 weeks of QD treatment. Dispense MFNS if needed. Instruct patient to record usage in the e-diary.
- Advise patients with comorbid atopic conditions (such as asthma) not to adjust their treatment without consultation with their physicians.
- Schedule appointment for next visit.

10.1.11 Visit 9 (Week 36)

- PRO patient administration in the e-diary:
  - Daily symptoms of NC, loss of smell, and anterior and posterior rhinorrhea.
  - SNOT-22.
  - VAS for rhinosinusitis.
- Inquire about AEs/SAEs and background therapy tolerability.
- Collect IMP and NIMP boxes
- Record all medication use with start date and dose in the e-CRF.
  - Complete rescue medication/surgery page(s) of e-CRF. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.
- Call IVRS/IWRS to register visit and obtain next NIMP (NASONEX) box(es), if needed.
- Download e-diary/NPIF and review the data.

- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination
- Perform nasal endoscopy and send to central reader.
- Perform blood sampling for serum dupilumab concentration and ADA.
- Obtain urine β-hCG pregnancy test if WOCBP.
- Schedule appointment for next visit.

10.1.12 Visit 10 (Week 48): End of study

- PRO patient administration in the e-diary:
  - Daily symptoms of NC, loss of smell, and anterior and posterior rhinorrhea.
  - SNOT-22.
  - VAS for rhinosinusitis.
  - ACQ-6 (for patients with asthma).
- Inquire about aes/saes and background therapy tolerability.
- Collect IMP and NIMP boxes
- Record all medication use with start date and dose in the e-CRF.
  - Complete rescue medication/surgery page(s) of e-CRF. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.
- Call IVRS/IWRS to register visit.
- Download e-diary/NPIF and review the data.
- Perform spirometry (for patients with asthma) and record FEV1, FVC and FEF 25-75 results in the e-CRF.
- Perform nasal endoscopy and send to central reader.
- Administer smell test (UPSIT).
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Perform physical examination.
- Perform CT scan (unless not approved by local ethics committee).
- Perform blood sampling for serum dupilumab concentration and ADA.
- Obtain urine β-hcg pregnancy test if WOCBP.

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, endoscopy, CT scan, NPIF measurement, and patient diary meter will be considered source data. HCRU will be collected directly in the e-CRF.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Permanent treatment discontinuation with investigational medicinal product(s)

Patients who permanently discontinue treatment earlier than planned during the randomization period, will be assessed as soon as possible using the procedures normally planned for the EOT visit (Refer to Section 10.1.10 Visit 8 (Week 24 +/- 3 days): End of treatment)

Those patients who permanently discontinue during the post-treatment period will be assessed using the procedures normally planned for the EOS visit.

Furthermore, all patients will be instructed as follows:

- Return to the study site for evaluation of NPS, SNOT-22 for all remaining visits corresponding to study flowchart. .
  - CT Scan will be performed at time of early treatment discontinuation.
  - For those patients where discontinuation occurs during the treatment period, CT scan will be performed at W24 and not at ETD. An optional CT may be performed at Week 48.
  - For those patients where early treatment discontinuation occurs during the post-treatment period, the week 48 CT scan will not be performed.
- Perform PK, ADA sampling at the initially scheduled visits for ADA.
- Continue to complete the e-diary for NC, anterior and posterior rhinorrhea and loss of smell daily symptom evaluation up to Week 48.

- Continue on MFNS stable dose but patients are not required to complete the INCS use daily in the e-diary after ETD.
- Advise patients with comorbid atopic conditions (such as asthma) not to adjust their treatment without consultation with their physicians.
- Report any AE up to the last scheduled visit (Week 48).
- Contact the Investigator during the post treatment period up to the EOS visit if the symptoms worsen requiring medical attention
  - The Investigator will record in the corresponding e-CRF pages rescue medication prescribed or surgical interventions during the planned study treatment period. Use of oral steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, INN) will be informed. Details on planned date for surgery, type and outcome (whenever possible) of surgery will be recorded in a specific e-CRF page. If surgery is performed during the study treatment period or follow-up an AE or SAE page will be completed.

If surgery is scheduled after the planned end of study, EOS visit will not be delayed. A follow up contact(s) should be performed around the time of planned surgery to document the surgery date and outcome. Surgery data will be collected until e-CRF closure of the trial.

For patients undergoing surgery for NP please refer to Section 9.2.1.5.

Procedures to perform and/or report at Week 36 and 48 are as follows:

- Blood draw and laboratory studies as detailed in study flowchart for these visits
- NPIF
- Vital Signs

10.3.2 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of AEs. Reinitiation of treatment with the IMP will be made 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, any of the following conditions will be a cause for temporary treatment discontinuation:

- Infections or infestations that do not respond to medical treatment should have study drug discontinued until the infection is resolved
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix H.

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF. If the IMP is interrupted for more than 2 doses, then the patient should permanently discontinue the study treatment.

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 the study (ie, from any further IMP or study procedure) for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's wellbeing.
- In case of surgery for NP, refer to Section 9.2.1.5 for details.
- At the specific request of the Sponsor.
- In the event of a critical protocol deviation, at the request of the Investigator or the Sponsor.
- Any code broken requested by the Investigator will lead to permanent treatment discontinuation.
- In the event of an anaphylactic systemic allergic reaction that is related to IMP and that requires treatment.
- In the event that the patient is diagnosed with a malignancy during the study, excluding carcinoma in situ of the cervix or squamous or basal cell.
- Pregnancy
- Any opportunistic infection, such as tuberculosis or other infections whose nature or course may suggest an immunocompromised status (refer to Appendix J).
- Serum ALT >3 ULN and total bilirubin > 2ULN.
- Serum ALT >5 ULN if baseline ALT <2 ULN or ALT >8 ULN if baseline ALT >2 ULN.

Stopping rules described in Appendix H should be applied.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic and participate in follow-up assessments described in Section 10.3.1.

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

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 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 check. If possible, the patients should be assessed using the procedures normally planned for the end-of-study visit including a systemic drug concentration sample with the exception of CT scan.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

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.

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 re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

An 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, or
- 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 I for definition of anaphylaxis)
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse.
- ALT >3 x ULN + total bilirubin >2 x ULN.

- 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 or aggravated during the study.
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.1.3 Adverse event of special interest

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

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described Section 10.4.4, even if not fulfilling a seriousness criterion.

AESIs for this study include:

- Anaphylactic or systemic allergic reactions that are related to IMP and that require treatment (refer to Appendix I 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 (IV, IM, SC) antimicrobial therapy
  - Requires oral antimicrobial therapy for longer than 2 weeks
  - Is a parasitic infection
  - Is an opportunistic infection (see Appendix J)

  Note: Antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents. For safety instructions, please see Section 10.6.3.
- Significant elevation of ALT (see Appendix H)
  - ALT >5 × ULN in patients with baseline ALT $\leq$2 × ULN; or
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Section 10.4.1.2).
  - In the event of pregnancy in a female participant, IMP should be discontinued.

- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.

- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic syringes or pills count) and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

    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 for this study.

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.

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).

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.

When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined in Section 10.3.1.

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.

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10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designee 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. Instructions for AE reporting are summarized in Table 5.

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 H.

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 G/L) are to be reported as AEs.

NOTE: In some clinical trials these laboratory abnormalities can be considered as AESIs (see Section 10.4.1.3).

Table 5 - Summary of adverse event reporting instructions

Adverse event/laboratory abnormality		Reporting timeframe
Serious adverse event		Within 24 hours
Adverse Event (non-SAE, non-AESI)[a]		Routine
Pregnancy[b]		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 that 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		

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

a For reporting of epistaxis as an AE, use both AE form and Safety complementary form to provide date, features and outcome of the event.

b The Drug Exposure Via Parent (DEVP) form is not part of the Case Report Form, but needs to be completed for pregnancy

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 (suspected unexpected adverse drug reaction [SUSAR]), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

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 Authorities.

Authority of any SUSAR 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 CSR.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

An allergic reaction is a potential risk associated with the administration of most therapeutic mAB treatments.

Allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent is given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea or vomiting, and joint pain with fever. Allergic reactions may begin within a few hours and persist up to 24 hours post dosing. Refer to Appendix I "Definition of Anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should be monitored for at least 30 minutes (or minimum time required by your local regulator) after each study-site administered IMP administration for any signs or symptoms of a hypersensitivity reaction. Any instance of allergic reaction should be reported as an AESI. Any anaphylactic reactions or acute allergic reactions that require immediate treatment will be AESI with immediate reporting (within 24 hours) and study medication must be permanently discontinued. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Furthermore, the study patients will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitivity reaction for at least 30 minutes (or minimum time required by your local regulator) after administration.

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) in dupilumab studies, 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 completion resolution of the AESI for any additional analysis.

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

10.6.3 Infections, including opportunistic and parasitic infections

Some immuno-modulating biologics have been associated with an increased risk of infection, including opportunistic infection. Though dupilumab has not been shown to increase the

frequency of severe or serious infections in general, as a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness.

Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 binding and activation of their respective receptors, it inhibits the Th2 cytokines productions. 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 and IL-5, subsequently generating IgG1 [Immunoglobulin Gamma 1] 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 with treatment of dupilumab may potentially have an increased risk of parasitic infection.

Infections defined in Section 10.4.1.3 should be reported as AESIs 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 tuberculosis or other infections whose nature or course may suggest an immunocompromised status (see Appendix J), patients must be permanently discontinued from study medication.

In order to minimize this risk, any patient with an active parasitic infection is 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. Confirmed parasitic infections during the study should be reported as AESI with immediate notification.

10.6.4 Elevated liver function tests

No preclinical or clinical data have 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 liver function tests (LFT), 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 V1 adds hepatitis screen (HBsAg, HBsAb, HBcAb, hepatitis C antibodies [HCAb]). Active hepatitis or patients with positive or indeterminate HBsAg, HBcAb or positive HCAb at V1 are excluded from the study.

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

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size is chosen to enable an adequate characterization of the efficacy between dupilumab 300 mg q2w and placebo with regard to the 2 coprimary endpoints, changes from baseline in NC and NPS at Week 24.

The observed mean NC reduction of the dupilumab group with qw dosing in ACT12340 is 0.95 and the observed mean NC reduction of the placebo group is 0.26. To calculate the power, a conservative estimate is used that assumes the placebo adjusted NC reduction of the dupilumab 300 mg q2w group is 80% of the effect observed with dupilumab 300 mg qw. Thus, the mean NC reduction of the dupilumab 300 mg q2w is then assumed to be 0.81 = 0.8 * (0.95 – 0.26) + 0.26 at Week 24. Assuming normal distribution of the change in NC, a common standard deviation (SD) of 1.03, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 120 patients per group, the study will have 95% power to detect an effect size of 0.534 using a two-sided test with alpha = 0.05 for the change in NC at Week 24 in the dupilumab 300 mg q2w group versus placebo.

The observed mean NPS reduction of the dupilumab group with qw dosing in ACT12340 is 1.85 and the observed mean NPS reduction of the placebo group is 0.30. Using the same conservative approach that assumes the placebo adjusted NPS reduction with the dupilumab 300 mg q2w is 80% of the effect observed with dupilumab 300 mg qw, the mean NPS reduction of the dupilumab 300 mg q2w group is then assumed to be 1.54 = 0.8 * (1.85 – 0.30) + 0.30. Assuming normal distribution of the change in NPS, a common SD of 2.11, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 120 patients per group, the

study will have 98% power to detect an effect size of 0.588 using a two-sided test with alpha = 0.05 for the change in NPS at Week 24 in the dupilumab 300 mg q2w group versus placebo.

Therefore, with a sample size of 120 patients per group, the combined power of the 2 coprimary efficacy endpoints is at least 93% for dupilumab 300 mg q2w group with alpha = 0.05 assuming no negative correlation between the 2 endpoints.

The observed mean LMK reduction of the dupilumab group with qw dosing in ACT12340 is 9.07 and the observed mean LMK reduction of the placebo group is 0.23. Using same conservative approach that assumes the placebo-adjusted LMK reduction of the dupilumab 300 mg q2w group is 80% of the dupilumab 300 mg qw, the mean LMK reduction of the dupilumab 300 mg q2w group is then assumed to be 7.30 = 0.8*(9.07-0.23)+0.23. Assuming normal distribution of the change in LMK, a common standard deviation (SD) of 5.50, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 120 patients per group, the study will have 99% power to detect an effect size of 1.285 using a two-sided test with alpha = 0.05 for the change in LMK at Week 24 in the dupilumab 300 mg q2w group.

Therefore, with the same sample size of 120 patients per group, the combined power of the 3 coprimary efficacy endpoints for Japan is at least 92% for dupilumab 300 mg q2w group with alpha = 0.05 assuming no negative correlation between the 3 endpoints.

With the same sample size of 120 patients per group, the study will have greater than 99% power to detect difference between the treatment groups for key secondary endpoints change from baseline in TSS, UPSIT and loss of smell at Week 24, and will have 98% power to detect difference between the treatment groups for the key secondary endpoint change from baseline in SNOT-22 at Week 24, using a similar assumption procedure as the change from baseline in NC and NPS at Week 24.

The sample size calculations were performed using nQuery Advisor 7.0.

11.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all patients who have been allocated a treatment kit based on a randomization process. It will consist of all patients with a treatment kit number allocated and recorded in IVRS/IWRS database, and regardless of whether the treatment kit was used or not.

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The population considered for the efficacy analysis will be the intent-to-treat (ITT) population.

ITT population: 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 population considered for safety analysis will be the safety population.

Safety population: all patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

Treatment emergent period for the safety population is defined as the time between the first administration of study medication to Week 12 of the post treatment period.

In addition:

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

11.3.3 Systemic drug concentration population

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

11.3.4 Anti-drug antibody population

The ADA population will consist of all patients in the safety population with at least one evaluable ADA serum sample that was assayed successfully in the ADA assay following the first dose of the study medication. Patients will be analyzed according to the treatment actually received.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized according to 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. Compliance

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

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

Treatment compliance, above-planned and underplanned dosing percentages will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized. In addition, number and percentage of patients with at least 1 above planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%), and >20% underplanned dosing administrations.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of coprimary efficacy endpoint(s)

11.4.2.1.1 Coprimary efficacy variables

The coprimary efficacy variables are: change from baseline in NC and in NPS at Week 24 assessed for dupilumab 300 mg q2w (Arm A) versus placebo (Arm B).

For Japan only, in addition to the 2 coprimary endpoints above, the following will also be a coprimary endpoint:

- Change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 24.

The following null hypothesis and alternative hypothesis will be tested for dupilumab 300 mg q2w group against placebo:

- H0: No treatment difference between the dupilumab dose regimen and placebo.
- H1: There is a treatment difference between the dupilumab dose regimen and placebo.

11.4.2.1.2 Analysis of the coprimary efficacy variables

Each of the 2 coprimary efficacy endpoints (3 coprimary endpoints for Japan) will be analyzed using a hybrid method of the worst-observation carried forward (WOCF) and the multiple imputation (MI). With this approach, for patients who undergo surgery for NP or receive SCS for any reason, data collected postsurgery or post SCS will be set to missing, and the worst postbaseline value on or before the time of surgery or SCS intake will be used to impute missing

Week 24 value (for patients whose postbaseline values are all missing, the baseline will be used to impute). For patients who discontinue the treatment without being rescued by surgery or receiving SCS, an MI approach will be used to impute missing Week 24 value, and this MI will use all patients who have not been rescued by surgery or receiving SCS at Week 24 and data collected after treatment discontinuation will be included in the analysis. Each of the imputed complete data will be analyzed by fitting an analysis of covariance model with the baseline covariate and factors for treatment, asthma status, prior surgery history, and regions. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of subjects mean, standard error of the mean (SEM), and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

11.4.2.1.3 Sensitivity analyses

The reason and pattern of missing data will be carefully examined and tipping point analyses and other sensitivity analyses will be performed. Details of the sensitivity analyses will be provided in the SAP.

11.4.2.1.4 Subgroup analysis

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be conducted for the coprimary efficacy endpoints with respect to age group, gender, region, prior surgery history, race, INCS dose level, baseline NPS, baseline NC, baseline TSS, baseline LMK, prior SCS use, and asthma/NERD comorbidity. The details will be provided in the SAP.

11.4.2.2 Analyses of key secondary efficacy endpoints

11.4.2.2.1 Analysis of the change from baseline in TSS, UPSIT, daily loss of smell, LMK, and SNOT-22 at Week 24 for dupilumab 300 mg q2w versus placebo

The change from baseline in TSS, SNOT-22, UPSIT score, daily loss of smell, and LMK score at Week 24 will be analyzed using the hybrid method of the WOCF and the MI in the same fashion as for the coprimary endpoints.

Note: LMK will not be a secondary endpoint for Japan as it is already a coprimary endpoint.

11.4.2.2.2 Analysis of proportion of patients with SCS rescue or surgery (actual or planned) for NP during the 24-week treatment period for dupilumab 300 mg q2w versus placebo

Proportion of patients with first SCS rescue and/or surgery (actual or planned) for NP during the 24 weeks of treatment period will be derived and analyzed using the Cox proportional hazards model and log rank test stratified by asthma status, prior surgery history, and regions, by considering the first SCS rescue use or surgery (actual or planned) for NP as the event. Descriptive statistics including number of patients with rescue and/or surgery and number of patients without rescue or surgery (censored) and the corresponding rates will be provided by

treatment group. The estimates of the hazard ratio and corresponding 95% CI will be provided for dupilumab group versus placebo group.

11.4.2.3 Multiplicity considerations

The multiplicity procedure is proposed to control the overall type-I error rate for testing the coprimary and selected secondary endpoints dupilumab 300 mg q2w versus placebo. The overall alpha is 0.05. The comparisons with placebo will be tested based on the hierarchical order below at 2-sided $\alpha = 0.05$ for 300 mg q2w dose regimen versus placebo:

1. Co-primary efficacy endpoints:

In countries other than Japan:

- Change from baseline in NC and in NPS at Week 24.

In Japan:

- Change from baseline in NC, in NPS, and in CT LMK at Week 24.

2. Secondary efficacy endpoints:
   - Change from baseline in TSS at Week 24.
   - Change from baseline in UPSIT at Week 24.
   - Change from baseline in loss of smell daily symptoms at Week 24.
   - Change from baseline in SNOT-22 at Week 24.
   - Change from baseline in LMK score at Week 24. (This will not be a secondary endpoint for Japan as it is already a coprimary endpoint).
   - Proportion of patients with SCS rescue or surgery for NP during the treatment period.

In countries other than Japan, the study is considered positive when both coprimary endpoints, the change from baseline in NC and NPS at Week 24, achieve statistical significance.

In Japan, the study is considered positive when all coprimary endpoints, the change from baseline in NC, in NPS, and in CT LMK at Week 24, achieve statistical significance.

11.4.2.4 Analyses of other secondary efficacy endpoints and subgroup analysis

11.4.2.4.1 Comparisons for other secondary efficacy endpoints

Comparisons will be made between dupilumab and placebo in the following endpoints:

- Change from baseline at Week 24 in:
  - VAS for overall rhinosinusitis.
  - NPIF.

  - Rhinorrhea (anterior/posterior nasal discharge) daily symptom score assessed by the patient.
  - Patient reported outcomes including HRQoL scales (EQ-5D-5L VAS score).
- Proportion of responders at Week 24 (defined as patients with improvement by at least 1 point in NPS).
- Proportion of patients with improvement by at least 1 point in NPS and 0.5 reduction in NC by Week 24.
- Proportion and time-to-event of patients with SCS rescue for any airway exacerbated disease (included but not limited to NP, CRS, allergic rhinitis, and asthma).
- Proportion of patients with MCID ≥8.9 in SNOT-22 at Week 24.
- Proportion of patients with overall rhinosinusitis severity VAS ≤7 at Week 24.
- Safety (incidence of treatment-emergent AEs (TEAE), of treatment-emergent SAEs (TESAEs), and TEAEs leading to treatment discontinuation), laboratory values, vital signs.
- Dupilumab concentration in serum and ADA.

In the subgroups of patients with prior surgery, or comorbid asthma (including NERD history):

- Change from baseline and time course profiles in in NC, NPS, TSS, UPSIT, loss of smell daily symptoms, LMK score, and SNOT-22 at Week 24.
- Proportion and time-to-event of patients with SCS rescue and/or surgery (actual or planned) for nasal polyps during the treatment period.
- Proportion and time-to-event of patients with SCS use for any airway exacerbated disease.
- Proportion of patients with VAS ≤7 at Week 24.
- Change from baseline in ACQ-6 (in patients with asthma/NERD only) at Week 24.
- Proportion of responders at Week 24 (defined as patients with improvement by at least 1 point in NPS).
- Proportion of patients with improvement by at least 1 point in NPS and 0.5 reduction in NC by Week 24.

Through the 24-week follow-up period, the following endpoints will be analyzed:

- Change from baseline at Week 36 (12-week follow-up after the EOT) and Week 48 (24-week follow-up after the EOT) in:
  - NC and NPS.
  - TSS, UPSIT, LMK, SNOT-22, and VAS for overall rhinosinusitis.
- Change from Week 24 (the EOT visit) to Week 36 (12-week follow-up after the EOT) and change from Week 24 (the EOT visit) to Week 48 (24-week follow-up after the EOT) in:
  - NC and NPS.
  - TSS, UPSIT, LMK, SNOT-22, and VAS for overall rhinosinusitis.

11.4.2.4.2 Analysis of continuous secondary efficacy endpoints

Changes from baseline in continuous endpoints at week 24 will be analyzed using the hybrid method of the WOCF and the MI in the same fashion as for the coprimary endpoints.

11.4.2.4.3 Analysis of subgroups with comorbid asthma/NERD and prior surgery

For each subgroup factor, interaction tests will be carried out to investigate consistency of the dupilumab effect across different subgroups identified by that factor.

In addition to the analysis in the current study, statistical analysis for subgroups with comorbid asthma/NERD, and prior surgery will be further conducted using the pooled data of EFC14280 and EFC14146, and the details will be provided in the SAP for the Integrated Summary of Efficacy.

11.4.2.4.4 Analysis of the responder endpoints

For any responder type endpoint, including the proportion of responders at Week 24, the proportion of patients with MCID ≥8.9 in SNOT-22 at Week 24, and the proportion of patients with VAS ≤7 at Week 24, the Cochran-Mantel-Haenszel test stratified by asthma status, prior surgery history, and region will be used. Comparisons of the proportions of responders between dupilumab 300 mg q2w and placebo will be derived. Patients who are indicated for surgery for NP or receive SCS for any reason will be considered as nonresponders for time points after using SCS or surgery. For patients who discontinue treatment without using SCS or surgery, data collected during the off-treatment period will be used to determine the responder/nonresponder status. Missing data will be considered as nonresponders.

11.4.2.4.5 Analysis of the proportion and time-to-event of patients with SCS rescue for any airway exacerbated disease

Proportion and time-to-event of patients with SCS rescue for any airway exacerbated disease will be analyzed using a similar approach as the key secondary endpoint of the proportion of patients with SCS rescue or surgery (actual or planned) for NP.

11.4.2.4.6 Analysis of continuous efficacy endpoints through the 24-week follow-up period

For the change from baseline in continuous endpoints through the 24-week follow-up period, descriptive statistics including number of subjects, mean, SEM, and the corresponding 95% confidence interval (CI) will be provided by treatment.

11.4.2.5 Analyses of exploratory efficacy endpoints

Statistical analysis for exploratory efficacy endpoints will be provided in the final SAP.

11.4.2.6 Missing data handling

For all continuous efficacy endpoints, in the primary approach for missing data handling, for patients who are indicated to undergo surgery for NP or receive SCS for any reason, data collected postsurgery or post SCS will be set to missing, and the worst postbaseline value on or before the time of surgery or SCS will be used to impute missing value at the certain analyzed visit (for patients whose postbaseline values are all missing, the baseline will be used to impute), and for patients who discontinue the treatment without being rescued by surgery or receiving SCS on or before the analyzed visit, a MI approach will be used to impute missing value at the certain analyzed visit, and this MI will use all patients who have not been rescued by surgery or receiving SCS at that analyzed visit and data collected after treatment discontinuation will be included in the analysis.

For responder type endpoints, patients who are indicated for surgery for NP or receive SCS for any reason will be considered as nonresponders for time points after using SCS or surgery; for patients who discontinue treatment without using SCS or surgery, data collected during the off-treatment period will be used to determine the responder/non- responder status, and missing data will be considered as non-responders.

In addition, the reason and pattern of missing data will be carefully examined and tipping point analyses and other sensitivity analyses will also be performed.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment groups. 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 randomization.

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the 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.

Proportion of patients with at least one TEAE, serious TEAE and TEAE leading to permanent treatment discontinuation will be tabulated by treatment groups. 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 event of special interest (AESI)

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment groups.
- The time-to-first event analyzed using Kaplan-Meier (K-M) methods and displayed as K-M plots (cumulative incidence [%] versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.

AESI definitions and the method to identify AESIs will be specified in the SAP.

11.4.3.1.2 Death

The following deaths summaries will be generated:

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

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

11.4.3.1.3 Clinical laboratory evaluation, vital signs and electrocardiogram (ECG) data

Results and change from baseline for clinical laboratory evaluation and vital signs parameters will be summarized by treatment groups for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, SD, median, Q1, Q3, minimum and maximum.

The proportion of patients who had at least one incidence of PCSA at any time during the treatment emergent period will be summarized by treatment groups within each treatment phase. 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 pharmacokinetic and pharmacodynamic variables and antidrug metabolites

11.4.4.1 Functional dupilumab concentration analysis

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

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

11.4.4.2 Anti-drug antibodies analysis

Incidence of positivity in the ADA assay will be assessed on samples collected, as absolute occurrence (n) and percent of patients (%), presented by treatment groups. Listing of all ADA titer levels will be provided for patients positive in the ADA assay. Samples positive in the ADA assay will be further characterized for the presence of antidupilumab neutralizing antibodies.

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

ADA at baseline will be summarized by:

- Number (%) of patients with a baseline sample negative in the ADA assay.
- Number (%) of patients with a baseline sample positive in the ADA assay (pre-existing immunoreactivity).

Total subject number (%) will be provided for the following:

- Number (%) of patients with treatment-emergent positive response in the ADA assay. (ADA incidence).
- Number (%) of transient treatment-emergent positive patients.
- Number (%) of persistent treatment-emergent positive patients.
- Number (%) of treatment-boosted positive patients.
- Number (%) of undetermined treatment-emergent positive patients.

Titer values (Titer value category).

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

- Low (Titer <1000).

- Moderate (1000 ≤Titer ≤10 000).
- High (Titer >10 000).

Definitions of pre-existing immunoreactivity, treatment emergent, persistent response, transient response, treatment-boosted, and undetermined response will be specified in the SAP.

11.4.4.3 Pharmacodynamics

The values to be used as baselines will be those collected on Day 1 (predose assessments). If any of the scheduled assessments on Day 1 are technically disqualified (eg, insufficient sample) and the parameters are measured at any of the run-in period visits, then values determined at the run-in period visits can be used as baseline.

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

Summary plots (mean +/- SEM) on raw data, changes from baseline and percent changes from baseline will be provided by treatment arms.

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

Change from baseline in the quantitative variables of EQ-5D-5L (index score) and EQ-5D VAS (self-rated health) will be analyzed using the hybrid method of the WOCF and the MI in the same fashion as for the coprimary endpoints. Descriptive statistics including number of patients, mean, SEM, and LS means will be provided. In addition, difference in LS means and the corresponding 95% CI will be provided along with the p-values.

11.5 FIRST STEP ANALYSIS

A first step analysis may be performed when all patients complete the Week 24 visit, including early dropouts. Since this analysis is the final analysis of the coprimary endpoints and other 24-week endpoints and no decision on the conduct of the study will be made based on the first step analysis (in particular, no decision to prematurely stop the study), there will be no alpha adjustment due to the interim analysis. Specific steps will be taken to maintain the blind of the study to all individuals involved in the conduct of the study and/or analysis.

Individuals involved in the first step analysis of the study will not be involved in the conduct of the study afterwards; individual patient identification will not be released to anyone who is directly involved in the conduct of the study.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the International Conference for Harmonization (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/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 written informed consent form 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 informed consent form will be provided to the patient.

[redacted]

Depending on local regulations, prior to collection of blood for HIV testing, an optional respective informed consent form(s) (written) must be signed, name completed, 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(s) will be provided to the patient.

The informed consent form and the optional informed consent forms 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 IRB/IEC for approval/favorable opinion.

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

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

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure with any addenda or labeling documents (summary of product characteristics, package insert, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the preidentified 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, IRB/IEC, and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (eg, patient's medical file, appointment books, original laboratory records, 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).

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

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

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

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

The computerized handling of the data by the Sponsor may generate additional requests (DRFs) 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.

13.4 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 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 and ethnicity (Caucasian/White, Black, Asian/Oriental, Others) will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for Food and Drug Administration [FDA], on Japanese population for the Pharmaceuticals and Medical Devices Agency [PMDA] in Japan).

[redacted]

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

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are 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 CSR 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.

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

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 recollected if necessary.

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