CLINICAL TRIAL PROTOCOL

Protocol title:	**A randomized, double-blind, placebo-controlled efficacy and safety study of dupilumab, in Chinese adult participants with chronic rhinosinusitis with nasal polyposis (CRSwNP) on a background therapy with intranasal corticosteroids**
Protocol number:	**EFC17026**
Amendment number:	**Original protocol**
Compound number (INN/Trademark):	**SAR231893 dupilumab/Dupixent**
Brief title:	**Dupilumab in Chinese adult participants with CRSwNP**
Acronym:	**Not applicable**
Study phase:	**Phase 3**
Sponsor name:	**sanofi-aventis groupe**
Legal registered address:	**54, rue La Boétie, 75008 Paris, France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	Not applicable
EudraCT:	Not applicable
NCT:	NCT05878093
WHO:	U1111-1256-9711
EUDAMED:	Not applicable
Other:	Not applicable

Date: 14-Sep-2022 Total number of pages: 100

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A randomized, double-blind, placebo-controlled efficacy and safety study of dupilumab, in Chinese adult participants with chronic rhinosinusitis with nasal polyposis (CRSwNP) on a background therapy with intranasal corticosteroids

Brief title:

Dupilumab in Chinese adult participants with CRSwNP

Rationale:

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a clinical condition characterized by the bilateral presence of multiple polyps in the nasal cavity, long-term symptoms, and T helper (Th)-2 polarization with tissue eosinophilia, increased levels of interleukin (IL)-4, IL-5 and IL-13, as well as high local production of immunoglobulin E (IgE). The prevalence of CRSwNP was reported to be 1.1% in China (1). CRSwNP has a high burden of symptoms and relapse rate after treatment, which impacts greatly upon a patient's quality of life (QoL).

The therapeutic armamentarium of clinically proven medical interventions for CRSwNP is limited to topical corticosteroids (intranasal corticosteroid [INCS]), and short courses of oral steroids as adjunctive therapy to INCS. However, the effect of INCS in reducing polyp size and on improving the sense of smell, a cardinal symptom of CRSwNP is limited (2, 3). 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 (4). 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.

Dupilumab is a fully human monoclonal antibody (mAb) directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors type 1 and type 2, as well as the IL-13 type 2 receptor. The binding of dupilumab to IL-4Rα results in blockade of IL-4 and IL-13 intracellular signaling. Dupilumab has demonstrated efficacy across a broad range of diseases driven by type 2 inflammation, including atopic dermatitis (AD), asthma, CRSwNP and eosinophilic esophagitis (EoE). Clinically significant efficacy in reducing nasal polyps burden and nasal congestion (NC), in addition to statistically significant improvement in sinus opacification and well tolerated safety profile have been demonstrated with dupilumab treatment in two global pivotal studies in participants with CRSwNP (LIBERTY NP SINUS-24, LIBERTY NP SINUS-52) (5). For complete information regarding the preclinical and clinical evaluation of dupilumab to date, see the Investigator's Brochure (IB).

As there remains high unmet need for novel therapies to treat CRSwNP in China, the Sponsor will investigate the efficacy and safety of dupilumab on a background of INCS in Chinese patients with moderate-to-severe signs and symptoms of CRSwNP who are not controlled on standard of care.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab compared to placebo on a background of budesonide nasal spray in reducing endoscopic nasal polyps score (NPS) in Chinese participants with bilateral nasal polyposis (NP).	• Change from baseline in NPS at Week 24.
Secondary	
• To evaluate the efficacy of dupilumab in reducing nasal congestion/obstruction (NC) severity.	• Change from baseline in NC score (NCS) based on the participant daily morning assessment at Week 24.
• To evaluate the efficacy of dupilumab in improving total symptoms score (TSS).	• Change from baseline in TSS at Week 24: composite severity score consisting of the participant daily morning assessed NC, decreased/loss of sense of smell, anterior/posterior rhinorrhea.
• To evaluate the efficacy of dupilumab in improving sense of smell.	• Change from baseline in the severity of decreased/loss of smell assessed daily by participants at Week 24.
• To evaluate the effect of dupilumab on patient quality of life.	• Change from baseline in total score of 22-item sino-nasal outcome test (SNOT-22) at Week 24.
• To evaluate the ability of dupilumab to reduce proportion of participants who require treatment with systemic corticosteroid (SCS) or surgery for NP.	• Proportion of participants receiving SCS for any reason or undergo surgery for nasal polyps during the study treatment.
• To evaluate the safety of dupilumab in Chinese participants with bilateral NP.	• Safety (incidence of treatment-emergent adverse events [TEAEs], of treatment-emergent serious adverse events [TESAEs], and TEAEs leading to treatment discontinuation), laboratory values, vital signs.

Overall design:

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of dupilumab 300 mg every 2 weeks (Q2W) compared to placebo, in Chinese adult participants with moderate-to-severe signs and symptoms of bilateral nasal polyposis (NP) on a background treatment with intranasal corticosteroids.

Disclosure Statement: This is an interventional study with 2 arms that are blinded to both participants and investigators.

Brief summary:

This is a parallel group, Phase 3, 2-arm study for treatment.

The purpose of this study is to evaluate dupilumab subcutaneous (SC) injections compared to placebo in Chinese adult participants with CRSwNP, on a background therapy with intranasal corticosteroids (budesonide nasal spray).

Study details include:

- The study duration will be up to 40 weeks.
- The treatment duration will be up to 24 weeks.
- The number of visits will be 7.

Number of participants:

Approximately 62 participants (31 per arm) with CRSwNP will be randomized 1:1 to receive either dupilumab or matching placebo.

Intervention groups and duration:

Participants who satisfy the inclusion and exclusion criteria will be randomized (1:1) to one of the following investigational medicinal product (IMP) treatment groups:

- Arm A: dupilumab 300 mg Q2W up to Week 24.
- Arm B: placebo matching dupilumab Q2W up to Week 24.

Study intervention(s)

Investigational medicinal product(s)

Dupilumab 300 mg and placebo matching dupilumab 300 mg will be supplied in visually indistinguishable prefilled syringes.

Dupilumab:

- Formulation: a 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in a 2 mL injection
- Route of administration: SC injection
- Dose regimen: one injection of dupilumab 300 mg Q2W

Placebo:

- Formulation: identical formulation to the active 300 mg formulation without dupilumab, in a prefilled syringe to deliver placebo in a 2 mL injection
- Route of administration: SC injection
- Dose regimen: one injection of placebo matching dupilumab 300 mg Q2W

Noninvestigational medicinal product(s)

Budesonide (RHINOCORT®) 64 µg/actuation nasal spray, suspension.

- Formulation: nasal spray (suspension) is provided in a bottle that contains 120 actuations (64 µg/actuation) of product formulation.
- Route of administration: nasal spray.
- Dose regimen: budesonide nasal spray 2 actuations (64 µg/actuation) in each nostril each morning (QM), or 1 actuation in each nostril twice daily (BID) (total daily dose of 256 µg). One actuation in each nostril once daily (total daily dose of 128 µg) if the participants are unable to tolerate BID, in which case they can stay on a lower dose regimen (128 µg) of budesonide nasal spray.

Posttrial access to study medication

Posttrial access to study medication will not be provided.

Duration of study intervention

- Run-in period: 4 weeks +/-3 days
- Randomized treatment period: up to 24 weeks +/-3 days
- Follow-up period: 12 weeks +/-3 days

Statistical considerations:

Randomization

Participants will be randomized to dupilumab 300 mg Q2W or matching placebo in a 1:1 ratio at randomization visit (Day 1).

Plan to enroll at least 85% (approximately 52) participants with screening blood eosinophil count ≥300 cells/mm^3. Randomization will be stratified by screening blood eosinophil count (≥300 cells/mm^3 or <300 cells/mm^3).

To ensure enrollment according to the intended distribution of screening blood eosinophil count, alerts will be built into the IRT to control the number of participants in each stratification group as follows:

- ≥300 cells/mm^3: approximately 26 participants per arm,
- <300 cells/mm^3: up to approximately 5 participants per arm.

Sample size consideration

The primary endpoint is the change from baseline in nasal polyps score (NPS) at Week 24.
A sample size of 31 participants per arm will provide at least 90% power to detect a difference of -1.8 in the change from baseline in NPS at Week 24 between dupilumab 300 mg Q2W and matching placebo, assuming a common standard deviation (SD) of 1.83 at the 5% significance level (2-sided) and a 25% dropout rate. Assumptions are based on the following:

- Mean treatment difference = -1.8 (lowest observed effect size of NPS at Week24 in the EFC14146［SINUS-24] and EFC14280 [SINUS-52])
- SD=1.83 (highest SD of NPS reduction at Week24 in the EFC14146［SINUS-24] and EFC14280 [SINUS-52])
- Dropout rate 25% (higher than 10% due to COVID-19 uncertainties)

Primary analysis population

The analysis population for the efficacy endpoints will be the intent-to-treat (ITT) population, defined as all randomized participants analyzed according to the treatment group allocated by randomization, regardless of whether treatment kit is used or not.

Analysis of primary and main secondary endpoints

- **Primary endpoint:**

  In the primary analysis approach for the primary endpoint (change from baseline in NPS at Week 24), for participants who undergo surgery for NP or receive systemic corticosteroids (SCS) for any reason, data collected post-surgery or SCS will be set to missing and the worst post-baseline value on or before the time of surgery or SCS will be used to impute missing Week 24 values (ie, worst observation carried forward [WOCF] approach). For participants with no post-baseline values, the baseline value will be used. For participants taking other prohibited/rescue medications, all data collected after use will be used in the analysis. Participants who discontinue the study intervention prematurely are encouraged to follow the planned clinical visits. For participants who discontinue the study intervention without being rescued by surgery or receiving SCS by Week 24, data collected after study intervention discontinuation will be included in the analysis. In case there is missing data, a multiple imputation will be used to impute missing Week 24 values, and this multiple imputation will use all participants excluding those who have undergone surgery or received SCS on or before Week 24. Each of the imputed completed data will be analyzed by fitting an analysis of covariance (ANCOVA) model with the baseline covariate and factor for study intervention and screening blood eosinophil count strata. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, 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.

- **Main secondary endpoints:**

  Continuous secondary efficacy endpoints will be analyzed using the hybrid method of the WOCF and the MI in the same fashion as for the primary endpoint.

  Proportion of participants with first SCS rescue for any reason or surgery (actual or planned) for NP during the 24-week study intervention period will be derived and analyzed using the Cox proportional hazards model and log rank test stratified by screening blood eosinophil count strata, by considering the first SCS use or surgery for NP (actual or planned) as the event. Descriptive statistics including number of participants with rescue SCS or surgery and number of participants without rescue SCS or surgery (censored) and the corresponding rates will be provided by study intervention group. The estimates of the hazard ratio and corresponding 95% CI will be provided for the dupilumab group versus the placebo group.

  The safety variables, including adverse events (AEs), laboratory parameters, and vital signs, will be summarized using descriptive statistics.

Multiplicity considerations

A hierarchical procedure is proposed to strongly control the family wise type-I error rate at the 2-sided 0.05. The primary endpoint will be tested first, followed by selected secondary endpoints.

The detailed hierarchical testing procedures will be defined in the study statistical analysis plan (SAP).

Planned Database lock date

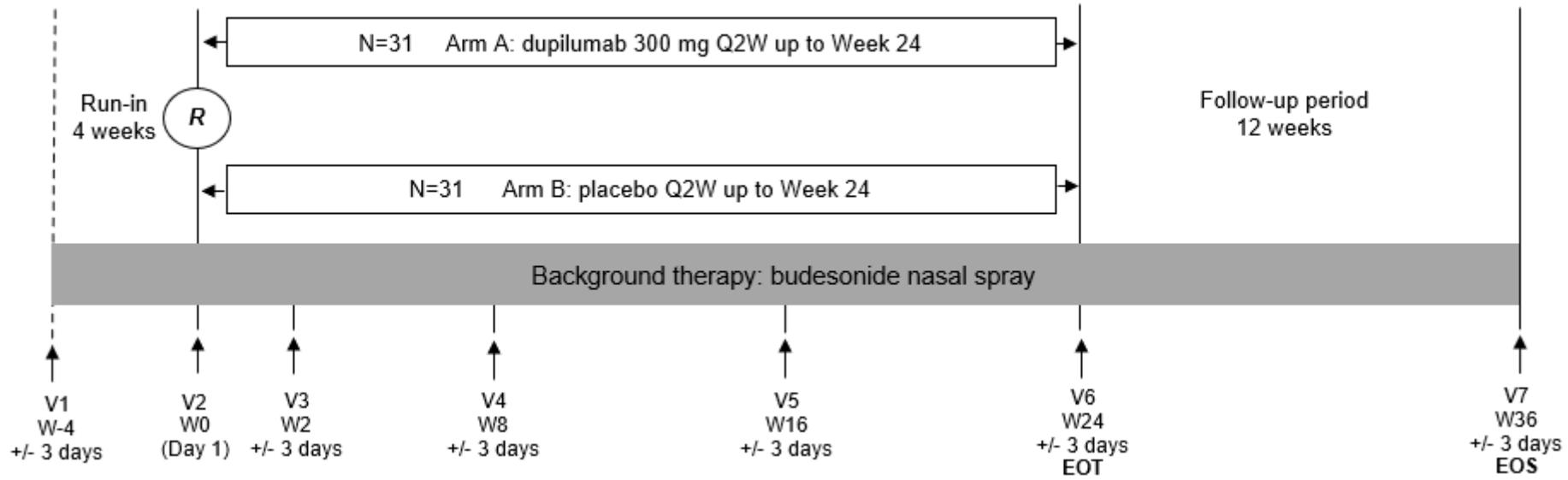
A primary database lock is currently planned to be performed when all randomized participants have completed the 24-week treatment period, including early dropouts.

The database will be updated at the end of the study for all participants to include the post-treatment follow-up information and updates for the events previously ongoing at the time of the primary lock. Additional data collected between the primary database lock and last participant completing last visit will be summarized in a separate clinical study report (CSR) addendum, as needed. Details will be included in the SAP.

Data Monitoring/Other committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



EOS: end of study; EOT: end of treatment; Q2W: every 2 weeks; R: randomization; V: visit; W: week

Investigational medicinal product (IMP): Regardless of the treatment group, all randomized participants will receive Q2W SC administrations of dupilumab 300 mg or placebo. Every other week IMP administrations must be separated by at least 11 days. At Day 1 (W0 [V2]) the Investigator or delegate will prepare and perform the injection, in front of the participant (or caregiver). The participant (or caregiver) will prepare and inject the IMP under the supervision of the Investigator or delegate at W2 (V3). From W4 (except W8 [V4] and W16 [V5]), every other week home administration of IMP is possible if the participant (or the caregiver) has been trained. If the participant (or caregiver) is unable or unwilling to administer IMP, arrangements (ie, unscheduled visits) 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. Patients will be monitored for at least 30 minutes after IMP administration. The planned last dose of IMP is at W22.

Non-investigational medicinal product (NIMP): Budesonide nasal spray will be self-administered by the participant every day. At each visit the Investigator must ensure that the participant has the necessary and sufficient doses up to the next visit.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Run-in[a]**	**Randomized treatment period**							**EOT[c]**	**EOS**
Visit	**1**	**2**	**3**		**4**		**5**		**6**	**7**
Week	**W-4**	**W0**	**W2**	**W4,6[b]**	**W8**	**W10, 12, 14[b]**	**W16**	**W18, 20, 22[b]**	**W24**	**W36**
Day +/-3 days	**D-28**	**D1**	**D15**		**D57**		**D113**		**D169**	**D253**
Informed consents	X									
Inclusion and exclusion criteria	X	X								
Participant demographics	X									
Medical/surgical/medication history[d]	X									
Chest X-ray[e]	X									
Electrocardiogram (ECG) (local reading)	X									
Randomization		X								
Treatment										
IMP: dupilumab/placebo injection[f]		X	X	X	X	X	X	X		
Call IVRS (IWRS) at scheduled and unscheduled visit as needed	X	----------X----------							X	X
Review IMP and/or NIMP compliance[g]		----------X----------							X	
Dispense or download electronic diary for symptoms[h]	----------X----------									
NIMP: Budesonide nasal spray	----------X----------									
Record concomitant medication	----------X----------									
Record planned surgery for NP, SCS use, and other rescue medication use[i]	----------X----------									

Procedure	Run-in[a]	Randomized treatment period							EOT[c]	EOS
Visit	**1**	**2**	**3**		**4**		**5**		**6**	**7**
Week	**W-4**	**W0**	**W2**	**W4,6[b]**	**W8**	**W10, 12, 14[b]**	**W16**	**W18, 20, 22[b]**	**W24**	**W36**
Day +/-3 days	**D-28**	**D1**	**D15**		**D57**		**D113**		**D169**	**D253**
Efficacy										
Nasal endoscopy[j]	X	X					X		X	
Patient reported outcomes/HRQoL[k]										
Severity score (0-3) for nasal congestion/obstruction	----------X----------									
Severity score (0-3) for rhinorrhea	----------X----------									
Severity score (0-3) for decreased/loss of sense of smell	----------X----------									
22-item sino-nasal outcome test (SNOT-22)	X	X					X		X	
Safety										
AE/serious adverse event (SAE) recording	----------X----------									
Vital signs, weight and height[l]	X	X	X		X		X		X	
Physical examination	X								X	X
Laboratory testing										
Clinical laboratory testing[m]	X	X			X		X		X	
Pregnancy test (for women of childbearing potential [WOCBP])[n]	X	X		X (W4)	X	X (W12)	X	X (W20)	X	X

a The run-in period is 28 days in duration to run in any participant on budesonide nasal spray, and to collect baseline data. Participants receiving rescue medication with SCS and/or surgery during this period will not be randomized. V2 will take place 28 days +/-3 days window after V1. Window for subsequent visits is also +/-3 days. Assessments/procedures at a site visit will be performed in the following order as applicable: Patient-reported outcomes and other questionnaires; Procedures; Safety and laboratory assessments; IMP administration. Although the screening assessments are grouped under the heading of a single visit, 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.

b IMP will be administered Q2W. Home administration can be performed at home by participant or caregiver at W4, 6, 10, 12, 14, 18, 20, 22 after 1st IMP administration performed by the study site team at W0 (V2) and successful preparation and injection performed by participant or caregiver at W2 (V3) under investigator supervision. Optional interim visits could be scheduled at site for IMP/NIMP supply or IMP administration. The planned last dose is at W22.

c Participants who discontinue treatment early should be assessed as soon as possible using the procedures normally planned for the EOT Visit and should be instructed to return to the study site.

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 electronic case report form (e-CRF).

e Chest X-ray if no chest imaging (X-ray, CT, magnetic resonance imaging [MRI]) is available within the previous year of V1.

f IMP should be administered after completion of all scheduled clinical assessments and sample collections at the visit or at home.

g For doses not given at the study site participants will complete a dosing e-diary to document compliance with self-injection (or caregiver) of IMP, location of injection, and any symptoms. The e-diary will also be used for daily recording of budesonide nasal spray use. The e-diary will be kept as source data in the participant's study file.

h Electronic diary will be used for daily recording of 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 of e-diary will be dispensed at V1 and information will be downloaded from this device on the other indicated days. For nasal congestion, a severity ≥2 on V1 and a weekly average severity greater than 1 at time of randomization (V2) is required and will be made available to the site to determine participant 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, prednisolone or equivalent can be prescribed by the investigate to the participant through a scheduled or unscheduled site visit. Use of systemic steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator (or designee) on the appropriate source document 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 period, 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/EOS visit and will be instructed to return to the study site. If surgery is scheduled after the planned end of study, end of study 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 (NE): endoscopy (including use of decongestants before the procedure) is performed after all other efficacy assessments have been completed for pre-specified visit; standard video sequences will be downloaded by the Investigator to the central reader's secured internet site. For eligibility, central reading of V1 is 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 participant 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 on each side. The final results of central reading from V2 onward will be made available to the site after the study completion.

k During the study the patient reported outcomes (PROs) will be completed by the participant in the e-diary, in the following order: daily symptoms of NC, decrease/loss of smell and anterior and posterior rhinorrhea; SNOT-22.

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

m Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with five-part differential count, and total red blood cell (RBC) count. Serum chemistry: creatinine, blood urea nitrogen, glucose [nonfasting], 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. Endocrinology: follicle stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). Clinical laboratory testing at V1 includes hepatitis screen covering hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), total hepatitis B core antibody (HBcAb), hepatitis C virus antibodies (HCVAb), Human Immunodeficiency Virus (HIV) screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg (negative), and HBcAb (positive), an HBV DNA testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCVAb (positive), HCV RNA testing will be performed and should be confirmed negative prior to randomization. Hematology testing at all visits will be performed by central lab. Other clinical lab testing will be performed by local or central lab.

n Serum pregnancy test at V1 and urine pregnancy tests every 4 weeks thereafter. A negative result is required between V1 and V2 prior to randomization visit. Urine pregnancy 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 should be withhold and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy resulted in definitive treatment discontinuation in all cases.

Abbreviations: AE: adverse event; D: day; EC: ethic committee; ECG: electrocardiogram; e-CRF: electronic case report form; EOS: end of study; EOT: end of treatment; FU: follow-up; HRQoL: health-related quality of life; IgE: immunoglobulin E; IMP: investigational medicinal product; IVRS: interactive voice response system; IWRS: interactive web response system; MRI: magnetic resonance imaging; NC: nasal congestion; NIMP: noninvestigational medicinal product; NE: nasal endoscopy; NP: nasal polyposis; PROs: patient reported outcomes; SAE: serious adverse event; SCS: systemic corticosteroids; SNOT-22: sino-nasal outcome test; V: visit; W: week; WBC: white blood cell; WOCBP: women of child bearing potential.

2 INTRODUCTION

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a clinical condition characterized by the bilateral presence of multiple polyps in the nasal cavity, originating from within the osteomeatal complex, and clinically characterized by long-term symptoms of nasal obstruction and congestion, reduction in or loss of sense of smell, anterior and posterior rhinorrhea, which impact greatly upon a patient's QoL. NP has a high burden of symptoms and a high relapse rate after treatment. The prevalence of CRSwNP was reported to be 1.1% in China (1).

Despite the significant morbidity associated with CRSwNP, treatment options are limited to local or systemic corticosteroids (SCS) and functional endoscopic sinus surgery (FESS). 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 (6, 7).

Both IL-4 and IL-13 signaling pathways are implicated in atopic diseases and by blocking the activity of these cytokines, dupilumab has been shown to be an effective treatment for atopic conditions, including CRSwNP, AD, EoE and asthma (eosinophilic type 2). Dupilumab (Dupixent®) is authorized for marketing in over 60 countries worldwide, and has been approved as add-on maintenance treatment for CRSwNP in more than 50 countries including United States (US), European Union (EU) and Japan. In China, dupilumab is authorized for the treatment of patients aged 6 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not advisable. This study is designed to evaluate the efficacy and safety of dupilumab in Chinese participants with moderate-to-severe signs and symptoms of CRSwNP who are not controlled on standard of care.

2.1 STUDY RATIONALE

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of dupilumab 300 mg every 2 weeks (Q2W) comparing to placebo on a background of INCS, in Chinese participants with moderate-to-severe signs and symptoms of CRSwNP who are not controlled on standard of care.

Dupilumab is a fully human mAb directed against the interleukin 4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors type 1 and type 2, as well as the IL-13 type 2 receptor. The binding of dupilumab to IL-4Rα results in blockade of IL-4 and IL-13 intracellular signaling. As a targeted/specific immunomodulatory agent, dupilumab is expected to inhibit selectively the Th2 pathway and is designed to achieve the desired therapeutic effect without the side effects typically associated with the use of less selective immunosuppressants. Dupilumab has demonstrated efficacy across a broad range of diseases driven by type 2 inflammation, including AD, asthma, CRSwNP and EoE. In the AD Phase 3 study in China (EFC15116), treatment with dupilumab 300 mg Q2W resulted in statistically significant and clinically meaningful improvements in the proportion of patients with both Investigator's global assessment (IGA) 0 or 1 and a reduction from baseline of ≥2 points compared to placebo at Week 16. Moreover, these results had comparable safety and efficacy to the overall global pivotal studies (SOLO1, SOLO2).

Dupilumab has been shown to be an effective treatment for CRSwNP in two successful Phase 3 pivotal studies (LIBERTY NP SINUS-24, LIBERTY NP SINUS-52) of 24- and 52-weeks duration in which participants with CRSwNP were dosed with 300 mg Q2W dupilumab as add-on treatment to background therapy of topical corticosteroids (mometasone nasal spray) in participants with CRSwNP. Significant efficacy was observed in these studies regarding reduction of endoscopic nasal polyps score, nasal congestion, and overall sinus opacification assessed by computed tomography (CT) scan. The effect extended to all analyzed secondary endpoints including QoL, sense of smell, and symptoms of rhinosinusitis as well as in asthma symptoms and lung function in participants with co-morbid asthma. Furthermore, dupilumab significantly reduced the need for systemic steroids for CRSwNP and sino-nasal surgery. In subgroups defined by eosinophils <300 cells/mm^3 or ≥300 cells/mm^3, the nasal polyp scores LS mean treatment difference in dupilumab versus placebo were similar (-1.56 [95%CI: -1.9, -1.21] and -2.13 [95%CI: -2.44, -1.82], respectively). In a pooled safety analysis of SINUS-24 and SINUS-52, the incidence of the most commonly reported AEs was more frequent with placebo than dupilumab. Dupilumab was generally well tolerated and had an acceptable safety profile in the treatment of participants with inadequately controlled CRSwNP as well as long-term treatment (5).

In global pivotal Phase 3 studies (SINUS-24 and SINUS-52) of CRSwNP, the trend of slightly higher exposure in Asians/Japanese compared to the Caucasians/Non-Japanese was mainly caused by differences in body weight, while there were no clinically significant differences in efficacy and safety across race groups or ethnic groups. In addition, the safety and efficacy of dupilumab in Chinese adult AD participants in study EFC15116 was similar to the global pivotal AD studies. Therefore, no clinically meaningful difference in efficacy and safety between Chinese and non-Asian participants with CRSwNP is expected. Dupilumab, therefore, offers promise of significant benefit above and beyond current standard of care and may provide an alternative for Chinese adult patients with inadequately controlled CRSwNP and may obviate the need for repeated surgeries.

As there remains high unmet need for novel therapies to treat CRSwNP in China, the Sponsor will investigate the efficacy and safety of dupilumab on a background of INCS in Chinese adult participants with moderate-to-severe signs and symptoms of CRSwNP who are not controlled on standard of care.

A detailed description of the chemistry, pharmacology, efficacy, and safety of dupilumab is provided in the Investigator's Brochure (IB).

2.2 BACKGROUND

Chronic rhinosinusitis is characterized by inflammation of the nasal mucosa and paranasal sinuses and can be further divided into chronic rhinosinusitis with and without nasal polyps. Nasal polyps are inflammatory hyperplastic growths that protrude into the nasal passages. Clinically, chronic rhinosinusitis with nasal polyposis (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 a patient's quality of life (QoL). The presence or absence of polyps is confirmed by performing endoscopy. With an estimated prevalence of 2.5% to 4% (in Europe and US), NP has a high burden of symptoms and a high relapse rate after

treatment (7). The prevalence of CRSwNP in China was reported to be 1.1% (1), corresponding to over 15 million patients. Despite the significant morbidity associated with CRSwNP, treatment options are limited to local or systemic corticosteroids (SCS) and functional endoscopic sinus surgery (FESS). 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 (6, 7).

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 (8, 9, 10).

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 (11, 12, 13). Uncontrolled severe CRSwNP is typically a 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 (14). The extent of sinomucosal involvement, the size of the polyps, and the severity of nasal disease correlate with the extent of eosinophilic inflammation (15). 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 IgE in the nasal polyps and local secretions (16). High tissue eosinophilia (HTE) appears to be the most significant predictor of polyp recurrence among several factors. Eosinophilic CRSwNP presents more uncontrolled severe clinical features and higher recurrence rate following surgery. In European and US populations, more than 80% of patients with CRSwNP have eosinophilic upper airway inflammation. In the past studies, it was shown the CRSwNP patients in Asian showed lower eosinophilic inflammation than Western patients (7). But some recent studies show that the proportion of eosinophilic CRSwNP has significantly increased from 59.1% to 73.7% over the recent decade in China, which is comparable to the data from Western countries (17, 18, 19). Type 2 CRSwNP is associated with elevated blood eosinophils (20); elevated blood eosinophils are associated with tissue eosinophilia in Chinese CRSwNP patients (21, 22).

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 (4), secretion, and sneezing to some extent. However, their effect in reducing polyp size and on improving the sense of smell, a cardinal symptom of CRSwNP is limited (2, 3). Overall, due to the relatively modest effects on the symptoms of CRSwNP, 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 (23); 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 (4).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 (24).

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. It was shown in a recent study in Chinese patients with CRSwNP and asthma who were randomly assigned to FESS, radical endoscopic sinus surgery (RESS), or RESS+Draf 3 surgery that recurrence rates were similarly high in all the groups at 5 years postoperatively, reaching 95.6-96.1% (25).

The goals of new treatments include reduction of symptoms and systemic corticosteroid use and avoidance of surgery, as well as improved quality of life. Recent therapeutic approaches have been focused on trying to control the Th2 response and clinical improvement in NP and associated symptoms were observed in other studies of biological therapies, including the anti-IgE mAB omalizumab (26), the anti-IL-5 mAB mepolizumab (27), or the anti-IL-4Rα mAB dupilumab (5). In China there are currently no advanced therapies that are approved specifically for the treatment of CRSwNP. There remains great unmet need in identifying a novel therapy that addresses inflammatory underpinnings of the disease processes, reduces polyp size, improves symptoms and HRQoL, prevents recurrence, minimizes the need for systemic corticosteroids and recurrent nasal polyps surgery, and is well tolerated.

2.3 BENEFIT/RISK ASSESSMENT

Dupilumab has shown clinically relevant benefit in several type 2 driven immunological disorders, such as AD, asthma, CRSwNP and EoE. Data showed similar efficacy, safety, and pharmacokinetics in adult and adolescents. A satisfactory safety profile has been observed so far in completed and ongoing studies, including those in AD, CRSwNP, asthma and EoE participants.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of dupilumab is available in the Investigator's Brochure.

2.3.1 Risk assessment

No tissue targets or specific hazards to humans were identified in nonclinical general and reproductive toxicology studies.

Dupilumab has an extensive safety database. As of 28 March 2022 (data cut-off date), 13 577 subjects were enrolled into the development program for dupilumab and are included in the safety population: 564 as healthy volunteers, 4998 from AD studies, 4195 from asthma studies, 880 from rhinosinusitis (chronic rhinosinusitis with nasal polyposis [CRSwNP], chronic rhinosinusitis without nasal polyposis [CRSsNP] and allergic fungal rhinosinusitis [AFRS]) studies, 468 from eosinophilic esophagitis (EoE) studies, 275 from allergy (grass and peanut) studies, 1495 from the chronic obstructive pulmonary disease (COPD) study, 309 from prurigo nodularis studies, 311 from urticaria (chronic spontaneous urticaria [CSU] and chronic inducible cold urticaria [CICU]) studies, 45 from the bullous pemphigoid (BP) study, and 37 from the allergic bronchopulmonary aspergillosis (ABPA) study. The number of subjects exposed to dupilumab in clinical studies was 10 828 (538 in healthy volunteer studies, 4496 in AD studies, 3591 in asthma studies, 526 in rhinosinusitis [CRSwNP, CRSsNP and AFRS] studies, 405 in EoE studies, 175 in allergy [grass and peanut] studies, and 748 in the COPD study, 152 in PN studies, 156 in the urticaria [CSU and CICU] studies, 22 in the BP study, and 19 in the ABPA study).

Based on the sales figure and World Health Organization's defined daily dose for dupilumab of 21.4 mg/day, the cumulative post marketing exposure to dupilumab could be estimated to be 706 212 patient-years from 01 March 2017 through 31 March 2022.

Dupilumab has been generally well tolerated in all populations tested in clinical development programs consistent with a positive benefit/risk profile. The adverse drug reactions (ADRs) identified to date for dupilumab include injection site reactions, conjunctivitis (including allergic and bacterial), oral herpes, herpes simplex, blepharitis, dry eye, eye pruritus, eosinophilia, serum sickness, angioedema, arthralgia, facial rash, and keratitis (including ulcerative). These ADRs were generally mild or moderate, transient, and manageable. These ADRs were not consistently observed in all indications (see IB for greater details). More significant serious allergic reactions were very rare. Importantly, no increased overall infection risk was observed in patients treated with dupilumab.

The important identified risks associated with dupilumab are:

- Systemic hypersensitivity: Anaphylactic reaction and angioedema are listed ADRs in addition to serum sickness and serum sickness-like reaction.
- Conjunctivitis and keratitis related events in AD patients: Conjunctivitis, keratitis and ulcerative keratitis are listed ADRs.

An important potential risk for dupilumab is "eosinophilia associated with clinical symptoms in asthma patients". The observed increase in eosinophil count is transient, which is consistent with the current understanding of the mechanism of action of dupilumab. In dupilumab asthma studies, a small number of patients with asthma experienced serious systemic eosinophilia presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA), conditions which are often treated with systemic corticosteroid therapy. These events have been seen in other drug development programs for severe asthma and usually, but not always, have been associated with the reduction of oral corticosteroid therapy suggesting possible unmasking of these conditions with tapering of corticosteroids during dupilumab therapy. The association of dupilumab treatment and these events has not been established. Health care providers should be alert to eosinophilia associated with vasculitic rash, worsening of pulmonary symptoms, pulmonary infiltrate, cardiac complications, and/or neuropathy presenting in their patients, especially upon reduction of systemic corticosteroids.

Patients with known helminth infections were excluded from participation in clinical studies, therefore it is not known if dupilumab will influence the immune response against helminth infections. Consequently, patients with pre-existing helminth infections should be treated for their helminth infection before initiating therapy with dupilumab. The dupilumab pediatric asthma study included patients age 6 to <12 years of age. The safety profile in these patients through Week 52 was similar to the safety profile from studies in adults and adolescents with moderate-to-severe asthma, with the additional adverse reaction of enterobiasis. Enterobiasis was reported in 1.8% (5 patients) in the dupilumab groups and none in the placebo group. All enterobiasis cases were mild to moderate and patients recovered with anti-helminth treatment without treatment discontinuation. An imbalance of cases of enterobiasis was not observed in other dupilumab clinical trials, including the study in patients 12 years and older with moderate-to severe asthma.

Other potential risks based on the safety profile in particular indications are discussed in the IB.

While long-term data are still accumulating, data from randomized, placebo-controlled trials and open-label extension studies to date have not identified any new safety concern in these populations. It is anticipated that dupilumab in patients with CRSwNP will have a favorable safety profile as observed across other type 2-driven immunological disorders.

COVID-19 related risk assessment

Currently, there are insufficient data in patients with Coronavirus Disease 2019 (COVID-19) who are being treated with dupilumab. Thus, the safety and efficacy of dupilumab in COVID-19 patients are unknown. During the course of clinical trials conducted during the COVID-19 pandemic, respiratory infections including viral infections and COVID-19 infections were monitored and these events are not listed as ADRs for dupilumab.

There are currently no clinical data available on concomitant use of dupilumab with any SARS-CoV-2 vaccine. Concomitant use of non-live SARS-CoV-2 vaccines is not prohibited. Based on available data, no attenuation of the vaccination response is expected.

The Sponsor also recognizes that the COVID-19 pandemic may have an impact on the conduct of clinical trials. The Sponsor will monitor the situation closely and ensure the integrity of the trial conduct and data (see Section 10.9).

2.3.2 Benefit assessment

Dupilumab has been shown to be an effective treatment for CRSwNP in two successful Phase 3 pivotal studies (LIBERTY NP SINUS-24, LIBERTY NP SINUS-52) of 24- and 52-weeks duration in which 300 mg Q2W of dupilumab used on top of topical corticosteroids (mometasone nasal spray) in participants with CRSwNP. Statistically significant and clinically relevant efficacy was observed in these studies regarding reduction of endoscopic nasal polyps score, nasal congestion, and overall sinus opacification assessed by CT scan. The effect extended to all analyzed secondary endpoints including QoL, sense of smell, and symptoms of rhinosinusitis as well as in asthma symptoms and lung function in participants with co-morbid asthma. Furthermore, dupilumab significantly reduced the need for systemic steroids and sino-nasal surgery. In a pooled safety analysis, the incidence of the most commonly reported AEs was more frequent with placebo than dupilumab. Dupilumab was generally well tolerated and had an acceptable safety profile in the treatment of participants with inadequately controlled CRSwNP as well as long-term treatment (5).

The CRSwNP patients who will participate in this study may have the potential benefit of receiving a novel treatment for the underlying type 2 inflammatory disease process. Based on the efficacy results observed for CRSwNP in global pivotal studies, and for other type-2 mediated disorders, it is anticipated that use of IMP will lead to reduced signs and symptoms associated with CRSwNP and improved function and quality of life for these patients.

Dupixent® (dupilumab) is authorized for marketing in over 60 countries worldwide including the US, European Union (EU) (Centralized Procedure), Japan, China, Canada, and Australia for the adult AD indication. Dupilumab is also authorized in the US, EU, and other jurisdictions for the pediatric (6 to <18 years of age) AD indications, and in the US, EU, Japan, and other jurisdictions for the adult and adolescent asthma indication. Dupilumab also has approval for its CRSwNP indication in the US, EU, and other jurisdictions.

2.3.3 Overall benefit/risk conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with dupilumab are justified by the anticipated benefits that may be afforded to participants with inadequately controlled CRSwNP patients on standard of care.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab compared to placebo on a background of budesonide nasal spray in reducing endoscopic nasal polyps score (NPS) in Chinese participants with bilateral nasal polyposis (NP).	• Change from baseline in NPS at Week 24.
Secondary	
• To evaluate the efficacy of dupilumab in reducing nasal congestion/obstruction (NC) severity.	• Change from baseline in NC score (NCS) based on the participant daily morning assessment at Week 24.
• To evaluate the efficacy of dupilumab in improving total symptoms score (TSS).	• Change from baseline in TSS at Week 24: composite severity score consisting of the participant daily morning assessed NC, decreased/loss of sense of smell, anterior/posterior rhinorrhea.
• To evaluate the efficacy of dupilumab in improving sense of smell.	• Change from baseline in the severity of decreased/loss of smell assessed daily by participants at Week 24.
• To evaluate the effect of dupilumab on patient quality of life.	• Change from baseline in total score of 22-item sino-nasal outcome test (SNOT-22) at Week 24.
• To evaluate the ability of dupilumab to reduce proportion of participants who require treatment with systemic corticosteroid (SCS) or surgery for NP.	• Proportion of participants receiving SCS for any reason or undergo surgery for nasal polyps during the study treatment.
• To evaluate the safety of dupilumab in Chinese participants with bilateral NP.	• Safety (incidence of treatment-emergent adverse events [TEAEs], of treatment-emergent serious adverse events [TESAEs], and TEAEs leading to treatment discontinuation), laboratory values, vital signs.
Exploratory	
Not applicable	

Primary estimands defined for primary efficacy endpoints are summarized in Table 2 below. More details are provided in Section 9.2.

For all these estimands, the comparison of interest will be the comparison of dupilumab 300 mg Q2W vs. placebo.

Table 2 - Summary of primary estimands for primary endpoint

Endpoint Category	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To evaluate the efficacy of dupilumab compared to placebo on a background of budesonide nasal spray in reducing endoscopic nasal polyps score (NPS) in Chinese participants with bilateral nasal polyposis (NP).				
Primary endpoint	Change from baseline in NPS at Week 24.	ITT	The intercurrent events will be handled as follows: • Undergoing surgery for CRSwNP or taking SCS for any reason prior to Week 24: data after surgery/SCS will be set to missing and the worst post-baseline value on or before the time of surgery/SCS will be used to impute missing Week 24 value (WOCF). For participants with no post-baseline values, the baseline value will be used (composite strategy). • Taking other prohibited/rescue medications: all data collected after use will be used in the analysis (treatment policy strategy). • Discontinuing the study intervention (but not undergoing surgery for CRSwNP or taking SCS for any reason prior to Week 24): all data collected after discontinuation will be used in the analysis (treatment policy strategy).	Mean change difference between interventions from ANCOVA model with study intervention and screening blood eosinophil count strata, and baseline measurement as covariates is used. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule. For missing data, a multiple imputation approach will be used to impute missing Week 24 values, and this multiple imputation will use all participants excluding those who have undergone surgery or received SCS for any reason on or before Week 24.

ITT: intent-to treat; CRSwNP: chronic rhinosinusitis phenotype with nasal polyps; SCS: systemic corticosteroids; ANCOVA: analysis of covariance; WOCF: worst observation carried forward.

3.1 APPROPRIATENESS OF MEASUREMENTS

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.

Endoscopic nasal polyps score (NPS)

The bilateral endoscopic NPS is chosen as the primary endpoint in this study. It was the objective component of the co-primary endpoints of global pivotal CRSwNP studies. 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) (26, 27, 28).

Nasal congestion/obstruction score (NCS)

Medical and surgical intervention decisions are mainly driven by the nasal polyp symptom burden and response to standard therapy with topical and SCS. Nasal congestion/obstruction is a major clinical symptom in CRSwNP and will be measured by a nasal congestion/obstruction score (patient reported outcomes [PRO]) to evaluate the disease activity as a secondary endpoint. Nasal congestion/obstruction severity score consisting of the monthly average of the daily morning (AM) patient-assessed daily symptom severity (using a 0 to 3 categorical scale). The NCS is assessed by the participant 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) (7).

Other measurements

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 assessments in other PRO (ie, total symptom score [TSS]) and patient health-related quality of life (HRQoL) and safety assessments to evaluate the potential real-life benefit will be performed too.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of dupilumab 300 mg every 2 weeks (Q2W) compared to placebo, in Chinese adult participants with moderate-to-severe signs and symptoms of bilateral nasal polyposis (NP) on a background treatment with intranasal corticosteroids.

Randomization will be stratified by screening blood eosinophil count (≥300 cells/mm^3 or <300 cells/mm^3).

To ensure enrollment according to the intended distribution of screening blood eosinophil count, alerts will be built into the IRT to control the number of participants in each stratification group as follows:

- ≥300 cells/mm^3: approximately 26 participants per arm,
- <300 cells/mm^3: up to approximately 5 participants per arm.

The clinical study consists of 3 periods:

- Run-in period (4 weeks +/-3 days): to determine a participant's eligibility and for run-in/standardization of background INCS (budesonide nasal spray) prior to randomization.
- Randomized dupilumab/placebo treatment period (24 weeks +/-3 days): to randomize the participant into a treatment arm and treat with dupilumab or placebo dose regimen.
  - Arm A: dupilumab 300 mg SC Q2W.
  - Arm B: placebo matching dupilumab SC Q2W.
- Follow-up period (12 weeks +/-3 days): to continue to collect data for safety after the participant has completed the study drug treatment period.

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

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 6.8.3.

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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The population of the EFC17026 will be composed of participants 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.

Older publications have noted Chinese population may have a lower prevalence of CRSwNP type 2 endotype compared to Western countries which have a prevalence of ~85% (29); however, one publication reports the type 2 CRSwNP prevalence is increasing in China (22). Elevated blood eosinophils are associated with tissue eosinophilia in CRSwNP (20); in studies of Chinese type 2 CRSwNP patients a blood eosinophil count of ≥300 cells/mm^3 is most closely associated with type 2 CRSwNP (21, 22). Given the possible lower prevalence of type 2 CRSwNP in China, the study will enrich for this population using blood eosinophils as a surrogate marker for type 2 CRSwNP.

The proposed participant selection criteria reflect standard of care in this severe uncontrolled participant setting by allowing enrollment of participants that received INCS, with or without SCS prior to the run-in period, and/or participants with previous surgeries.

Dupilumab or matched placebo will be added on top of background treatment of INCS (daily use of budesonide nasal spray). By allowing Investigators, at their discretion, to use SCS or surgery as a rescue therapy for worsening of CRSwNP, the study will also assess the effect of dupilumab on the need for surgery and OCS use over the randomized treatment period.

The 24-week treatment duration is considered sufficient for efficacy evaluation based on the efficacy results from global pivotal CRSwNP studies in which dupilumab 300 mg Q2W demonstrated statistically significant and clinically meaningful improvement across all primary and multiplicity adjusted secondary outcome measures at Week 24 and Week 52. Early beneficial effect was seen from Week 2 to Week 4, followed by a progressive improvement through 24 weeks and 52 weeks. The 24-week duration is also appropriate to evaluate safety considering the extensive safety experience with CRSwNP and the related condition of asthma. The post-treatment 12-week follow-up period is based on the expected PK profile of dupilumab after the last dose, ie, the time for systemic concentrations to decline to non-detectable levels in most participants.

Among objective measures of disease burden, radiologic and endoscopic scoring system have been the primary foci of outcomes research in rhinology. The presence or absence of polyps is confirmed by performing endoscopy. In this study, endoscopic NPS is selected as the primary endpoint to evaluate the nasal polyps burden, which was the objective component of co-primary endpoints in global pivotal studies (LIBERTY NP SINUS-24, LIBERTY NP SINUS-52). Nasal congestion/obstruction is a major clinical symptom in CRSwNP and will be measured by a nasal congestion/obstruction score patient-reported outcome (PRO) to evaluate the disease activity as secondary endpoint. Other symptoms including rhinorrhea and decreased/loss of sense of smell, and participants' QoL will also be evaluated using the tools similar to the dupilumab CRSwNP global program.

4.3 JUSTIFICATION FOR DOSE

Based on the known clinical PK, efficacy and safety of dupilumab observed in studies conducted globally and locally in healthy participants and participants with AD, asthma, and CRSwNP, dupilumab 300 mg Q2W was selected as the dosing regimen for this study in Chinese adult patients with CRSwNP.

In the global pivotal studies in CRSwNP participants (LIBERTY NP SINUS-24, LIBERTY NP SINUS-52), dupilumab 300 mg Q2W demonstrated statistically significant and clinically meaningful improvement across all primary and multiplicity adjusted secondary outcome measures at Week 24 and Week 52 and had an acceptable safety profile. The 300 mg Q2W dose regimen was approved in EU and US for the treatment of adult participants with inadequately controlled CRSwNP.

In addition to participants with CRSwNP, the 300 mg Q2W dose regimen was also selected for adult and adolescent participants with moderate-to-severe AD and moderate-to-severe asthma in previous global Phase 3 pivotal studies. In all of these studies, the 300 mg Q2W dose regimen achieved concentrations in serum that saturate the target-mediated clearance pathway and has been proven to be effective and have an acceptable safety profile. Additionally, 300 mg Q2W was studied in Chinese participants with AD in the Phase 3 study EFC15116, showing statistically significant and clinically meaningful improvements compared to placebo at Week 16 and an acceptable safety profile in Chinese participants with AD.

As a monoclonal antibody dupilumab PK is insensitive to ethnic factors. In prior global population PK analysis with dupilumab for CRSwNP population, race was not identified as the significant covariate impacting PK and body weight was the only covariate identified with a meaningful impact on dupilumab PK. In global pivotal Phase 3 studies in participants with CRSwNP, the trend of slightly higher exposure in Asians/Japanese compared to the Caucasians/Non-Japanese is mainly the result of differences in body weight, while there are no clinically significant differences in efficacy and safety across race groups or ethnic groups. In addition, the safety and efficacy of dupilumab in Chinese adult AD participants was similar to the global pivotal studies.

The insensitivity to ethnic factors of dupilumab with regard to PK, efficacy, and safety has been thoroughly demonstrated in participants with AD based on the completed studies conducted globally and locally, leading to the approval of AD indication in adults in China with the same dose regimen as EU and US. It further supports to select the same regimen 300 mg Q2W as the dose regimen approved globally for the CRSwNP development in Chinese participants. Therefore, there is no ethnic difference in dupilumab PK that translates to a clinically meaningful difference in dupilumab efficacy and safety. It is reasonable to assume that no clinically meaningful difference in dupilumab efficacy and safety between Chinese participants with CRSwNP and participants enrolled in global CRSwNP studies following 300 mg Q2W treatment will be observed.

The collective PK, clinical efficacy and safety data of dupilumab across diverse disease populations suggest that the selected dose regimens 300 mg Q2W for this study will be efficacious and safe for the treatment of Chinese adult CRSwNP participants.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study including the end of his or her 12-week follow-up period or prematurely discontinues from the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be at least 18 years of age at the time of signing the informed consent.

Type of participant and disease characteristics

Participants with bilateral sino-nasal polyposis that despite prior treatment with SCS anytime within the past 2 years; and/or who have a medical contraindication/intolerance to SCS; and/or had prior surgery for NP at Visit 1 have:

I 02. An endoscopic bilateral NPS at Visit 1 of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) as per central assessment (refer to Section 8.1.1)

I 03. Ongoing symptoms (for at least 8 weeks before Visit 1) of:

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

  AND

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

  NOTE: Plan to enroll at least 85% (approximately 52) participants with CRSwNP meeting following criterion:

- Participants with peripheral blood eosinophil count ≥300/mm^3

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 04. All (Male and/or Female)

Contraceptive use by women should be consistent with the regulations regarding the methods of contraception for those participating in clinical studies (Additional details can be found in Appendix 4: Section 10.4).

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
  - Is a woman of non-childbearing potential (WONCBP) as defined in Appendix 4 (Section 10.4 Contraceptive and barrier guidance).

OR

- Is a woman of childbearing potential (WOCBP) and agrees to use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 (Section 10.4 Contraceptive and barrier guidance) during the study intervention period and for at least 12 weeks after the last administration of study intervention.

A WOCBP must have a negative highly sensitive pregnancy test at screening (serum) and on Day 1 (urine) before the first administration of study intervention, see Section 8.2.5 Pregnancy testing. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Informed Consent

I 05. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Participants with conditions/concomitant diseases making them non-evaluable at Visit 1 or for the primary efficacy endpoint (ie, NPS) such as:

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

E 02. Participants with nasal cavity malignant tumor and benign tumors (eg, papilloma, hemangioma, etc).

E 03. Participant with historical spirometry results which showed 50% or less of predicted normal of forced expiratory volume in one second (FEV1).

E 04. Diagnosed with; suspected of, or at high risk of endoparasitic infection, and/or use of antiparasitic drug within 2 weeks before Visit 1 or during the screening period.

E 05. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at Visit 1.

E 06. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or otherwise recurrent infection of abnormal frequency or prolonged duration suggesting an immune-compromised status, as judged by the Investigator.

E 07. Participants with active TB, non-tuberculous mycobacterial infection or a history of incompletely treated TB will be excluded from the study unless it is well documented by a specialist that the participant has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing will be performed according to local guidelines if required by regulatory authorities or ethics boards, or if TB is suspected by the investigator.

E 08. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before Visit 1 or during the screening period.

E 09. Active malignancy or history of malignancy within 5 years before the baseline visit, except completely treated in situ carcinoma of the cervix and completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

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

E 11. History of systemic hypersensitivity or anaphylaxis to dupilumab including any excipient.

E 12. Participants meet any contraindications or warning on product labeling for budesonide nasal spray.

E 13. Severe concomitant illness(es) that, in the Investigator's judgement, would adversely affect the participant's participation in the study. Examples include, but are not limited to participants with short life expectancy, participants with uncontrolled diabetes (hemoglobin A1c ≥9%), participants with cardiovascular conditions (eg, Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, participants on dialysis), hepato-biliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating disease), autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, psychiatric, or lymphatic diseases. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, case report forms [CRFs], etc).

E 14. Participants with any other medical or psychological condition including relevant laboratory or electrocardiogram (ECG) abnormalities at screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant as a result of his/her participation in this clinical trial, may make participant's participation unreliable, or may interfere with study assessments. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, case report form [CRF], etc).

Prior/concomitant therapy

E 15. Planned major surgical procedure during the participant's participation in this study.

E 16. Participants who have taken:

- Biologic therapy/systemic immunosuppressant/immunomodulator within 4 weeks before Visit 1 or 5 half-lives, whichever is longer.
- Any investigational monoclonal antibody (mAb) within 5 half-lives or within 6 months before Visit 1 if the half-life is unknown.
- Anti-immunoglobulin E therapy (omalizumab) within 4 months prior to Visit 1.

E 17. Treatment with a live (attenuated) vaccine within 4 weeks prior to Visit 1.

NOTE: For participants who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the end of study (EOS), or preponed to before the start of the study without compromising the health of the participant:

- Participants for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.
- Participants who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

E 18. Participants who are receiving leukotriene antagonists/modifiers within 4 weeks before V1 or 5 half-lives, whichever is longer, unless patient is on a continuous treatment for at least 4 weeks before Visit 1.

E 19. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy or change its dose during the run-in or randomized treatment period.

E 20. Participants who have undergone any intranasal and/or sinus surgery (including polypectomy) within 6 months prior to Visit 1 or sino-nasal surgery changing the lateral wall structure of the nose making the evaluation of NPS impossible.

E 21. Use of any prohibited medications (Section 6.8.1) and procedures during screening period or planned use during screening or study treatment period.

E 22. Either intravenous immunoglobulin (IVIG) therapy and/or plasmapheresis within 4 weeks before Visit 1.

Prior/concurrent clinical study experience

E 23. Current participation in any clinical trial of an investigational drug or device or participation within 3 months before V1 or 5 half-lives of the investigational compound, whichever is longer.

E 24. Participation in a prior dupilumab clinical study or have been treated with commercially available dupilumab.

Diagnostic assessments

E 25. Patients with any of the following result at the screening visit (Visit 1):

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

Noncompliance to completion of the patient diary or noninvestigational medicinal product (NIMP)

E 26. NIMP noncompliance at Visit 2 (<80%)

E 27. Any condition that could make the participant noncompliant with the study procedures and daily assessment in the e-diary.

Other exclusions

E 28. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 29. Participants not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 30. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 31. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Participants who are rescreened are required to sign a new ICF.

In cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the participant can be rescreened one time for this study.

5.5 CRITERIA FOR TEMPORARILY DELAYING

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency) should be considered for screening, randomization, and administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

A concomitant therapy is any treatment received by the participant concomitantly to any IMP(s) or NIMP. This includes medications that were started before the first dose of study intervention and are ongoing during the study.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Participants who satisfy the inclusion and exclusion criteria will be randomized (1:1) to one of the following IMP treatment groups:

- Arm A: dupilumab 300 mg Q2W.
- Arm B: placebo matching dupilumab Q2W.

Duration of study intervention:

- Run-in period: 4 weeks +/-3 days
- Randomized treatment period: up to 24 weeks +/-3 days
- Follow-up period: 12 weeks +/-3 days

Table 3 - Study intervention(s) administered

Intervention label	Dupilumab	Placebo	Budesonide nasal spray
Intervention name	Dupilumab 300 mg	Placebo	Budesonide nasal spray
Intervention description	Dupilumab 300 mg Q2W via SC injection	Placebo matching dupilumab 300 mg Q2W via SC injection	Budesonide nasal spray at total daily dose of 256 µg
Type	Biological/Vaccine	Other	Drug
Dose formulation	A 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in a 2 mL injection	Identical formulation to the active 300 mg formulation without dupilumab, in a prefilled syringe to deliver placebo in a 2 mL injection	Nasal spray suspension is provided in a bottle, that contains 120 actuations of product formulation
Unit dose strength(s)	150 mg/mL	NA	64 µg/actuation
Dosage level(s)	Dupilumab 300 mg Q2W up to 24 weeks, the planned last administration is at Week 22	Placebo matching dupilumab 300 mg Q2W up to 24 weeks, the planned last administration is at Week 22	Budesonide nasal spray 2 actuations (64 µg/actuation) in each nostril QM or 1 actuation in each nostril BID (total daily dose of 256 µg). One actuation in each nostril once daily (total daily dose of 128 µg) if the participants are unable to tolerate total daily dose of 256 µg, in which case they can stay on a lower dose regimen (128 µg) of budesonide nasal spray.
Route of administration	subcutaneous (SC) injection	subcutaneous (SC) injection	Nasal spray
Use	Experimental	Placebo	Background treatment
IMP and NIMP	IMP	IMP	NIMP
Packaging and labeling	One prefilled syringe packed in a patient kit box. Both the prefilled syringe and the box will be labeled as required per country requirement.	One prefilled syringe packed in a patient kit box. Both the prefilled syringe and the box will be labeled as required per country requirement.	Nasal spray is provided in a bottle. Each container will be labeled as required per country requirement.
[Current/former name(s) or alias(es)]	Dupixent®	NA	Rhinocort

Q2W: every 2 weeks; SC: subcutaneous; QM: every morning; BID: twice a day; IMP: investigational medicinal product; NIMP: noninvestigational medicinal product.

Table 4 - Study arm(s)

Arm title	Arm A	Arm B
Arm type	Experimental	Experimental
Arm description	Dupilumab 300 mg Q2W via SC injection	Placebo matching dupilumab 300 mg Q2W via SC injection
Associated intervention labels	Dupilumab	Placebo

Q2W: every 2 weeks; SC: subcutaneous.

6.1.1 Investigational medicinal product(s)

Regardless of the treatment arm, all randomized participants will receive Q2W SC administrations of either dupilumab or placebo starting from Day 1 (V2). Every other week IMP administrations must be separated by at least 11 days (See Section 1.2). The planned last IMP administration is at Week 22.

The first IMP administration should be performed at the study center.

For the doses that are not scheduled to be given at the study site, home administration of IMP is allowed after appropriate training of the participant (or caregiver). Investigator or delegate will prepare and inject the first dose of IMP at Week 0 (Visit 2), in front of the participant (or caregiver). The participant (or caregiver) will prepare and inject the IMP under the supervision of the Investigator or delegate at Week 2 (Visit 3). The training must be documented in the participant's study file. In case of emergency (eg, natural disaster, pandemic, etc) different training ways (eg, training remotely with instruction provided by phone, etc) can be performed (and will be documented in the participant's study file).

From Week 4 (except Week 8 [Visit 4] and Week 16 [Visit 5]), every other week home administration of IMP is possible if the participant (or the caregiver) has been trained. If the participant (or caregiver) is unable or unwilling to prepare and inject IMP, injections can be performed at the study site by way of unscheduled visits; or arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP at participant's home.

The participant/caregiver should be trained by the site staff to recognize potential signs and symptoms of hypersensitivity reaction in order to self-monitor/monitor at home for at least 30 minutes following injection. In case of hypersensitivity symptoms, the participant should contact healthcare provider/emergency.

When the participant has a study visit, the IMP will be administered after clinical procedures and blood collection are performed. Participants should be monitored for at least 30 minutes. The monitoring period may be extended as per country specific or local site-specific requirements.

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 participants themselves.

For doses not given at the study site participants will complete a 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 participant's study file.

Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the participant. In case of emergency (eg, natural disaster, pandemic, etc), IMP may be supplied from the site to the participant via a Sponsor-approved courier company if allowed by regulations and approved by the participant.

6.1.2 Non-investigational medicinal product(s)

6.1.2.1 Intranasal corticosteroid background therapy

On a daily basis throughout the study, the participant will use an e-diary to record daily use of budesonide nasal spray 64 µg/actuation nasal spray suspension, (refer to the package insert & SmPC for a description, administration details and precautions for use). Budesonide nasal spray is provided in a bottle that contains 120 actuations of product formulation.

Non-investigational medicinal products will be supplied by Sponsor's local affiliate as locally required or by sites. Reimbursement will be provided when deemed necessary and as per regulation.

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

Run-In Period

After V1, once participant eligibility for study entry has been confirmed, all participants will enter a run-in period of 4 weeks during which they will receive starting at V1 budesonide nasal spray:

- Two actuations (64 µg/actuation) in each nostril QM, or 1 actuation in each nostril BID (total daily dose of 256 µg). One actuation in each nostril once daily (total daily dose of 128 µg) if the participants are unable to tolerate total daily dose of 256 µg, in which case they can stay on a lower dose regimen (128 µg) of budesonide nasal spray.

Budesonide nasal spray will be self-administered by the participant, and at each visit the Investigator must ensure that the participant has the necessary and sufficient doses up to the next visit.

Participants 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 5.4.

Randomized treatment period

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

Follow-up period

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

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.1.3 Devices

No devices will be used for administration of study drug in this study.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP/NIMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

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

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomized intervention kit number list is generated centrally by Sanofi, and IMPs are packaged in accordance with this list. The randomization and intervention allocation are performed centrally by IRT. The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.

All participants will be centrally assigned to randomized study intervention in a 1:1 ratio using an IRT.

Randomization will be stratified by screening blood eosinophil count (≥300 cells/mm^3 or <300 cells/mm^3).

Before the study is initiated, the telephone number and call-in directions for the interactive voice respond system (IVRS) and/or the log in information and directions for the interactive web response system (IWRS) will be provided to each site.

At Screening (Visit 1), the Investigator or designee will contact the IRT to receive the participant number. If a participant who had previously failed screening is approached for re-screening, a new ICF must be signed. In such case, a new participant number will be assigned by IRT.

A randomized participant is defined as a participant who has been allocated to a randomized intervention regardless of whether the treatment was administered or not (ie, participant registered by the IRT). A participant cannot be randomized more than once in the study.

Study intervention will be dispensed at the study visits as summarized in the SoA. Returned study intervention should not be re-dispensed to the participants.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

Methods of blinding

Dupilumab 300 mg and placebo matching dupilumab 300 mg will be provided in identically matched 2 mL pre-filled syringes that are visually indistinguishable for each dose. Syringes and box will be labeled with a treatment kit number.

Code breaking

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

If the code is broken at the site level, the participant must withdraw permanently from IMP administration.

6.4 STUDY INTERVENTION COMPLIANCE

The Investigator or his/her delegate must ensure that IMP is administered to each participant according to the labeling instructions.

IMPs/NIMP accountability:

- Intervention units are returned by the participant at each visit. In case of direct mail to participant process, the intervention units can be returned by the carrier (if defined in the contract),
- The Investigator or his/her delegate counts the number of remaining kits/pre-filled syringes and fills in the Intervention Log Form,
- The Investigator or his/her delegate records the dosing information on the appropriate source document,
- The monitor in charge of the study then checks the source document data by comparing them with the IMP that he/she has retrieved, and the intervention log forms.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. All medication treatment kits (whether empty or unused) will be returned by the participant at each visit when a treatment dispensing is planned, and at the end of treatment (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. Participants will also return used prefilled syringes to the site in a sharps container. Compliance will be assessed by diary, and by counting the number of used and unused treatment kits and syringes during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of IMP and NIMP dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5 DOSE MODIFICATION

Dose modification for an individual participant is not allowed.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

The participants will have no access to study intervention after EOS.

6.7 TREATMENT OF OVERDOSE

Of note, asymptomatic overdose has to be reported as a standard AE. No antidote is available for dupilumab.

For this study, any dose of IMP at least twice the intended dose during an interval of less than 11 days and any dose of NIMP at least twice the maximum prescribed daily dose, within the intended therapeutic interval (≥512 µg; 8 sprays or more) will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose for IMP or NIMP.

In the event of an overdose, the Investigator should:

- Provide symptomatic care.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (until dupilumab can no longer be detected systemically [at least 98 days]).
- Evaluate the participant to determine whether study intervention should be interrupted.
- Document appropriately in the CRF.
- Contact the Sponsor as soon as possible.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Prohibited concomitant medication

The following concomitant treatments are not permitted during the screening period and the treatment period:

- Treatment with an investigational drug (other than dupilumab)

- Any systemic immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, and cyclophosphamide.
- Allergen immunotherapy (except if initiated more than 3 months prior to Visit 1 and dose stable 1 month prior to Visit 1).
- Intranasal corticosteroid drops; intranasal steroid emitting devices/stents.
- Use of intranasal decongestants except for preparation of nasal endoscopy (NE).
- Long term courses (>2 weeks) of systemic steroids.
- Short term courses (≤2 weeks) of IV, IM, subcutaneous (SC) systemic corticosteroids (SCS) except as indicated treatment of NP or to treat other serious coexisting disease (such as asthma).
- Short term courses (≤2 weeks) of systemic corticosteroids (SCS) only between Visit 1 and Visit 2.
- Live (attenuated) vaccine within 4 weeks prior to Visit 1.
- Other monoclonal antibodies (biological immunomodulators), including but not limited to anti-IgE, anti-IL-5 and anti-TNF, etc.

Participants who between Visit 1 and Visit 2 receive any of the prohibited treatments, treatment with systemic (oral, IV, IM) steroids or undergo surgery will not be enrolled. They may however be re-screened following the procedures described in the protocol.

6.8.2 Permitted concomitant medication

The following treatments are allowed:

- Budesonide nasal spray during the run-in period and throughout the whole study as background treatment (as described in Section 6.1.2).
- 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 β2-adrenergic receptor agonists (SABA), long-acting β2-adrenergic receptor agonists (LABA), and long-acting muscarinic acetylcholine receptor antagonists (LAMA).
- Methylxanthines (eg, theophylline, aminophyllines)
- Inhaled corticosteroids
- Systemic antihistamines
- Leukotriene antagonists/modifiers are permitted during the study, only for participants who were on a continuous treatment for ≥30 days prior to Visit 1.

- Allergen immunotherapy in place for >3 months prior to Visit 1 is permitted.
- Rescue medication including short courses of SCS for treatment of NP as described in Section 6.8.1 or short courses of SCS to treat other serious co-existing diseases (such as asthma exacerbation) are allowed.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

6.8.3 Rescue medicine

During the study treatment period and post-treatment follow-up period, 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 (only considered rescue if initiated after Visit 2) and/or systemic antibiotics (up to 2 weeks in case of acute infection).
- Short course SCS (oral prednisone, prednisolone or equivalent up to 2 weeks).
- Surgery for nasal polyps. Based on the observations from previous studies, 8 weeks of IMP treatment is recommended prior to surgery to allow onset of treatment effect.

Participants receiving rescue treatment other than surgery during the study should continue on study drug unless the Investigator decides to withdraw the study treatment. Systemic steroids for rescue treatment of nasal polyps or for another reason will be provided to the participant by the site. Before starting treatment with SCS participants should come to the study site for the clinical assessments including endoscopy and SNOT-22.

Participants scheduled for surgery may continue IMP up to the time of surgery or EOT whichever date comes first. At time of surgery participants will be permanently discontinued from study treatment and perform as soon as possible the efficacy and safety assessments planned at the EOT visit and will be instructed to return to the study site for additional visits as described in Section 7.1.1. An AE or SAE page will be completed.

If the surgery is performed during the post-treatment follow-up period, at the time of surgery the participants will be assessed according to the procedures normally planned for the EOS Visit and will be instructed to return to the study site for additional visits as described in Section 7.1.1. 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 electronic case report form (e-CRF) closure of the trial.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

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 any case, the participant should remain in the study as long as possible.

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The participants 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 eCRF.

Participants must be withdrawn from the study intervention 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 participant to the participant'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 participant's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the investigator or the Sponsor
- Any code broken at the request of the investigator.
- Pregnancy.
- Anaphylactic reactions or systemic hypersensitivity reactions that are related to IMP and require treatment (see Section 10.10.3).
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or non-metastatic squamous or basal cell carcinoma of the skin.
- Any opportunistic infection or other infections whose nature or course may suggest an immunocompromised status (see Section 10.10.4 for list).

- Serum ALT >3 ULN and Total Bilirubin >2 ULN (see Section 10.6).
- Serum ALT >5 ULN if baseline ALT ≤2 ULN or ALT >8 ULN if baseline ALT >2 ULN (see Section 10.6); baseline is defined as the latest value before the first IMP administration.
- If they miss more than 2 consecutive IMP doses.
- If they are treated with the specific prohibited medications requiring IMP discontinuation mentioned in Section 6.8.1.
- In case of surgery for NP, refer to Section 6.8.3 for details.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures 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.

In any case participants who prematurely discontinued 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.

Furthermore, all participants will be instructed as follows:

- Return to the study site for evaluation of NPS, SNOT-22 for all remaining visits corresponding to SoA.
- Continue to complete the patient diary for NC, anterior and posterior rhinorrhea and decreased/loss of smell daily symptom evaluation up to Week 36.
- Continue on budesonide nasal spray stable dose but participants are not required to complete the INCS use daily in the e-diary after early treatment discontinuation (ETD).
- Advise participants 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 36).
- Contact the Investigator during the follow-up 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 systemic steroids for rescue treatment of worsening nasal polyps or for another reason will be captured by the Investigator on the appropriate page(s) of the e-CRF page and the date and dosing information (daily dose, duration, international nonproprietary name [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 period, an AE or SAE page will be completed.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Appendix 6 (Section 10.6) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 QTc stopping criteria

Not applicable.

7.1.4 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

7.1.5 Rechallenge

Re-initiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

7.1.5.1 Study intervention restart or rechallenge after liver stopping criteria are met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are not allowed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The procedures normally planned for the EOS Visit will be performed at early discontinuation visit.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested. The Investigator must document this in the site study records and inform sponsor in written timely.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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
  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.
- The result of central reading of nasal endoscopy that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Blood sampling details including volume for all laboratory assessments will be provided in the ICF.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

8.1 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Nasal polyps score (NPS)

Change from baseline in NPS at Week 24 is the primary endpoint of this study. NPS is assessed by central video recordings of bilateral nasal endoscopy. The score (NPS) is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy (26, 27, 28). Polyps on each side of the nose is graded based on polyp size described in Table 5.

Table 5 - 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 participant 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 on 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 (EOT) 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.

8.1.2 Nasal congestion/obstruction scores (NCS)

Change from baseline in NCS at Week 24: NCS is assessed by the participant 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) (7).

Nasal congestion/obstruction score is a reflective score of the worst symptom severity over the past 24 hours by the participant (see Table 6).

Table 6 - 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 used for daily recording of participant's answers to the questionnaires. This device will be dispensed at the Screening Visit (V1), including instructions for use. Participants will be instructed on the use of the device. Recorded information will be downloaded from this device daily. At EOS Visit, the e-diary will be downloaded and returned to the site.

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 participant 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.

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

SCS rescue

Systemic steroids for rescue treatment of nasal polyps or for another reason will be prescribed to the participant by the site. PROs and a nasal endoscopy should be performed before starting treatment with SCS. The Investigator 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 participants who have a surgery or have a scheduled date for 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 e-CRF page.

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

On a daily basis from V1 and throughout the study, the participant 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) (7):

- 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). Higher scores on TSS indicate greater overall symptom severity. TSS is a reflective score of the worst symptom severity over the past 24 hours by the participant.

The psychometric properties of nasal congestion as an individual item, including validity, reliability and ability to detect changes have been demonstrated in adult patients with CRSwNP. Within-person (responder definition) meaningful threshold has been determined in the CRSwNP population as follows: -0.48 to -1.14 for NC, -0.88 to -1.00 for loss of smell, and -1.15 to -3.60 for TSS.

8.1.5 Decreased/loss of sense of smell

The decreased/loss of sense of smell severity is assessed by the participant on a daily basis from V1 and throughout the study, using an e-diary and using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). This is a reflective score of the worst symptom severity over the past 24 hours by the participant.

8.1.6 22-Item sino-nasal outcome test (SNOT-22)

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on HRQoL (Section 10.10.2). 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 with 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 (30). 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.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.3.

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- Physical examination will include, at a minimum, assessments of the general appearance, skin, eyes, ear/nose/throat, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the sitting position using the same arm (preferably) at each visit with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests and IMP administration) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

8.2.3 Electrocardiograms

Local single 12-lead ECG will be obtained for screening purpose only.

8.2.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. The hematology testing will be performed by central lab. Other clinical laboratory testing will be performed by local or central labs.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor should be notified.

- All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded.

8.2.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
- Pregnancy testing (urine or serum) should be conducted every four weeks during intervention
- Pregnancy testing (urine or serum) must be conducted corresponding with the time frame for female participant contraception in Section 5.1 Inclusion Criteria
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of adverse event of special interest (AESI) is provided in Section 8.3.6.

The definitions of unsolicited and solicited adverse events can be found in Appendix 3 (Section 10.3).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the informed consent form (ICF) until the End of Study (EOS) visit at the timepoints specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to regulatory authorities, Investigators, and IRBs/IECs as follows:
    - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days,

- For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.

- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 12 weeks after the last administration of study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Adverse events 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, modified 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 in Appendix 3 (Section 10.3), even if not fulfilling a seriousness criterion, using the corresponding form.

- Pregnancy of a female participant entered in a study with IMP;
  - Pregnancy occurring in a female participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant is mandatory until the outcome has been determined (See Section 8.3.5)
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant 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 overdose form.
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the maximum prescribed daily dose, within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form.
- Increase in alanine transaminase (ALT):
  - ALT >5 x the upper limit of normal (ULN) in participants with baseline ALT ≤2 x ULN;
  - ALT >8 x ULN if baseline ALT >2 x ULN.
- Other project specific AESI(s)
  - Anaphylactic reactions.
  - Systemic hypersensitivity reactions.
  - Helminthic infections.
  - Any severe type of conjunctivitis or blepharitis.
  - Keratitis.
  - Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms).

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.3.7.1 Medical device deficiencies

Not applicable.

8.4 PHARMACOKINETICS

PK parameters are not evaluated in this study.

8.5 GENETICS

Genetics are not evaluated in this study.

8.6 BIOMARKERS

Biomarkers are not evaluated in this study.

8.7 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments are not performed in this study.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, mechanism of action, or possible toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining (leftover) and/or extra (additional) clinical samples, data and samples may be used for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used in alignment with the information provided to participants in the ICF Part 2 (future research). For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Participant's coded datasets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

In this China study, samples for storage to support future research will not be collected. All biological samples will be disposed of following completion of the CSR. Coded data will be stored for up to 25 years after the signature of the final study report and then will be disposed.

9 STATISTICAL CONSIDERATIONS

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined.

Table 7 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	The randomized population includes all participants with a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.
Intent-to-treat (ITT)	All randomized participants analyzed according to the treatment group allocated by randomization, regardless of whether the treatment kit was used or not.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually receive. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who receive a different treatment from the planned one, the participants who take at least one dose of dupilumab will be allocated to dupilumab group, otherwise will be allocated to placebo group.

ICF: informed consent form; IRT: interactive response technology, ITT: intent-to-treat.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

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

9.2 STATISTICAL ANALYSES

The SAP will be finalized prior to the primary analysis at Week 24 and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.2.1 General considerations

Planned Database lock date

A primary database lock is currently planned to be performed when all randomized participants have completed the 24-week treatment period, including early dropouts.

The database will be updated at the end of the study for all participants to include the post-treatment follow-up information and updates for the events previously ongoing at the time of the primary lock. Additional data collected between the primary database lock and last participant completing last visit will be summarized in a separate CSR addendum, as needed. Details will be included in the SAP.

Analysis considerations

The baseline value of efficacy parameters is defined as the last available value before randomization unless otherwise specified (see below for daily Diary of NCS, TSS and severity of decreased/loss of sense of smell).

The calculation of the baseline for endpoints collected on a daily basis, baseline is defined as the average of the scores in the 7 days prior to randomization. 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.

The baseline value of the other parameters is defined as the last available value prior to the first dose of IMP if the participant is treated, or the last available value up to randomization if the participant is not exposed to IMP.

Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).

The observation period will be divided into 4 segments:

- The **pre-treatment** period is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + 98 days. The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP + 14 days
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

9.2.2 Primary endpoint(s) analyses

The primary endpoint will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: Change from baseline in NPS at Week 24.
- Treatment condition: dupilumab 300 mg Q2W will be compared to placebo, on top of background therapy.
- Analysis population: ITT population
- Intercurrent events (IE):
  - Undergoing surgery for CRSwNP or taking SCS for any reason prior to Week 24: data after surgery/SCS will be set to missing and the worst post-baseline value on or before the time of surgery/SCS will be used to impute missing Week 24 value (WOCF). For participants with no post-baseline values, the baseline value will be used (composite strategy).
  - Taking other prohibited/rescue medications: all data collected after use will be used in the analysis (treatment policy strategy).
  - Discontinuing the study intervention (but not undergoing surgery for CRSwNP or taking SCS for any reason prior to Week 24): all data collected after discontinuation will be used in the analysis (treatment policy strategy).
- Population-level summary: mean change difference between dupilumab 300 mg Q2W and placebo from ANCOVA. Model with study intervention and screening blood eosinophil count strata, and baseline measurement as covariates is used. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule. Missing data at Week 24 will be imputed using the multiple imputation and this multiple imputation will use all participants excluding those who have undergone surgery or received SCS on or before Week 24.

In the primary analysis approach for the primary endpoint, for participants who undergo surgery for NP or taking SCS for any reason, data collected after surgery or SCS will be set to missing and the worst post-baseline value on or before the time of surgery or taking SCS will be used to impute missing Week 24 value (ie, WOCF approach). For participants with no post-baseline values, the baseline value will be used. For participants taking other prohibited/rescue medications, all data collected after use will be used in the analysis. Participants who discontinue the study intervention prematurely are encouraged to follow the planned clinical visits and, in these participants, who did not undergo surgery or take SCS for any reason, all data collected after study intervention discontinuation will be used in the analysis. In case there is missing data, a multiple imputation will be used to impute missing Week 24 values, and this multiple imputation will use all participants excluding those who have undergone surgery or taking SCS for any reason on or before Week 24. Each of the imputed completed data will be analyzed by fitting an ANCOVA model with the baseline covariate and factor for study intervention and screening blood eosinophil count strata. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, 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.

Sensitivity/supplementary analyses

Additional analyses including the following will be performed to confirm robustness of the results with respect to intercurrent event and missing data handling strategy:

- Data collected after initiation SCS for any reason will be included in the analysis.
- Tipping point analysis.

Subgroup analysis

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoints with respect to age group, gender, and other factors that will be specified in the SAP.

9.2.3 Secondary endpoint(s) analyses

The secondary endpoints detailed in this section are as below:

- Change from baseline in NCS at Week 24
- Change from baseline in TSS at Week 24
- Change from baseline in the severity of decreased/loss of smell daily assessed by the participant at Week 24
- Change from baseline in SNOT-22 at Week 24
- Proportion of participants receiving SCS for any reason or undergo surgery for nasal polyp during the study treatment

The change from baseline in NCS, TSS, severity of decreased/daily loss of smell, and SNOT-22 at Week 24 will be analyzed using the same analysis approach as for the primary endpoint.

Proportion of participants with first SCS rescue for any reason 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 screening blood eosinophil count, by considering the first SCS rescue use for any reason or surgery (actual or planned) for NP as the event. Descriptive statistics including number of participants with rescue SCS or surgery and number of participants without rescue SCS or surgery (censored) and the corresponding rates will be provided by study intervention group. The estimates of the hazard ratio and corresponding 95% CI will be provided for the dupilumab group versus the placebo group.

Other secondary endpoints analyses are defined in Section 9.2.6.1 (AE, SAE), Section 9.2.6.2 (laboratory abnormalities).

9.2.4 Tertiary/exploratory endpoint(s) analyses

Not applicable.

9.2.5 Multiplicity adjustment

A hierarchical procedure is proposed to strongly control the family wise type-I error rate at the 2-sided 0.05. The primary endpoint will be tested first, followed by selected secondary endpoints.

The detailed hierarchical testing procedures will be defined in the study statistical analysis plan (SAP).

9.2.6 Other safety analyses

All safety analyses will be performed on the safety population.

9.2.6.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation. In addition, TEAEs will be described according to maximum intensity and relation to the study intervention. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

The incidence of each type of AESI and other AE groupings will be tabulated by treatment group. For each type of AESI, the following analysis will be generated:

- A summary of the number (%) of participants with:
  - Any TEAE,
  - Any SAE (regardless of treatment-emergent status),

- Any TESAE,
- Any AE leading to death,
- Any TEAE leading permanent study intervention discontinuation,
- Any TEAE related to study intervention reported by the Investigator,
- Any TEAE by maximum intensity, corrective treatment, and final outcome.

The method to identify AESIs and other AE groupings will be specified in the SAP.

Deaths will also be analyzed.

9.2.6.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

When relevant, for laboratory variables, vital signs, descriptive statistics for results and changes from baseline will be provided for each planned visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables.

Analyses according to potentially clinical significant abnormality (PCSA)

PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, and vital signs, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

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

9.2.7 Other analyses

Data collected regarding the impact of the COVID-19 or other pandemics, on the participants will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 or other pandemics requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

9.3 INTERIM ANALYSES

No interim analysis will be performed before the final database lock for this study.

9.4 SAMPLE SIZE DETERMINATION

Approximately 62 participants will be randomized to study intervention.

A total sample size of about 62 participants (randomization ratio [1:1], ie, [31 per intervention group]) was determined to demonstrate superiority of dupilumab 300mg Q2W versus placebo with 90% power and 2-sided test with 5% significance level based on the following assumptions on the primary endpoint:

- True mean difference of -1.8 between dupilumab 300 mg Q2W and placebo
- Common SD of 1.83
- A 25% dropout rate

Calculations were made based on two sample t-test using nQuery Advisor 7.0.

Assumptions are based on the following:

- Mean treatment difference= -1.8 (lowest observed effect size of NPS at Week24 in the EFC14146 [SINUS-24] and EFC14280 [SINUS-52])
- SD=1.83 (highest SD of NPS reduction at Week24 in the EFC14146 [SINUS-24] and EFC14280 [SINUS-52])
- Dropout rate 25% (higher than 10% due to COVID-19 uncertainties)

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator's brochure, IDFU, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and

- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study , including the risks and benefits, to the participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

No committee will be adopted in this study.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, ClinicalTrialRegister.eu, and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF Completion Instruction.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in source data location list.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The signature of the informed consent by the first participant is considered the first act of recruitment and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 8 will be performed by the local or central laboratory except that hematology will be performed by central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Pregnancy testing should be conducted at screening (serum), on Day 1 before the first administration of IMP (urine) and every 4 weeks during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure corresponding with the time frame for female participant contraception in Section 5.1, Inclusion Criteria.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	Blood urea nitrogen (BUN)
	Creatinine
	Glucose [nonfasting]
	Electrolytes (Potassium, Sodium, Chloride)
	Uric acid
	Total cholesterol
	Alkaline phosphatase
	Total bilirubin[b]
	Total protein
	Albumin
	Alanine aminotransferase
	Aspartate aminotransferase
	Lactate deshydrogenase
	Bicarbonate
	Creatine phosphokinase

Laboratory tests	Parameters
Pregnancy testing	Serum (at screening) or highly sensitive urine (at other timepoints) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Other screening tests	Serology (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], total hepatitis B core antibody [HBcAb], hepatitis C virus antibodies [HCVAb], Human Immunodeficiency Virus [HIV] screen [anti-HIV-1 and HIV-2 antibodies] and antinuclear antibody [ANA])[c]
	Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only).

NOTES :

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 (Liver chemistry stopping criteria) and Appendix 6 (Section 10.6) (Liver and other safety: Suggested actions and follow-up assessments). All events of ALT >5 ULN if baseline ALT is ≤2 ULN or ALT >8 ULN if baseline ALT is >2 ULN which may indicate severe liver injury (possible Hy's Law) must be reported to Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

b In case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin.

c In case of results showing HBsAg (negative), and HBcAb total or HBcAb IgM (positive), an HBV DNA testing will be performed prior to randomization to rule out a false positivity if the Investigator believed the participant is a false positive, or to clarify the serological status if the Investigator find it unclear to interpret in absence of known HBV infection. In case of results showing hepatitis C virus antibody (HCVAb) (positive), an HCV RNA testing will be performed to rule out a false positivity, if the Investigator believed the participant is a false positive. Note: Anti-ds DNA antibody will be tested if ANA was positive (≥1:160 titer).

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - 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
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a) Results in death

b) Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant 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.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- 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
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions
  - Cancers diagnosed during the study or aggravated during the study
  - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the site file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the site file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

Women in the following categories are considered WONCBP:

1. Any female with permanent infertility due to one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

2. Postmenopausal female

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

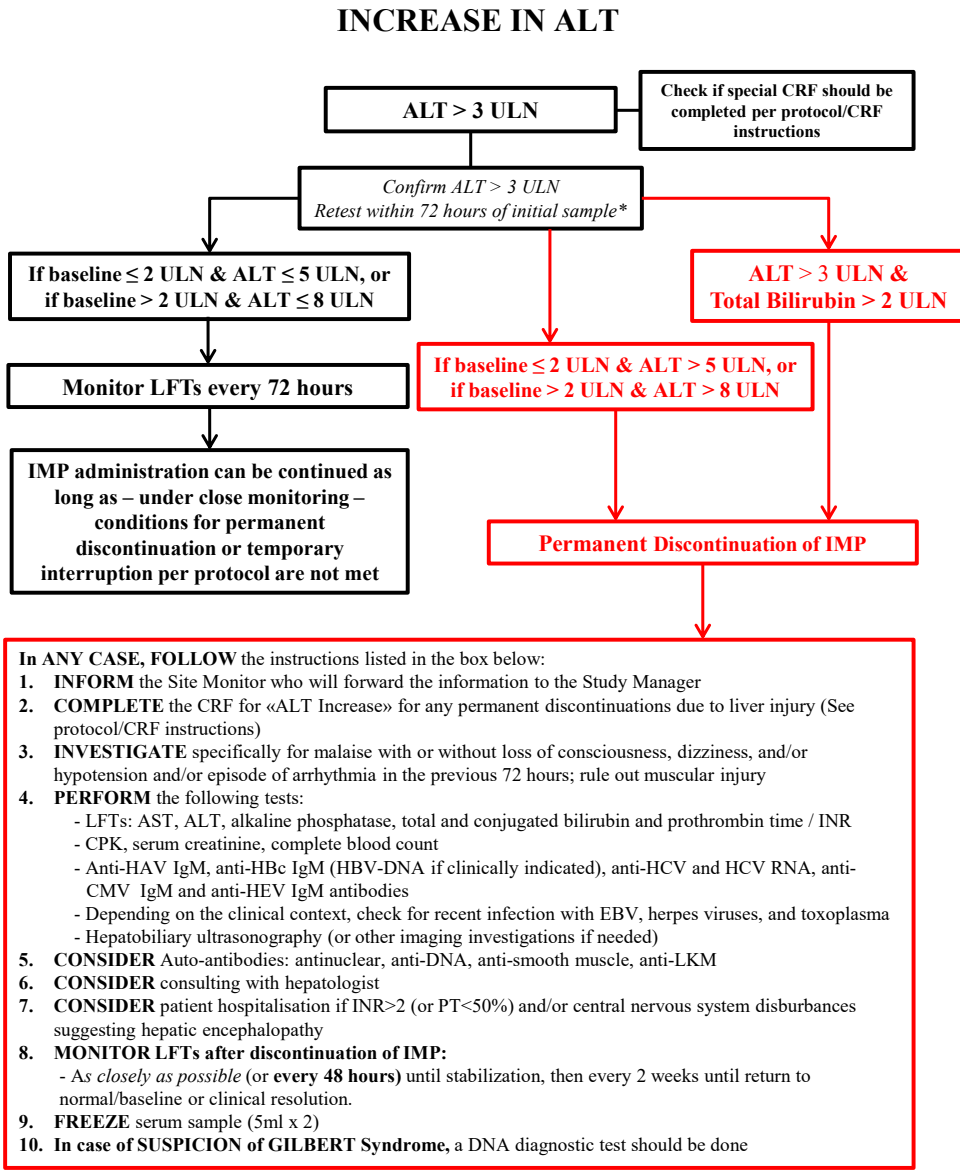
10.4.2 Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] –oral –intravaginal –transdermal –injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] –oral –injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. *b* Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. *c* Male condoms must be used in addition to hormonal contraception Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 APPENDIX 5: GENETICS

Not applicable.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS



Note:

Normalization is defined as < ULN or baseline value if > ULN.

As soon as seriousness criterion is met or the event leads to permanent treatment discontinuation, the monitoring team should be notified within 24 hours.

* If unable to retest in 72 hours, use original lab results to decide on further monitoring/discontinuation.

"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 8.3.4 for guidance on safety reporting.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

The decision for each individual participant to remain and/or start in the study should be made on a case-by-case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the site. However, in case new participant is eligible for the trial, the PI/site should assess the capacity to maintain these participants into the trial before any screening procedures will start. If the site cannot guarantee an accurate follow-up in the context of the trial, alternative treatment outside the clinical trial should be proposed.

When participants are already randomized and/or treated, attempts should be made to perform all assessments in accordance with the protocol to the extent possible.

When possible, the focus should be on IMP administration and safety blood collection (eg, biochemistry and hematology). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints (eg, nasal endoscopy) (Section 8.1). The deviations from the study protocol (eg, treatment delay, omission, tests not performed…) should be documented in the source document and collected in the appropriate pages of the eCRF.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data (eg, safety assessments, efficacy assessments).

- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.
- The DTP supply of the IMP from the site/sponsor where allowed by local regulations and agreed upon by participant. (Section 6.1).

Contingencies implemented due to emergency will be documented.

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs) (Section 10.1.3).

10.10 APPENDIX 10: ADDITIONAL APPENDICES

10.10.1 List of prohibited live attenuated vaccines

- Bacillus Chickenpox (Varicella)
- Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted
- Measles (Rubeola)
- Measles-mumps-rubella (MMR) combination
- Measles-mumps-rubella-varicella (MMRV) combination
- Mumps
- Oral polio (Sabin)
- Oral typhoid
- Rotavirus
- Rubella
- Smallpox (Vaccinia)
- Varicella Zoster (shingles)
- Yellow fever

This list is indicative and not exhaustive.

10.10.2 [redacted]

[redacted]

10.10.3 Definition of anaphylaxis

“Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."(31)

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

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

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

10.10.4 List of opportunistic infections

- Aspergillosis.
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers).
- Candidiasis – only systemic or extensive mucosal or cutaneous cases.
- Coccidioides immitis (endemic south-western US and Central and South America).
- Cryptococcus.
- Cytomegalovirus.
- Herpes Simplex (disseminated).
- Herpes Zoster (disseminated; ophthalmic; involvement of 2 or more dermatomes).
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins).
- Listeriosis.
- Mycobacterium TB
- Mycobacterium avium.
- Nontuberculosis mycobacteria.
- Pneumocystis pneumonia (PCP).

This list is indicative and not exhaustive.

10.11 APPENDIX 11: ABBREVIATIONS

ABPA:	allergic bronchopulmonary aspergillosis
AD:	atopic dermatitis
AE:	adverse events
AESI:	adverse event of special interest
AFRS:	allergic fungal rhinosinusitis
ALT:	alanine transaminase
AM:	ante meridiem
ANA:	antinuclear antibody
ANCOVA:	analysis of covariance
BID:	twice a day
BP:	bullous pemphigoid
CI:	confidence intervals
CICU:	chronic inducible cold urticaria
COPD:	chronic obstructive pulmonary disease
COVID-19:	Coronavirus Disease 2019
CRF:	case report form
CRSsNP:	chronic rhinosinusitis without nasal polyposis
CRSwNP:	chronic rhinosinusitis phenotype with nasal polyps
CSR:	clinical study report
CSU:	chronic spontaneous urticaria
CT:	computed tomography
D:	day
DNA:	deoxyribonucleic acid
DTP:	direct-to-patient
EC:	ethic committee
ECG:	electrocardiogram
e-CRF:	electronic case report form
EoE:	eosinophilic esophagitis
EOS:	end of study
EOT:	end of treatment
FESS:	functional endoscopic sinus surgery
FU:	follow-up
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCVAb:	hepatitis C antibody
HIV:	human immunodeficiency virus
HRQoL:	health related quality of life
IB:	Investigator’s Brochure
ICF:	informed consent form
IEC:	Independent Ethics Committees
IgE:	immunoglobulin E
IL:	interleukin

IL-4Rα:	interleukin 4 receptor alpha subunit
IM:	intramuscular
IMP:	investigational medicinal product
INCS:	intranasal corticosteroid
INN:	international nonproprietary name
IRB:	Institutional Review Boards
IRT:	interactive response technology
ITT:	intent-to-treat
IV:	intravenous
IVRS:	interactive voice respond system
IWRS:	interactive web response system
LS:	least squares
mAb:	monoclonal antibody
MRI:	magnetic resonance imaging
NC:	nasal congestion
NCS:	nasal congestion/obstruction score
NE:	nasal endoscopy
NIMP:	noninvestigational medicinal product
NP:	nasal polyposis
NPS:	nasal polyps score
PCSA:	potentially clinical significant abnormality
PROs:	patient reported outcomes
Q2W:	every 2 weeks
QM:	every morning
QoL:	quality of life
RBC:	red blood cell
RESS:	radical endoscopic sinus surgery
RNA:	ribonucleic acid
SAE:	serious adverse event
SC:	subcutaneous
SCS:	systemic corticosteroids
SD:	standard deviation
SNOT-22:	sino-nasal outcome test
SUSAR:	suspected unexpected serious adverse reaction
TEAEs:	treatment-emergent adverse events
Th:	T helper
TSS:	total symptom score
ULN:	upper limit of normal
W:	week
WBC:	white blood cell
WOCBP:	women of child bearing potential
WOCF:	worst observation carried forward

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

Not applicable.

11 REFERENCES

1. Zhang Y, Gevaert E, Lou H, Wang X, Zhang L, Bachert C, et al. Chronic rhinosinusitis in Asia. J Allergy Clin Immunol. 2017;140(5):1230-9.

2. Lund VJ. Where are we in the medical treatment of nasal polyps? In: Önerci TM and Ferguson BJ, editors. Nasal polyposis: Pathogenesis, medical and surgical treatment. Berlin Heidelberg: Springer-Verlag; 2010. p. 239-48.

3. Hox V, Bobic S, Callebaut I, Jorissen M, Hellings PW. Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. Rhinology. 2010;48:426-32.

4. Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ. Topical steroids for nasal polyps. Cochrane Database Syst Rev. 2012;12:CD006549.

5. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, doubleblind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638-50.

6. Thomas M, Yawn BP, Price D, Lund V, Mullol J, Fokkens W. EPOS Primary Care Guidelines: European position paper on the primary care diagnosis and management of rhinosinusitis and nasal polyps 2007 - a summary. Prim Care Respir J. 2008;17:79-89.

7. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. EPOS 2020: European position paper on rhinosinusitis and nasal polyps 2020. Rhinology. 2020;58(Suppl S29):1-464.

8. Bryson JM, Tasca RA, Rowe-Jones JM. Local and systemic eosinophilia in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis with and without polyposis. Clin Otolaryngol Allied Sci. 2003;28:55-8.

9. Slavin RG. Nasal polyps and sinusitits. JAMA. 1997;278:1849-54.

10. Bhattacharyya N. The role of infection in chronic rhinosinusitis. Curr Allergy Asthma Rep. 2002;500-6.

11. Staikuniene J, Vaitkus S, Japertiene LM, Ryskiene S. Association of chronic rhinosinusitis with nasal polyps and asthma: clinical and radiological features, allergy and inflammation markers. Medicina (Kaunas). 2008;44:257-65.

12. Ferguson BJ. Categorization of eosinophilic chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2004;12(3):237-42.

13. Sakuma Y, Ishitoya J, Komatsu M, Shiono O, Hirama M, Yamashita Y, et al. New clinical diagnostic criteria for eosinophilic chronic rhinosinusitis. Auris Nasus Larynx. 2011;38:583-8.

14. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Congdon DJ, Adolphson CR, et al. Striking deposition of toxic eosinophil major basic protein in mucus: implications for chronic rhinosinusitits. J Allergy Clin Immunol. 2005;116:362-9.

15. Zacharek MA, Krouse JH. The role of allergy in chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2003;11:196-200.

16. Bhattacharyya N, Vyas DK, Fechner FP, Gliklich RE, Metson R. Tissue eosinophilia in chronic sinusitis: quantification techniques. Arch Otolaryngol Head Neck Surg. 2001;127:1102-5.

17. Wang W, Gao Y, Zhu Z, Zha Y, Wang X, Qi F, et al. Changes in the clinical and histological characteristics of Chinese chronic rhinosinusitis with nasal polyps over 11 years. Int Forum Allergy Rhinol. 2019;9(2):149-57.

18. Jiang WX, Cao PP, Li ZY, Zhai GT, Liao B, Lu X, et al. A retrospective study of changes of histopathology of nasal polyps in adult Chinese in central China. Rhinology. 2019;57(4):261-7.

19. Hellquist HB. Nasal polyps update. Histopathology. Allergy Asthma Proc. 1996;17:237-42.

20. Bachert C, Marple B, Hosemann W, Cavaliere C, Wen W, Zhang N. Endotypes of Chronic Rhinosinusitis with Nasal Polyps: Pathology and Possible Therapeutic Implications. J Allergy Clin Immunol Pract. 2020;8(5):1514-9.

21. Hu Y, Cao PP, Liang GT, Cui YH, Liu Z. Diagnostic significance of blood eosinophil count in eosinophilic chronic rhinosinusitis with nasal polyps in Chinese adults. Laryngoscope. 2012;122(3):498-503.

22. Wei B, Liu F, Zhang J, Liu Y, Du J, Liu S, et al. Multivariate analysis of inflammatory endotypes in recurrent nasal polyposis in a Chinese population. Rhinology. 2018;56: 216-26.

23. Alobid I, Mullol J. Role of medical therapy in the management of nasal polyps. Curr Allergy Asthma Rep. 2012;12:144-53.

24. Peters AT, Spector S, Hsu J, Hamilos DJ, Baroody FM, Chandra RK, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. Ann Allergy Asthma Immunol. 2014;113:347-85.

25. Zhang L, Zhang Y, Gao Y, Wang K, Lou H, Meng Y, et al. Long-term outcomes of different endoscopic sinus surgery in recurrent chronic rhinosinusitis with nasal polyps and asthma. Rhinology. 2020;58:126-35.

26. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 2013;131:110-6.

27. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K., Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol. 2011;128:989-95.

28. Van Zele T, Gevaert P, Holtappels G, Beule A, Wormald PJ, Mayr S, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. J Allergy Clin Immunol. 2010;125:1069-76.

29. Staudacher AG, Peters AT, Kato A, Stevens WW. Use of endotypes, phenotypes, and inflammatory markers to guide treatment decisions in chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2020;124(4):318-25.

30. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item sinonasal outcome test. Clin Otolaryngol. 2009;34:447-54.

31. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

Signature Page for VV-CLIN-0633795 v1.0
efc17026-16-1-1-protocol

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]