NCT04998604

AMENDED CLINICAL TRIAL PROTOCOL 03

Protocol title:	**A randomized, double-blind, head-to-head comparison of dupilumab versus omalizumab in severe Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and comorbid asthma patients**
Protocol number:	**LPS16747**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR231893** **dupilumab/Dupixent®**
Study phase:	**Phase 4**
Short title:	**EVEREST: EValuating trEatment RESponses of dupilumab versus omalizumab in Type 2 patients** **EVEREST**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**82 Avenue Raspail, 94250 Gentilly, France**
Monitoring Team's Representative Name and Contact Information	

Regulatory agency identifier number(s):

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Approval Date: 14-May-2024 Total number of pages: 117

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	14 May 2024, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	13 December 2022, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	10 June 2021, version 1 (electronic 1.0)
Original Protocol		15 March 2021, version 1 (electronic 1.0)

Amended protocol 03 (14 May 2024)

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation No 536/2014 of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main objective of this amendment is to reduce the sample size due to enrollment challenges and optimization of the targeted patient population to focus on Nasal Function endpoints while maintaining the favorable benefit-risk of the study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Title page, header, protocol amendment summary of changes section and Table of Content, etc is updated.	Updated to reflect the current amendment, ie, amended protocol 03.
Title page	Changed Sponsor's registered address	Updated as per new address
Section 1.1 Synopsis Section 3.0 Objectives and Endpoints Section 9.4.3 Secondary Endpoints	Secondary objective and corresponding endpoint downgraded to exploratory: Objective: "To evaluate the efficacy of dupilumab in improving lung function at Week 24 compared to omalizumab" Endpoint: "Change from baseline to Week 24 in pre bronchodilator forced expiratory volume in 1 second (FEV1)"	The study is powered on primary endpoints, hence the FEV1 assessment was downgraded to exploratory endpoint

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3.0 Objectives and Endpoints Section 9.4.3 Secondary Endpoints	Secondary objective and corresponding endpoint downgraded to exploratory: Objective: "To evaluate the effect of dupilumab on asthma control at Week 24 compared to omalizumab" Endpoint: "Change from baseline to Week 24 in 7 item Asthma Control Questionnaire (ACQ-7)"	The study is powered on primary endpoints, hence the ACQ-7 assessment was downgraded to exploratory endpoint.
Section 1.1 Synopsis Section 4.1 Overall Design	Sample size reduced from 422 participants (211 participants per group) to a minimum of 320 participants (160 participants per group) based on enrollment projections at the moment of sample size reduction	Sample size was reduced due to low recruitment rate
Section 1.1 Synopsis Section 9.2 Sample Size Determination	Deleted text describing sample size rationale	Text removed as FEV1 is downgraded to exploratory endpoint
Appendix 1 (Section 10.1.4): Data Protection	Added statements regarding Sanofi Data Protection Officer: "Personal data of professionals will be retained by Sanofi for up to twenty-five (25) years, unless further retention is required by applicable regulations. 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 - 46 avenue de la Grande Armee-75017-PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact)."	To align with OneDoc template V10
Section 11.0 references	References number 65 through 67 were deleted	References were used only once in the sample size section for FEV1, which was downgraded to exploratory endpoint.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A randomized, double-blind, head-to-head comparison of dupilumab versus omalizumab in severe Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and comorbid asthma patients

Short title: EVEREST: EValuating trEatment RESponses of dupilumab versus omalizumab in Type 2 patients

Rationale:

Severe Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is a serious, chronic inflammatory disease, predominantly driven by type 2 inflammation in at least 80% of patients (in western countries) and 50% (in Asian countries) (1). Chronic Rhinosinusitis with Nasal Polyps is characterized by bilateral nasal polyps and rhinosinusitis, which cause a range of persistent debilitating symptoms, including loss of smell, nasal obstruction/congestion, and nasal discharge (2, 3, 4). Chronic Rhinosinusitis with Nasal Polyps has an estimated prevalence of 2% to 4% in Europe and the United States (US) (4, 5) and is frequently associated with multiple type-2 coexisting diseases such as asthma, allergic rhinitis, and/or Non-Steroidal Anti-Inflammatory Drug Exacerbated Respiratory Disease (NSAID-ERD, which further contribute to greater disease severity and overall disease burden (6). In CRSwNP the type 2 inflammatory signature is characterized by the involvement of type 2 cytokines interleukin(IL)-4 (IL-4)/IL-13 and IL-5 in its pathophysiology, and high levels of tissue Immunoglobulin E (IgE) (7, 8, 9, 10, 11) or presence of coexisting diseases such as asthma, NSAID-ERD, allergic rhinitis, or atopic dermatitis (AD) (4, 12, 13, 14).

Approximately 50% to 70% of patients with asthma (15, 16, 17, 18, 19, 20), have evidence of type 2 airway inflammation (10, 11, 12, 21), and up to 65% of CRSwNP patients have comorbid asthma.

- In patients with asthma, type 2 inflammation is associated with poor asthma control, increased bronchial hyperresponsiveness, greater lung function impairment, and more frequent severe exacerbations compared with patients with a lower type 2 inflammatory signature.
- In patients with CRSwNP, the presence of type 2 inflammation is associated with more severe disease, a greater risk for post-surgical recurrence, and a higher frequency of comorbid asthma.

As stated above, a high proportion of patients with CRSwNP have comorbid asthma, which adds substantially to the overall disease burden, including greater disease severity of both CRSwNP and asthma leading to more frequent asthma exacerbations, higher rates of postsurgical polyp recurrence, greater cumulative systemic corticosteroids (SCS) use, and an impaired health related quality of life (HRQoL) (22, 23, 24). As a result of the shared inflammatory pathway underpinning their pathophysiology, type 2 inflammatory airway diseases share several common

clinical features, notably airway obstruction and/or congestion, and excessive mucus production. Increased nasal sinus opacification (reduced upper airway volume) has been associated with evidence of type 2 inflammation (blood/tissue eosinophilia) in patients with CRSwNP (25, 26, 27, 28).

First-line treatment options for CRSwNP comprises intranasal corticosteroid sprays (INCS) and saline nasal irrigations to improve the symptoms of disease such as nasal obstruction (29) but INCS show little effect in reducing nasal polyp size and improving sense of smell, the most important symptoms reported by CRSwNP patients (30, 31). In addition, SCS is prescribed to decrease polyp size and symptom burden, but continuous treatment with SCS is not recommended and should be avoided due to the known serious systemic side effects - both short and long term (32). In some patients, medical management fails and therefore, functional endoscopic sinus surgery (FESS) is indicated to improve sino-nasal symptoms (33). Surgical removal of nasal polyps does not specifically target the underlying type 2 inflammation (mediated by key type 2 cytokines IL-4, IL-13, and IL-5) in the sinuses, leading to high rates of recurrence and revision surgery, and may not restore the sense of smell in many patients (22, 34, 35, 36).

Recent therapeutic approaches have been focused on the use of biologics in order to control the T-helper Type 2 cell (Th2) pathway with subsequent improvement of clinical signs in CRSwNP and associated comorbidities. Some biologics are currently approved for the treatment of this disease (dupilumab, omalizumab, and recently mepolizumab), while other biologics are in development (eg, benralizumab).

Dupilumab is a human monoclonal antibody (mAb) that binds specifically to the shared receptor component for IL-4 and IL-13, thus inhibiting the dual signaling pathways of IL-4 and IL-13, key and central drivers of type 2 inflammation in CRSwNP and other type 2 inflammatory diseases. Dupilumab's blockade of IL-4 and IL-13 signaling has demonstrated a favorable efficacy and safety profile and is approved for the treatment of a variety of type 2 disease states, including AD (37), asthma (38), and CRSwNP (39) where type 2 inflammation is a key driver of the underlying disease process.

Omalizumab is approved in the European Union (EU) and the US for the treatment of allergic asthma and chronic spontaneous urticaria (CSU). In the US, omalizumab is approved for the treatment of nasal polyps, and in EU is approved for the treatment of CRSwNP.

In CRSwNP, the results from both dupilumab and omalizumab pivotal studies suggest that a head-to-head (H2H) comparison of dupilumab versus omalizumab has the potential to demonstrate the superiority of dupilumab in reducing the bilateral endoscopic nasal polyp score (NPS) and improving the sense of smell in patients with severe CRSwNP and comorbid asthma.

Therefore, the purpose of this study is to evaluate whether the efficacy profile of dupilumab is superior compared to omalizumab in treating participants with severe CRSwNP and comorbid asthma.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab compared to omalizumab in reducing the polyp size and improving sense of smell	• Change from baseline to Week 24 in Nasal Polyp Score (NPS) • Change from baseline to Week 24 in University of Pennsylvania Smell Identification Test (UPSIT)
Secondary	
Key secondary objectives: • To evaluate the efficacy of dupilumab in improving chronic rhinosinusitis with nasal polyps (CRSwNP) symptoms at Week 24 compared to omalizumab	Key secondary endpoints: • Change from baseline to Week 24 in the loss of smell score of the CRSwNP Nasal Symptom Diary • Change from baseline to Week 24 in the nasal congestion (NC) score of the CRSwNP Nasal Symptom Diary
Secondary objectives: • To evaluate the efficacy of dupilumab in improving CRSwNP total symptom score (TSS) at Week 24 compared to omalizumab	Secondary endpoints: • Change from baseline to Week 24 in TSS derived from the CRSwNP Nasal Symptom Diary
• To evaluate the effect of dupilumab on health related quality of life (HRQoL) at Week 24 compared to omalizumab	• Change from baseline to Week 24 in 22-Item Sino-nasal Outcome Test (SNOT-22) total score • Change from baseline to Week 24 in SNOT-22 nasal domains score
• To evaluate the efficacy of dupilumab in improving nasal peak inspiratory flow at Week 24 compared to omalizumab	• Change from baseline to Week 24 in Nasal Peak Inspiratory Flow (NPIF)
• To evaluate the effect of dupilumab on CRSwNP overall disease severity at Week 24 compared to omalizumab	• Change from baseline to Week 24 in rhinosinusitis visual analogue (VAS)
• To evaluate the safety of dupilumab and omalizumab	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Incidence of adverse events of special interest (AESIs)

Overall design:

This is a Phase 4, multicenter, parallel group, randomized (1:1), double-blind, active-controlled study to compare the efficacy of dupilumab with omalizumab over 24 weeks of treatment in adult participants with severe CRSwNP and comorbid asthma.

A minimum of 320 participants (160 per group) will be randomized in a 1:1 ratio to receive either dupilumab or omalizumab. Randomization will be stratified by prior surgery, inhaled corticosteroids (ICS) doses (low versus medium/ high dose ICS), presence of Aspirin-exacerbated respiratory disease (AERD) and region (Eastern European [EE] versus Rest of the World [ROW]). Based on the subgroup analysis from prior SINUS clinical trials, different treatment effects over placebo were observed in the EE countries versus ROW, across a few endpoints of interest. Therefore, the stratification factor by region (EE versus ROW) is included.

Disclosure Statement:

This is an interventional, parallel group, study with 2 groups that are participant and Investigator blinded.

Number of participants:

Based on enrollment projections at the moment of sample size reduction, a minimum of 320 participants will be randomized in the study with approximately 160 participants per group.

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:

- Dupilumab: 300 mg every 2 weeks (Q2W)
- Omalizumab: 75 to 600 mg Q2W or every 4 weeks (Q4W). Participant's dosing and frequency will be based on pretreatment serum total IgE levels and body weight (see Figure 2 [Section 10.8])

Duration of study period (per participant)

Study duration per participant will be 38 weeks. The study will comprise 3 periods:

- Screening and run-in period (28±3 days).
- Randomized IMP intervention period (24 weeks).
- Follow-up period (up to 12 weeks after the last IMP dose [Week 22] or until the participant switches to commercialized dupilumab/omalizumab [or other biologic product], whichever comes first). For the participants who switch to commercialized dupilumab/omalizumab (or other biologic product), the follow-up phone call visit should be performed prior to the first injection with commercialized dupilumab/omalizumab (or other biologic product).

Study intervention(s)

Investigational medicinal products

- Dupilumab 300 mg.
- Omalizumab 150 mg and 75 mg.
- Placebo (to blind the number of active dupilumab and omalizumab injections): dupilumab placebo 2 mL.

Dupilumab

- Formulation: dupilumab 300 mg: a 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in a 2 mL injection.
- Route of administration: subcutaneous (SC) injection.
- Dose regimen: 1 injection of 300 mg Q2W.

Omalizumab

- Formulation: omalizumab 150 mg: a 150 mg/mL omalizumab solution in a prefilled syringe to deliver 150 mg in a 1 mL injection. Omalizumab 75 mg: a 150 mg/mL omalizumab solution in a prefilled syringe to deliver 75 mg in a 0.5 mL injection.
- Route of administration: SC injection.
- Dose regimen: 75 to 600 mg Q2W/Q4W according to the dosing table (see Figure 2).

Placebo

- Formulation:
  - Dupilumab placebo: identical formulation to the active formulation without dupilumab, in a prefilled syringe to deliver placebo 2 mL.
- Route of administration: SC injection.
- Dose regimen: as needed to blind number of active dupilumab and omalizumab injections.

The IMP will be prepared and administered by the unblinded study site personnel. All participants will wear an eye sleep mask to minimize the risk of unblinding. When operationally feasible and if treating physician determines that is appropriate and safe, administration of IMP at study participant's home by qualified and trained healthcare professionals as well as direct to participant shipment may be arranged. These approaches will only be implemented if allowed by local regulations, approved labelling and agreed by the treating physician, while ensuring blinding measures are maintained.

Noninvestigational medicinal products

Background therapies and rescue therapies will be supplied by the Sponsor's local affiliate as locally required or by the sites. Reimbursement will be provided when deemed necessary and as per country regulation.

Intranasal corticosteroid background therapy

Throughout the study, the participants will use a diary to record daily use of mometasone furoate nasal spray (MFNS) 50 µg/actuation Nasal Spray, suspension.

Before study entry, treatment with intranasal mometasone ≥200 µg once daily (QD) or equivalent of another INCS is required for 1 month prior to Visit 1. After Visit 1 only MFNS is allowed for a better standardization of background medication.

Screening/Run-in period

After Visit 1 (screening visit), once the eligibility for study entry has been confirmed, all participants will enter a run-in period of 28 days where they will receive MFNS:

- Two actuations (50 µg/actuation) in each nostril twice a day (BID) (total daily dose of 400 µg) starting at Visit 1. If the participants are unable to tolerate the BID regimen or this dose is not approved in specific countries, they will follow a QD regimen (total daily dose of 200 µg).
- Participant's MFNS dose will be stabilized during the run-in period.

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

Participants who receive rescue medication including INCS drops or systemic (oral, intravenous [IV], intramuscular [IM]) steroids between Visit 1 and Visit 2 will not be randomized, but they can be rescreened.

Randomized IMP intervention period

During the randomized intervention period, all participants will continue on the stable dose of MFNS.

Post-treatment period (ie, follow-up period)

Upon completing the randomized intervention period (or following early discontinuation of the IMP), participants can continue treatment with the stable dose of MFNS maintained over the randomized intervention period until the end of study (EOS), or modify the treatment based on medical judgment.

Asthma background therapy

Screening/Run-in period

Participants should be on a stable dose of low, medium or high dose ICS in combination with a second controller medication (eg, long-acting beta-2 adrenergic receptor agonists [LABA], leukotriene receptor antagonists [LTRA]) ≥1 month prior to screening visit and during the screening and run-in period.

Participants requiring a third controller for their asthma will be considered eligible for this study, also, at a stable dose ≥1 month prior to screening visit and during the screening and run-in period.

- Formulation and route(s) of administration: as per label.
- Dose regimen: as prescribed.

Randomized IMP intervention period

The asthma background therapy should be maintained on a stable dose during the study intervention period.

An asthma background therapy diary will be provided to collect information related to noninvestigational medicinal product (NIMP) use.

Post-treatment period (ie, follow-up period)

Upon completing the randomized IMP intervention period (or following early discontinuation of IMP), participants can continue treatment with the stable dose of ICS maintained over the randomized intervention period until the EOS, or modify the treatment based on medical judgment.

Statistical considerations:

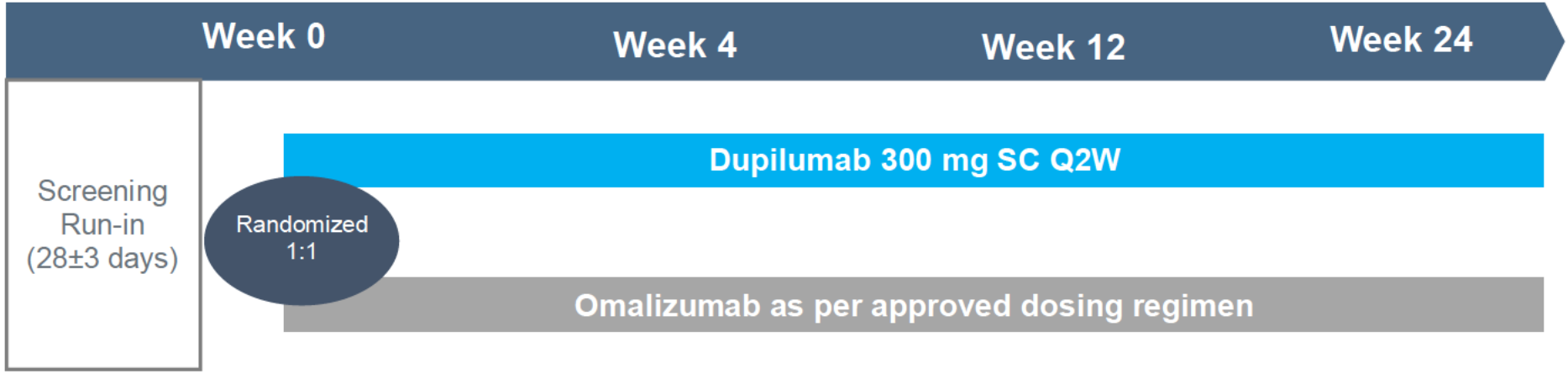
The original sample size of 422 was estimated to power the key secondary endpoint, change from baseline in pre-BD FEV1 at Week 24, at [redacted]. By downgrading this endpoint to an exploratory endpoint and [redacted].

- **Primary endpoints**: Each of the 2 primary endpoints will be analyzed using a hybrid method of the worst observation carried forward (WOCF) and the multiple imputation (MI). With this approach, for participants who undergo surgery for NP or receive SCS for any reason during the study, data collected postsurgery or post SCS will be set to missing, and the worst postbaseline value on or before the time of surgery or SCS intake will be used to impute missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute). For participants who discontinue the treatment without being rescued by surgery or receiving SCS, an MI approach will be used to impute the missing Week 24 value. This MI will use all participants who have not been rescued by surgery or receiving SCS by Week 24. The data collected after treatment discontinuation will be included in the analysis. Each of the imputed complete data will be analyzed by fitting an analysis of covariance (ANCOVA) model with corresponding baseline value, treatment group, and stratification factors as the covariates. Statistical inference on treatment comparisons for the 2 primary endpoints at Week 24 will be derived from the ANCOVA model. Descriptive statistics including number of participants, mean, standard deviation, and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CIs) will be provided along with the p -values.
- **Main secondary endpoints**: The change from baseline in the continuous endpoints to Week 24 will be analyzed using the hybrid method of the WOCF and the MI with ANCOVA model in the same fashion as for the 2 primary endpoints.

Data Monitoring Committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



Q2W: every 2 weeks; SC: subcutaneous

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening /run-in (28±3 days before Day 1)[a]	Intervention Period (24 weeks)													E/D[c]	Follow-up (up to 12 weeks after last IMP dose)[d]	Notes
		Day 1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24 EOT			
Visit	**1**	**2**	**3**	**4**	**5[b]**	**6**	**7[b]**	**8**	**9[b]**	**10**	**11[b]**	**12[b]**	**13[b]**	**14**			
Informed consent	X																
Inclusion and exclusion criteria	X	X															Recheck clinical status before randomization and/or first dose of study intervention.
Demography	X																Including race and ethnicity
Full physical examination[e]	X	X												X	X		
Body weight (kg) and height (cm)	X	X		X				X						X	X		Height will be measured only at screening visit
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius)

Procedure	Screening /run-in (28±3 days before Day 1)[a]	Intervention Period (24 weeks)													E/D[c]	Follow-up (up to 12 weeks after last IMP dose)[d]	Notes
		Day 1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24 EOT			
Visit	**1**	**2**	**3**	**4**	**5[b]**	**6**	**7[b]**	**8**	**9[b]**	**10**	**11[b]**	**12[b]**	**13[b]**	**14**			
Medical/Surgical history (includes substance usage)	X	X															Substances: tobacco usage collected at screening; alcohol usage will be collected in case of ALT increase.
Past and current medical conditions[f]	X	X															It will also include atopic comorbidities (eg, AD) and asthma diagnosis
Spirometry (pre-bronchodilator FEV1, FVC, FEF 25% to 75%)[g]		X	X	X		X		X		X				X	X		Central reading
Nasal endoscopy[h]	X	X		X				X						X	X		Central reading

Procedure	Screening /run-in (28±3 days before Day 1)[a]	Intervention Period (24 weeks)													E/D[c]	Follow-up (up to 12 weeks after last IMP dose)[d]	Notes
		Day 1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24 EOT			
Visit	**1**	**2**	**3**	**4**	**5[b]**	**6**	**7[b]**	**8**	**9[b]**	**10**	**11[b]**	**12[b]**	**13[b]**	**14**			
FeNO		X	X	X		X		X		X				X	X		FeNO should be conducted prior to spirometry and the participant should refrain from eating and drinking for ≥1 hour before the procedure. Further details on the procedure will be provided in a separate instruction manual
Serum or urine pregnancy tests (WOCBP only)	X	X						X						X	X		Serum pregnancy test at screening visit and then urine or serum pregnancy test as required by the local regulations (local laboratory)
Hepatitis B and C screening, HIV screening, TB screening[i]	X																HBs Ag, HBs Ab, total HBc Ab, HCV Ab, HIV screen (Anti HIV-1 and HIV-2 Abs), TB test, (local laboratory).

Procedure	Screening /run-in (28±3 days before Day 1)[a]	Intervention Period (24 weeks)													E/D[c]	Follow-up (up to 12 weeks after last IMP dose)[d]	Notes
		Day 1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24 EOT			
Visit	**1**	**2**	**3**	**4**	**5[b]**	**6**	**7[b]**	**8**	**9[b]**	**10**	**11[b]**	**12[b]**	**13[b]**	**14**			
Laboratory assessment		X		X				X						X	X		Eosinophils will be done by central laboratory
12-lead ECG	X																Locally collected and read
Serum total IgE, allergen-specific IgE	X	X												X	X		To be done by the central laboratory
Randomization		X															
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IMP preparation and administration[j]		X	X	X	X	X	X	X	X	X	X	X	X				At site, by the unblinded healthcare professional only following instructions provided in the pharmacy manual.
NIMP: background therapy for CRSwNP and asthma diary	X	← ---------- →													X		Diary for both MFNS and asthma background therapy

Procedure	Screening /run-in (28±3 days before Day 1)[a]	Intervention Period (24 weeks)														Follow-up (up to 12 weeks after last IMP dose)[d]	Notes
		Day 1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24 EOT	E/D[c]		
Visit	1	2	3	4	5[b]	6	7[b]	8	9[b]	10	11[b]	12[b]	13[b]	14			
Dispense or download eDiary[k]	X			←---→											X		eDiary will be dispensed at screening visit (including instructions for use). At EOT, the eDiary will be returned to the site.
Prior/ Concomitant medication review	X			←---→											X	X	Relevant prior medication at screening visit. Record rescue therapy if applicable.
Record planned surgery for NP, SCS use, and other rescue medication use[l]	X			←---→											X		
Smell test (UPSIT)		X	X	X				X						X	X		Collect baseline value ahead of first dose of IMP
Nasal Peak Inspiratory Flow (NPIF)	X		←----------------- daily morning (AM) from V1 up to Week 24 -------------→												X		eDiary on eDevice[k]

Procedure	Screening /run-in (28±3 days before Day 1)[a]	Intervention Period (24 weeks)														Follow-up (up to 12 weeks after last IMP dose)[d]	Notes
		Day 1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24 EOT	E/D[c]		
Visit	**1**	**2**	**3**	**4**	**5[b]**	**6**	**7[b]**	**8**	**9[b]**	**10**	**11[b]**	**12[b]**	**13[b]**	**14**			
Clinical Outcomes Assessment Measures and Resource Use[m]																	
22-item sino-nasal outcome test (SNOT-22)		X		X				X						X	X		ePRO on eDevice
Asthma Daytime/ Symptom Diary (ADSD)	X	X		X				X						X	X		Completed by the participant at home daily between V1 and V2 and 30 days prior to W4, W12, and W24 on eDevice[k]
CRSwNP nasal symptom diary	X	← - - - - - - - - - - - - - - - - - - daily morning (AM) from V1 up to Week 24 - - - - - - - - - - - - - - →													X		eDiary on eDevice[k]
ACQ-7[n]	X	X		X				X						X	X		ePRO on eDevice
AQLQ(S)		X		X				X						X	X		ePRO on eDevice
EQ-5D		X		X				X						X	X		ePRO on eDevice
Rhinosinusitis VAS		X		X				X						X	X		ePRO on eDevice
WPAI-chronic rhinosinusitis		X		X				X						X	X		ePRO on eDevice
HCRU		X		X				X						X	X		Investigator assessment at site (from eCRF)

Procedure	Screening /run-in (28±3 days before Day 1)[a]	Intervention Period (24 weeks)													E/D[c]	Follow-up (up to 12 weeks after last IMP dose)[d]	Notes
		Day 1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24 EOT			
Visit	1	2	3	4	5[b]	6	7[b]	8	9[b]	10	11[b]	12[b]	13[b]	14			
Patient global impression of control (PGI-Control)		X		X				X						X	X		Participant assessment/ eDevice
Patient global impression of change (PGI-Change)				X				X						X	X		Participant assessment/ eDevice
Investigator Global Assessment of Severity (IGA-Severity) and Control (IGA-Control)		X		X				X						X	X		Investigator assessment at site (from eCRF)
Investigator Global Assessment of Change (IGA-Change)				X				X						X	X		Investigator assessment at site (from eCRF)
AE/SAE, TEAE, and AESI review	X	←------------------------------------→													X	X	

ACQ-7: Asthma Control Questionnaire-7 item; AD: atopic dermatitis; ADSD: Asthma Daytime Symptom Diary; AE: adverse event; AESI: adverse event of special interest; ALT: alanine aminotransferase; AQLQ(S): Asthma Quality of Life Questionnaire with Standardized Activities; CRSwNP: chronic rhinosinusitis with nasal polyps; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eCRF: electronic case report form; eDevice: electronic device; eDiary: electronic diary; E/D: early discontinuation; EQ-5D-5L: EuroQol-5 Dimensions 5 Levels; EOT: end of treatment; ePRO: electronic PRO; FeNO: fractional exhaled nitric oxide; FEF: forced expiratory flow; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HBc Ab: hepatitis B core antibody; HBs Ab: hepatitis B surface antibody; HBs Ag: hepatitis B surface antigen; HCRU: health-care resource utilization; HCV Ab: hepatitis C virus antibodies; HIV: human immunodeficiency virus; HIV-Abs: human immunodeficiency virus-antibodies; IgE: immunoglobulin E; IMP: investigational medicinal product; INCS: intranasal corticosteroid sprays; IWRS: Interactive Web Response System; MFNS: mometasone furoate nasal spray; NC: nasal congestion; NIMP: noninvestigational medicinal product;

NP: nasal polyps; NPIF: Nasal Peak Inspiratory Flow; NPS: nasal polyp score; PRO: patient-reported outcome; SAE: serious adverse event; SCS: systemic corticosteroids; SNOT-22: sino-nasal outcome test-22 Items; TB: tuberculosis; TEAE: treatment-emergent adverse event; UPSIT: University of Pennsylvania Smell Identification Test; V: visit; VAS: visual analogue scale; W: week; WOCBP: woman of childbearing potential; WPAI: Work Productivity and Activity Impairment.

a Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the run-in period window prior to Day 1 (V2) is respected. These participants do not need to sign a new consent form and be allocated a new participants number within this same window.
The run-in period is 28 days in duration to run-in any participant on MFNS and to collect baseline data. Participants who receive rescue medication including INCS drops or systemic (oral, intravenous, intramuscular) steroids and/or surgery during this period will not be randomized, but they can be rescreened. V2 will take place 28±3 days window after V1. Window for subsequent visits is also ±3 days.
Assessments/procedures at a site visit are performed in the following order (if applicable): PRO and other questionnaires; procedures; safety and laboratory assessments; IMP administration.

b Interim visits at site for IMP administration.

c Participants who discontinue treatment early will be assessed as soon as possible using the procedures scheduled for the EOT visit.

d Phone call visit: The safety follow-up period will be up to 12 weeks after the last IMP dose (Week 22) or until the participant switches to commercialized dupilumab/omalizumab or other biologics, whichever comes first. For the participants who switch to commercialized dupilumab/omalizumab (or other biologic product), the phone call visit should be performed prior to the first injection with commercialized dupilumab/omalizumab (or other biologic product).

e A complete physical examination will include, at a minimum, assessments of the skin, nasal cavities, eyes and ears, cardiovascular, respiratory, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

f 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. The 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 eCRF. Non-steroid anti-inflammatory drug (NSAID) Exacerbated Respiratory Disease (ERD) will be assessed through a specific questionnaire (Section 10.12).

g Spirometry test should be performed before IMP administration, in the morning if possible. If test can only be performed at another time during the day, then it should be done approximately at the same time of the day at each visit throughout the study. Spirometry will be performed after a washout period of bronchodilators according to their duration of action. This will be verified before performing the measurements.

h Nasal endoscopy: endoscopy (including use of decongestants before the procedure) will be performed after all other efficacy assessments have been completed for each visit. Standard video sequences will be downloaded by the Investigator and sent to the central reader's secured internet site. For eligibility, central reading of V1 will be used. At V2, the Investigator will review V1 results from the 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 nasal endoscopy to confirm eligibility score. 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 each side. The final results of central reading from V2 onward will be made available to the site after the end of study. Nasal endoscopy can be repeated once per time point (for quality or safety issues). Nasal endoscopy can be repeated once during screening (at the latest 1 week before randomization) in case of not meeting eligibility criteria as per the Investigator discretion.

i Hepatitis screening, comprising HBs Ag, hepatitis B surface antibody (HBs Ab); total HBc Ab; HCV Ab. In case of results showing HBs Ag (negative), HBs Ab (negative), and HBc Ab (positive), the hepatitis B virus (HBV) DNA testing will be performed prior to randomization to rule out a false positivity if the Investigator believes the participant is a false positive or to clarify the serological status if the Investigator finds it unclear to interpret in the absence of known HBV infection. In case of results showing HCV Ab (positive), the hepatitis C virus (HCV) RNA testing may be performed to rule out a false positivity. Human immunodeficiency virus screening: anti-HIV-1 and HIV-2 antibodies. Tuberculosis testing will be performed only on a country-by-country basis according to the routine clinical practice and the local guidelines if required by the Regulatory Authorities or Ethics Committees or if TB is suspected by the investigator.

j During the intervention period, IMP will be administered at site after completion of all scheduled clinical assessments (including PROs) and blood sample collection. When operationally feasible and if treating physician determines that is appropriate and safe, administration of IMP at study participant's home by qualified and trained healthcare professionals as well as direct to participant shipment may be arranged. These approaches will only be implemented if allowed by local regulations, approved labelling and agreed by the treating physician, while ensuring blinding measures are maintained.

k Electronic diary/NPIF meter is used for daily recording of MFNS use, morning NPIF (daily), ADSD, and daily symptoms severity (CRSwNP Nasal Symptom Diary) from V1 to EOT. The CRSwNP Nasal Symptom Diary will measure: 1) nasal congestion/obstruction; 2) anterior rhinorrhea (runny nose); 3) posterior rhinorrhea (postnasal drip); and 4) loss of sense of smell, scored using a 0 to 3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms. This device is dispensed at V1 and information is downloaded from this device on the other indicated days. Nasal congestion/blockade/obstruction 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's 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.

l At V1 and V2 eligibility for surgery will be assessed based on the Investigator's opinion. During the study intervention and follow-up period, if rescue medication with oral corticosteroids is required, oral prednisone or prednisolone will be dispensed by the site to the participant through a scheduled or unscheduled on-site visit. Use of oral steroids for rescue treatment of worsening NP or for another reason will be captured by the Investigator (or designee) on the appropriate page(s) of the eCRF and the date and dosing information (daily dose, duration, international nonproprietary name [INN]) will be informed. Details on actual or planned date for surgery for NP, type and outcome (whenever possible) of surgery will be recorded in a specific eCRF page. If surgery is performed during the study intervention period or follow-up, a TEAE or SAE page will be completed. Participants will be discontinued from study intervention and assessed as soon as possible using the procedures scheduled for the EOT visit.

m During the study, for the visits during the Intervention Period electronic PRO will be completed by participant in the following order: CRSwNP Morning Diary, NPIF Morning Diary (completed by participant at home or after visit, between 04:00 in the morning and 12:30 in the afternoon), SNOT-22, Rhinosinusitis VAS, PGI-Control, PGI-Change, WPAI, ACQ-7, AQLQ, EQ-5D-5L (when participant at site), ADSD evening questionnaire (completed by participant at home daily between V1 and V2 and 30 days before the next confirmed visit, between 05:00 in the afternoon and before 11:59 in the evening).

n Asthma Control Questionnaire-7 (ACQ-7): participants are asked to recall how their asthma has been during the previous week and to respond to the first 6 questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). Clinic staff will score the FEV1% predicted also on a 7-point scale. At screening visit, Asthma Control Questionnaire (ACQ-5) scores (sum of the responses to the first 5 questions) will be derived from ACQ-7. For the statistical analysis, centrally read values pre-bronchodilator FEV1 will be used.

2 INTRODUCTION

Dupilumab is a human mAb that binds specifically to the shared receptor component for IL-4 and IL-13, thus inhibiting the dual signaling pathways of IL-4 and IL-13, key and central drivers of type 2 inflammation in CRSwNP and other type 2 inflammatory diseases.

Dupilumab is indicated for the treatment of AD patients aged six months and older, asthma in patients aged six years and older, CRSwNP in adult patients, eosinophilic esophagitis (EoE) in patients aged 12 years and older and prurigo nodularis (PN) in adult patients.

Omalizumab is a recombinant deoxyribonucleic acid (DNA)-derived humanized mAb that selectively binds to human IgE. The antibody is an immunoglobulin G1 (IgG1) kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

Omalizumab is approved in the EU and the US for the treatment of allergic asthma and CSU. In the US, omalizumab is approved for the treatment of nasal polyps, and in EU is approved for the treatment of CRSwNP.

Despite the availability of several biologic therapies to treat asthma and CRSwNP, there is no evidence to compare the clinical efficacy of these treatments against each other given that no H2H studies have been conducted so far. Head-to-head studies are necessary to determine the best therapeutic option for a patient, and to support treating physicians in the decision-making process. Therefore, there is a data gap in providing direct comparative data for key clinical outcomes in CRSwNP and asthma.

2.1 STUDY RATIONALE

Data from dupilumab and omalizumab CRSwNP pivotal studies suggest that dupilumab has the potential to demonstrate superiority compared to omalizumab in reducing the bilateral endoscopic NPS and the improving the sense of smell in participants with severe CRSwNP and comorbid asthma.

Additionally, post-hoc results from the indirect treatment comparison (ITC) of dupilumab versus omalizumab in CRSwNP showed that dupilumab was associated with statistically significant improvements in NPS and the University of Pennsylvania Smell Identification Test (UPSIT) changes from baseline at Week 24 when comparing to omalizumab. Among additional key endpoints evaluated in this analysis, dupilumab was associated with statistically significant improvement in nasal congestion (NC)/obstruction score, loss of smell score, and total symptom score (TSS) at Week 24 when comparing to omalizumab. Dupilumab improvements over omalizumab were also demonstrated in NPS and NC score in the comorbid asthma population (40).

With regards to asthma-related outcomes, the overall weight of evidence from asthma patients as well as patients with CRSwNP and comorbid asthma suggest that dupilumab treatment is

associated with greater improvements in pre-bronchodilator forced expiratory volume in 1 second (FEV1) than omalizumab. Dupilumab has consistently demonstrated clinically and statistically significant FEV1 improvements across populations while omalizumab FEV1 data is limited and often not clinically meaningful.

Therefore, the purpose of this study is to evaluate whether the efficacy profile of dupilumab is superior compared to omalizumab in treating participants with severe CRSwNP and comorbid asthma.

The study is designed to assess the superiority of dupilumab versus omalizumab in key clinical outcomes, potentially establishing dupilumab as the treatment of choice in the respiratory space across type 2 inflammatory diseases.

2.2 BACKGROUND

Severe CRSwNP is a serious, chronic inflammatory disease, predominantly driven by type 2 inflammation in at least 80% of patients (in western countries) and 50% (in Asian countries) (1). Chronic Rhinosinusitis with Nasal Polyps is characterized by bilateral nasal polyps and rhinosinusitis, which cause a range of persistent debilitating symptoms, including loss of smell, nasal obstruction/congestion, and nasal discharge (2, 3, 4). Chronic Rhinosinusitis with Nasal Polyps has an estimated prevalence of 2% to 4% in Europe and the US (4, 5) and is frequently associated with multiple type-2 coexisting diseases such as asthma, allergic rhinitis, and/or NSAID-ERD, which further contribute to greater disease severity and overall disease burden (6). In CRSwNP the type 2 inflammatory signature is characterized by the involvement of type 2 cytokines interleukin-4 (IL-4)/IL-13 and IL-5 in its pathophysiology, and high levels of tissue IgE (7, 8, 9, 10, 11) or presence of coexisting diseases such as asthma, NSAID-ERD, allergic rhinitis, or AD (4, 12, 13, 14).

Approximately 50% to 70% of patients with asthma (15, 16, 17, 18, 19, 20), have evidence of type 2 airway inflammation (10, 11, 12, 21), and up to 65% of CRSwNP patients have comorbid asthma.

- In patients with asthma, type 2 inflammation is associated with poor asthma control, increased bronchial hyperresponsiveness, greater lung function impairment, and more frequent severe exacerbations compared with patients with a lower type 2 inflammatory signature.
- In patients with CRSwNP, the presence of type 2 inflammation is associated with more severe disease, a greater risk for post-surgical recurrence, and a higher frequency of comorbid asthma.

As stated above, a high proportion of patients with CRSwNP have comorbid asthma, which adds substantially to the overall disease burden, including greater disease severity of both CRSwNP and asthma leading to more frequent asthma exacerbations, higher rates of postsurgical polyp recurrence, greater cumulative SCS use, and an impaired HRQoL (22, 23, 24). As a result of the shared inflammatory pathway underpinning their pathophysiology, type 2 inflammatory airway diseases share several common clinical features, notably airway obstruction and/or

congestion, and excessive mucus production. Increased nasal sinus opacification (reduced upper airway volume) has been associated with evidence of type 2 inflammation (blood/tissue eosinophilia) in patients with CRSwNP (25, 26, 27, 28).

First-line treatment options for CRSwNP comprises INCS and saline nasal irrigations to improve the symptoms of disease such as nasal obstruction (29) but INCS show little effect in reducing nasal polyp size and improving sense of smell, the most important symptoms reported by CRSwNP patients (30, 31). In addition, SCS is prescribed to decrease polyp size and symptom burden, but continuous treatment with SCS is not recommended and should be avoided due to the known serious systemic side effects - both short and long term (32). In some patients, medical management fails and therefore, FESS is indicated to improve sino-nasal symptoms (33). Surgical removal of nasal polyps does not specifically target the underlying type 2 inflammation (mediated by key type 2 cytokines IL-4, IL-13, and IL-5) in the sinuses, leading to high rates of recurrence and revision surgery, and may not restore the sense of smell in many patients (22, 34, 35, 36).

Recent therapeutic approaches have been focused on the use of biologics in order to control the Th2 pathway with subsequent improvement of clinical signs in CRSwNP and associated comorbidities. Some biologics are currently approved for the treatment of this disease (dupilumab, omalizumab, and recently mepolizumab), while other biologics are in development (eg, benralizumab).

Dupilumab

Dupilumab is a fully human VelocImmune-derived mAb that inhibits signaling by IL-4 and IL-13, which both have an important role in the type 2 inflammation cascade (41, 42, 43). Dupilumab is directed against IL-4-Rα, a component of IL-4 receptors Type I and Type II. Type II receptor mediate signaling of both, IL-4 and IL-13, whereas Type I receptor just interact with IL-13. By binding to IL-4-Rα, dupilumab prevents the activation of IL-4 and IL-13 receptors by the respective cytokines.

Several studies evaluated the impact of dupilumab on positive treatment outcome in patients with CRSwNP. In a proof-of-concept study (ACT12340), 60 patients with bilateral NP and chronic symptoms of sinusitis refractory to INCS were randomized to dupilumab 300 mg once weekly SC administration for 16 weeks or placebo, with background intranasal MFNS (Nasonex). In this study, dupilumab demonstrated significant improvement in endoscopic, radiographic and clinical measures of NP and sinusitis, as well as improvements in lung function and disease control in patients with comorbid asthma (44). Based on these data, the SINUS-24 (EFC14146) and SINUS-52 (EFC14280) trials were conducted. The current clinical studies demonstrated the robust efficacy of dupilumab in reducing the burden of all facets of CRSwNP disease including NPS, NC, and sinus inflammation, in restoring olfactory function, and in improving QoL. Dupilumab significantly reduced the proportion of patients requiring SCS and sino-nasal surgery. In patients with asthma, treatment with dupilumab improved lung function and asthma control.

Omalizumab

Omalizumab interrupts the allergic cascade triggered by cross-linking IgE on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with omalizumab (Xolair) also reduces the number of FcεRI receptors on basophils in atopic patients (45).

The pivotal clinical program in CRSwNP consisted of 2 studies (POLYP 1 and POLYP 2) designed to determine the efficacy and safety of omalizumab (Xolair) compared with placebo in adult patients with CRSwNP who have had an inadequate response to intranasal corticosteroids. Both trials met the coprimary endpoints of change from baseline to Week 24 in average daily NC score and NPS. Participants in the studies were administered either omalizumab or placebo by SC injection every 2 to 4 weeks in addition to background intranasal corticosteroid (46).

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

The anticipated safety risks for dupilumab and omalizumab are outlined below. Please refer to dupilumab Investigator's Brochure and omalizumab locally approved labels.

Several measures will be taken to ensure the safety of participants enrolled in this study. Eligibility criteria have been designed to exclude participants at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events (AEs). In addition, guidelines for managing AEs, including criteria for treatment interruption or discontinuation are provided in the protocol (see Section 10.3 and Section 7.1).

Dupilumab

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, 13 577 participants were enrolled into the development program for dupilumab and are included in the safety population. The number of participants exposed to dupilumab in clinical studies was 10 828 (538 in healthy volunteer studies, 4496 in AD [including hand and foot dermatitis] studies, 3591 in asthma studies, 526 in rhinosinusitis [CRSwNP, chronic rhinosinusitis without nasal polyposis and allergic fungal rhinosinusitis] studies, 405 in EoE studies, 175 in allergy [grass and peanut] studies, 748 in chronic obstructive pulmonary disease [COPD] studies, 152 in PN studies, 156 in the urticaria [CSU and chronic inducible cold urticaria] studies, 22 in the bullous pemphigoid study, and 19 in the allergic bronchopulmonary aspergillosis study).

Based on the available sales figures and World Health Organization defined daily dose of 21.4 mg for parenteral formulations, the cumulative patient exposure in marketed experience could be estimated to be 706 212 patient years from 01 March 2017 through 31 March 2022.

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

Based on the postmarketing safety data, events of angioedema, arthralgia, keratitis, ulcerative keratitis, and facial rash have been added as ADRs to the postmarketing section of the company core data sheet (CCDS).

Systemic hypersensitivity is established as an important identified risk with dupilumab. As protein therapeutics, all mAbs are potentially immunogenic. Rare serious and systemic hypersensitivity reactions have been observed in the dupilumab program including serum sickness/serum sickness-like reaction in the adult AD program and anaphylaxis related to dupilumab in the adult asthma clinical trials.

The 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, conditions which are often treated with SCS 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 with these events has not been established. Therefore, health-care providers should be alerted 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 SCS.

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 common ADR across all indications is injection site reactions. Other potential risks based on the safety profile in particular indications are discussed in the Investigator's Brochure.

To date, the safety profile of dupilumab has been similar among adult and adolescent patients with asthma, AD, EoE, and PN and in adult patients with CRSwNP. While long-term data are still accumulating, data from randomized, placebo-controlled trials and open-label extension studies have not identified any new safety concern in these populations.

It is anticipated that dupilumab in patients with CRSwNP and comorbid asthma will have a favorable safety profile as observed across other type-2-driven immunological disorders.

Omalizumab

In the Phase 3 studies conducted in patients with CRSwNP, omalizumab was well tolerated, with no new or unexpected safety concerns identified in the pooled data. The most common AEs observed (headache, injection site reactions, arthralgia, dizziness, upper abdominal pain) have been previously reported with omalizumab (47, 48, 49).

The safety profile of omalizumab is well established in patients with allergic asthma and chronic idiopathic urticaria (50), with a cumulative exposure of >16 000 patient-years in clinical trials and an estimated cumulative patient exposure of >1 300 000 patient-years to date in the postmarketing setting.

In POLYP 1 and 2 studies, the proportion of patients who experienced ≥1 treatment emergent adverse event (TEAE) was 58.5% in placebo-treated patients and 50.4% in omalizumab-treated patients. Number of AEs was greater in placebo-treated versus omalizumab-treated patients. Most events across both studies were of mild-to-moderate intensity. Two serious adverse events (SAEs) were reported in placebo-treated patients (1.5%; myocardial infarction, n = 1; pneumonia, n = 1) and 3 in omalizumab-treated patients (2.2%; snake bite, n = 1; hand fracture, n = 1; asthma exacerbation/worsening, n = 1). The proportion of patients experiencing ≥1 AE suspected to be omalizumab related by the Investigator was 3.8% in placebo-treated patients and 6.7% in omalizumab-treated patients. These AEs were mild-to-moderate in intensity and most occurred within 24 hours of study drug administration. The most common adverse reactions (≥3% of patients) in clinical studies with adult patients included the following: headache, injection site reaction, arthralgia, upper abdominal pain, and dizziness. An episode of anaphylaxis, later adjudicated as not meeting Sampson's criteria by an independent anaphylaxis adjudication committee, led to discontinuation in placebo-treated patients (46). Please refer to omalizumab label for further details (45, 51).

2.3.2 Benefit assessment

Dupilumab solution for injection is currently authorized:

- In over 60 countries worldwide including the US, EU (Centralized Procedure), and Japan for the treatment of adults with inadequately controlled moderate-to-severe AD, in over 60 countries for use in adolescent patients (≥12 years) with AD and in over 50 countries for use in pediatric patients (age 6-11 years) with AD. In the US dupilumab is also approved for pediatric patients of 6 months to <6 years of age.
- In over 60 countries worldwide including the US, EU (Centralized Procedure), and Japan, as an add-on maintenance treatment for asthma in patients aged 12 years and older, dupilumab is approved for the treatment of children aged six years to <12 years with asthma in more than 30 countries and is currently under review for the treatment of asthma in this age group in multiple countries.

- In over 50 countries worldwide including the US for use in adults with inadequately controlled CRSwNP, the EU as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control, Canada as an add-on maintenance treatment with intranasal corticosteroids in adult patients with severe CRSwNP inadequately controlled by SCS and/or surgery, and in Japan for use in adults with CRSwNP (only patients not adequately controlled with existing therapies). Review of this indication is ongoing in other countries worldwide.
- In the US for the treatment of adult and pediatric patients, aged 12 years and older, weighing at least 40 kg, with EoE and is currently under review for this indication in multiple countries, including the EU.
- In the US for the treatment of adult patients with PN and is currently under review for this indication in multiple countries, including the EU and Japan.

The participants in this study may benefit from receiving a novel treatment for the underlying type 2 inflammatory disease process. Based on the efficacy results observed for both dupilumab and omalizumab, it is anticipated that the use of both IMP will lead to a reduction on signs and symptoms associated with CRSwNP and asthma.

2.3.3 Benefit/risk assessment related to Coronavirus Disease 2019 (COVID-19)

The Sponsor recognizes that the “Coronavirus Disease 2019” (COVID-19) pandemic is having 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 Appendix 9 [Section 10.9]).

Currently, the Sponsor does not have sufficient data in patients with COVID-19 who are being treated with dupilumab. Thus, the safety and efficacy of dupilumab in patients with COVID-19 is unknown. There are no data regarding the incidence nor severity of patients with COVID-19 receiving omalizumab (52). During the course of the clinical trial program, respiratory infections including viral infections were monitored and these events are not listed as ADRs with dupilumab.

2.3.4 Overall benefit: risk conclusion

Dupilumab has shown clinically relevant benefits in several type-2-driven immunological disorders including AD, asthma, and CRSwNP. A satisfactory safety profile for dupilumab has been observed so far in completed and currently ongoing studies, as well as postmarketing experience. Omalizumab has also shown benefits in allergic asthma, CSU, and CRSwNP with a satisfactory safety profile observed to date.

This study will give all enrolled participants an opportunity to receive a therapy which may improve both CRSwNP and asthma-related outcomes. Taking into account risk mitigation measures for study participants, the potential risks identified in association with dupilumab and omalizumab are justified by the anticipated benefits that may be afforded to participants with CRSwNP and comorbid asthma.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab compared to omalizumab in reducing the polyp size and improving sense of smell	• Change from baseline to Week 24 in Nasal Polyp Score (NPS) • Change from baseline to Week 24 in University of Pennsylvania Smell Identification Test (UPSIT)
Secondary	
Key secondary objectives: • To evaluate the efficacy of dupilumab in improving chronic rhinosinusitis with nasal polyps (CRSwNP) symptoms at Week 24 compared to omalizumab	Key secondary endpoints: • Change from baseline to Week 24 in the loss of smell score of the CRSwNP Nasal Symptom Diary • Change from baseline to Week 24 in the nasal congestion (NC) score of the CRSwNP Nasal Symptom Diary
Secondary objectives: • To evaluate the efficacy of dupilumab in improving CRSwNP total symptom score (TSS) at Week 24 compared to omalizumab	Secondary endpoints: • Change from baseline to Week 24 in TSS derived from the CRSwNP Nasal Symptom Diary
• To evaluate the effect of dupilumab on health related quality of life (HRQoL) at Week 24 compared to omalizumab	• Change from baseline to Week 24 in 22-Item Sino-nasal Outcome Test (SNOT-22) total score • Change from baseline to Week 24 in SNOT-22 nasal domains score
• To evaluate the efficacy of dupilumab in improving nasal peak inspiratory flow at Week 24 compared to omalizumab	• Change from baseline to Week 24 in Nasal Peak Inspiratory Flow (NPIF)
• To evaluate the effect of dupilumab on CRSwNP overall disease severity at Week 24 compared to omalizumab	• Change from baseline to Week 24 in rhinosinusitis visual analogue scale (VAS)
• To evaluate the safety of dupilumab and omalizumab	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Incidence of adverse events of special interest (AESIs)
Tertiary/exploratory	
• To evaluate the efficacy of dupilumab in improving lung function at Week 24 compared to omalizumab	• Change from baseline to Week 24 in pre-bronchodilator forced expiratory volume in 1 second (FEV1)
• To evaluate the effect of dupilumab on asthma control at Week 24 compared to omalizumab	• Change from baseline to Week 24 in 7-item Asthma Control Questionnaire (ACQ-7)
• To evaluate the efficacy of dupilumab to improve asthma outcomes including lung function and patient reported outcomes at Week 24 compared to omalizumab	• Annualized rate of severe asthma exacerbations during the 24-week intervention period • Change from baseline to Week 24 in Asthma Quality of Life Questionnaire (AQLQ) • [redacted]

Objectives	Endpoints
	• Change from baseline to Week 24 in FeNO • [redacted] • [redacted]
• To evaluate the effect of dupilumab on additional HRQoL measures at Week 24 compared to omalizumab	• Change from baseline to Week 24 in SNOT-22 sleep and functional domains score
• To evaluate the efficacy of dupilumab on improving health status at Weeks 24 compared to baseline	• [redacted]
• [redacted]	• [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted] • [redacted] • [redacted]
• To evaluate the efficacy of dupilumab on productivity, health-care resource utilization (HCRU) and global impression of control/change at Week 24 compared to omalizumab	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

Objectives	Endpoints
• [redacted]	• [redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy assessments consist of clinical endpoints and patient-reported outcome (PRO) endpoints which are relevant for the management and monitoring of CRSwNP and asthma. See specific information on each measurement in Section 8.1.

Endpoints for CRSwNP assessment include:

- NPS
- UPSIT
- NC
- Nasal Peak Inspiratory Flow (NPIF)
- Rhinosinusitis Visual Analogue Scale (VAS)
- TSS
- Loss of smell
- Sino-Nasal Outcome Test-22 (SNOT-22)
- Patient Global Impression of Control (PGI-Control)
- Patient Global Impression of Change (PGI-Change)
- Investigator Global Assessment of Severity (IGA-Severity)
- Investigator Global Assessment of Control (IGA-Control)
- Investigator Global Assessment of Change (IGA-Change)
- Work Productivity and Activity Impairment (WPAI) Questionnaire -CRSwNP.

Endpoints for asthma assessment include:

- Pre-bronchodilator FEV1
- Forced vital capacity (FVC)
- Forced expiratory flow (FEF) 25% to 75%

- Asthma Daytime Symptom Diary (ADSD)
- Asthma Control Questionnaire-7 (ACQ-7)
- Asthma Quality of Life Questionnaire (AQLQ)
- Severe exacerbations.

Generic endpoints include EuroQol Visual Analogue Scale (EQ VAS).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 4, multicenter, parallel group, randomized (1:1), double-blind, active-controlled study to compare the efficacy of dupilumab with omalizumab over 24 weeks of treatment in adult participants with severe CRSwNP and comorbid asthma.

Based on enrollment projections at the moment of sample size reduction, a minimum of 320 participants (160 per group) will be randomized in a 1:1 ratio to receive either dupilumab or omalizumab. Randomization will be stratified by prior surgery, ICS doses (low versus medium/high dose ICS), presence of AERD and region (EE versus ROW). Based on the subgroup analysis from prior SINUS clinical trials, different treatment effects over placebo were observed in EE countries versus ROW, across a few endpoints of interest. Therefore, the stratification factor by region (EE versus ROW) is included.

Study duration per participant will be 38 weeks. The study will comprise 3 periods:

- Screening and run-in period (28±3 days):
  - Screening and run-in period: after Visit 1 (screening visit), once the eligibility for study entry has been confirmed, participant will enter a run-in period of 28 days to determine participant's eligibility and for run-in/standardization of background INCS (MFNS) prior to randomization. All participants will receive MFNS, 2 actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg), starting at Visit 1. If the participants are unable to tolerate the BID regimen or this dose (400 µg daily) is not approved in specific countries, they will follow a lower dose regimen of 200 µg QD.
  - Participant's MFNS dose will be stabilized during the run-in period.
  - Participants should also be on a stable dose of low, medium or high dose ICS in combination with a second controller medication (eg, LABA, LTRA) ≥1 month prior to screening visit and during the screening and run-in period.
  - Participants who receive rescue medication including INCS drops or systemic (oral, IV, IM) steroids between Visit 1 and Visit 2 will not be randomized. However, they may be rescreened following the procedures described in the protocol.
- Randomized IMP intervention period (24 weeks from baseline [Day 1, Visit 2]):
  - Participant will be randomized to receive dupilumab or omalizumab on Day 1. During the randomized intervention period, all participants will continue on the stable dose of intranasal MFNS as well as ICS.
- Follow-up period: up to 12 weeks after the last IMP dose (Week 22) or until the participant switches to commercialized dupilumab/omalizumab (or other biologic product), whichever comes first. For the participants who switch to commercialized dupilumab/omalizumab (or other biologic product), the follow-up phone call visit should be performed prior to the first injection with commercialized dupilumab/omalizumab (or other biologic product).

During the study, participants who report deterioration and requiring medical/surgical intervention may come to the site for an endoscopy and clinical evaluation. An unscheduled visit may be considered for this purpose and if necessary, the Investigator may consider one of the treatment alternatives described in Section 6.5.3. If the date of surgery is scheduled after the planned EOS, the EOS will be postponed, and follow-up contact(s) may be required to document the surgery date and outcome.

The schedule of the visits is described in the specific flow chart in Section 1.3.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The aim of this study is to demonstrate the superiority of dupilumab over omalizumab in improving key clinical endpoints and PRO endpoints in participants with severe CRSwNP and comorbid asthma.

The 2 primary efficacy endpoints are change from baseline to Week 24 in bilateral endoscopic NPS (0 to 8 scale) as graded by the independent physician reviewer and change from baseline to Week 24 in UPSIT (0 to 40), administered and graded by blinded study Investigators. These endpoints provide both a subjective and objective assessment of efficacy in the target population.

Secondary and exploratory endpoints will evaluate clinical outcomes, such as nasal and lung function, coupled with PROs, such as upper and lower airway respiratory symptoms.

The 24-week randomized, double-blind period is considered relevant for the efficacy assessments and adequate to meet the study goal, since it is in line with the duration of omalizumab Phase 3 studies (POLYP-1 and 2) as well as dupilumab phased 3 trial (SINUS-24) in CRSwNP, which demonstrated significant improvements in the endpoints examined at Week 24. Longer studies establishing the efficacy and safety profile of each biologic have already been conducted (eg, SINUS-52 and other long-term studies in asthma).

The goal of this study is to demonstrate superiority of dupilumab over another biologic therapy, therefore an active-arm design versus omalizumab is appropriate. The study participants will be appropriately informed and will provide written consent to the eventuality of receiving either dupilumab or omalizumab during the randomized double-blind intervention period. They may withdraw from the study intervention or from the study at any time. In addition, a mitigation strategy will be implemented to limit the number of injections in each treatment arm.

The safety follow-up period will be up to 12 weeks after the last IMP dose (Week 22) or until the participant switches to other biologics (including commercialized dupilumab and omalizumab), considering that after the last steady-state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, estimated by population pharmacokinetic (PK) analyses was 10 to 12 weeks for the 300 mg Q2W.

4.2.1 Participant input into design

In collaboration with the patient advocacy group Allergy & Asthma Network in the USA, a patient experience survey was conducted on 61 patients with CRSwNP and comorbid asthma to assess different protocol design challenges related to medical procedures, treatment administration and PROs. The survey showed a high rate of acceptability on most of the study procedures. Only computed tomography scan assessments (originally planned) raised some concerns. These assessments were finally not considered for this study. Some recommendation was given to decrease patient burden.

4.3 JUSTIFICATION FOR DOSE

The dose regimen for both IMPs will be according to the approved regulatory dose and posology in CRSwNP.

The regulatory approved dose for dupilumab in adult participants with CRSwNP is 300 mg Q2W. This dose was evaluated in the pivotal CRSwNP trials and was safe and well tolerated with an overall positive benefit/risk profile for dupilumab in comparison to placebo.

Omalizumab dosing and frequency depends on the participant's baseline IgE levels and body weight, and ranges from 75 to 600 mg administered either Q2W or Q4W. This regimen was evaluated in the pivotal CRSwNP studies.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the post-treatment follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in 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 (or the legal age of consent in the jurisdiction in which the study is taking place) of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with bilateral sino-nasal polyposis, that despite prior treatment with SCS anytime within the past 2 years; and/or medical contraindication/intolerance to SCS; and/or prior surgery for NP have:

- An endoscopic bilateral NPS of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) at Visit 1 (screening visit);
  Note: the participant is considered eligible based on a Visit 1 central reading followed by a Visit 2 local reading NPS score AND
- Ongoing symptoms of NC/blockade/obstruction and loss of smell for at least 8 weeks before screening (Visit 1), AND
- Nasal congestion/blockade/obstruction and a weekly average severity greater than 1 in the 7 days before randomization (Visit 2), AND
- Loss of smell symptom severity score 2 or 3 at screening (Visit 1) and a weekly average severity of greater than 1 in the 7 days before randomization (Visit 2).

I 03. Participants with a physician diagnosis of asthma based on the Global Initiative for Asthma (GINA) 2020 (53) treated with low, medium or high dose ICS and a second controller (ie, LABA) A third controller is allowed but not mandatory. The dose regimen should be stable for at least 1 month before Visit 1 (screening visit) and during the screening and run-in period.

I 04. Deleted in Amended protocol 02

I 05. Asthma Control Questionnaire 5-question version (ACQ-5) score ≥1.5 at Visit 1 or 2.

I 06. Treatment with intranasal mometasone ≥200 µg QD (or equivalent of another INCS) for 1 month prior to Visit 1 and during the run-in period (for CRSwNP).

Weight

I 07. Eligibility as per omalizumab drug-dosing table (serum IgE level ≥30 to ≤1500 IU/mL and body weight ≥30 to ≤150 kg) and ability to be dosed per the dosing table (see Figure 2).

Sex

I 08. Male and/or female

Contraceptive use by female participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP).

    OR
  - Is a 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) during the intervention period and for at least 12 weeks after the last dose of the study intervention.
  - A WOCBP must have a negative highly sensitive serum pregnancy test at Visit 1 (screening visit) and urine or serum pregnancy test (as required by the local regulations) on Day 1 before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test will be required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are specified in Appendix 2 (Section 10.2).
- The Investigator is responsible for reviewing the participant's medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female participant with an early undetected pregnancy.

Informed Consent

I 09. Capable of giving signed informed consent as described in Section 10.1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Participants who have undergone any sinus intranasal surgery (including polypectomy) within 6 months before Visit 1.

E 02. Participants who have had a sino-nasal surgery changing the lateral wall structure of the nose, making impossible the evaluation of NPS.

E 03. Participants with conditions/concomitant diseases making them non evaluable at Visit 1 or for the primary efficacy endpoint such as:

- Antrochoanal polyps.
- Nasal septal deviation that would occlude at least one nostril.
- Acute sinusitis, nasal infection, or upper respiratory infection.
- Ongoing rhinitis medicamentosa.
- Known or suspected diagnosis of cystic fibrosis, primary ciliary dyskinesia (eg, Kartagener syndrome) or other dyskinetic ciliary syndromes, hypogammaglobulinemia or other immune deficiency syndrome, chronic granulomatous disease and granulomatous vasculitis, granulomatosis with polyangiitis (eg, Wegener's Granulomatosis), eosinophilic granulomatous with polyangiitis (EGPA) or Allergic granulomatous angiitis (Churg-Strauss syndrome).
- Radiologic suspicion or confirmed invasive or expansive fungal rhinosinusitis.

E 04. Participants with nasal cavity malignant tumors and benign tumors (eg, papilloma, blood boil).

E 05. Severe asthma exacerbation requiring treatment with SCS in the last 4 weeks prior to Visit 1 and during screening.

E 06. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the participant's participation in the study. Examples include, but are not limited to, participants with short life expectancy, uncontrolled diabetes (hemoglobin A1c ≥9%), 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 diseases), autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis), or other severe endocrinological, gastrointestinal, metabolic, pulmonary, psychiatric, or lymphatic diseases. The specific justification for participants excluded under this criterion will be noted in the study documents (chart notes, case report forms [CRFs], etc).

E 07. Participants with active tuberculosis (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 subsequently start treatment with a biologic agent, in the medical judgment of the Investigator and/or an infectious disease specialist. Tuberculosis testing will be performed on a country-by-country basis according to the routine clinical practice and the local guidelines if required by the regulatory authorities or ethics committees or if TB is suspected by the investigator.

E 08. Diagnosed with, suspected of, or at high risk of endoparasitic infection, and/or use of antiparasitic drugs within 2 weeks before Visit 1 (screening visit) or during the screening and run-in period.

E 09. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at Visit 1 (screening visit).

E 10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antifungals, or receiving only symptomatic treatment (eg, influenza or COVID-19) within 2 weeks before Visit 1 (screening visit) or during the screening and run-in period.

E 11. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, TB, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the Investigator.

E 12. Active malignancy or history of malignancy within 5 years before Visit 1 (screening 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 13. History of systemic hypersensitivity or anaphylaxis to dupilumab and omalizumab, including any excipient.

E 14. Recent history of myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, or a known history of a hypercoagulable disorder.

E 15. History or clinical evidence of COPD or any other significant respiratory disease.

E 16. Current smoker or cessation of smoking within 6 months prior to Visit 1.

E 17. Known or suspected alcohol and/or drug abuse.

E 18. 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, eCRF, etc).

Prior/concomitant therapy

E 19. Any biologic therapy (including dupilumab and omalizumab) or any immunosuppressant/immunomodulator within 4 weeks prior to Visit 1 or 5 half-lives, whichever is longer.

E 20. Current participation to any clinical trial of an investigational drug or device or participation within 3 months before the screening visit or 5 half-lives of the investigational compound, whichever is longer.

E 21. Participants who have taken leukotriene antagonists/modifiers within 4 weeks before Visit 1 (screening visit) or 5 half-lives, whichever is longer, unless the participant is on a continuous treatment for at least 4 weeks before Visit 1 (screening visit).

E 22. Initiation of allergen immunotherapy within 3 months prior to Visit 1 (screening visit) or a plan to begin therapy or change its dose during the run-in period or the randomized intervention period.

E 23. Treatment with a live (attenuated) vaccine (see Section 6.5.1 for examples of vaccine) within 4 weeks before Visit 1 (screening visit).

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 the vaccine can be postponed until after the EOS, or preponed to before the start of the study without compromising the health of the participant:

- Participant 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 24. Either intravenous immunoglobulin (IVIG) therapy and/or plasmapheresis within 4 weeks before Visit 1 (screening visit).

E 25. Planned or anticipated use of any prohibited medications and procedures during the screening and study intervention periods (see Section 6.5).

Diagnostic assessments

E 26. Participants with any of the following result at Visit 1 (screening visit):

- Positive (or indeterminate) hepatitis B surface antigen (HBs Ag) or,
- Positive total hepatitis B core antibody (HBc Ab) confirmed by positive hepatitis B virus (HBV) DNA or,
- Positive hepatitis C virus antibody (HCV Ab) confirmed by positive hepatitis C virus (HCV) RNA.

Other exclusions

E 27. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 28. Participant 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 29. Participants who 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 International Council for Harmonisation [ICH]-Good Clinical Practice [GCP] Ordinance E6).

E 30. Any specific situation during study implementation/course that may raise ethics considerations.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

Participants should not eat or drink 1 hour prior to having the fractional exhaled nitric oxide (FeNO) levels measured, as this may affect the results.

5.3.2 Activity

Participants should avoid engaging in strenuous exertion for at least 30 minutes prior to FeNO and FEV1 assessments.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. 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 SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) during the run-in period may be rescreened.

The participants may be rescreened once during the open screening period. There is no requirement for a waiting period between the screen failure date and the rescreening date. Participants who are rescreened must sign a new consent form and all screening procedures must be repeated. A different participant identification number will be issued. The Interactive Web Response System (IWRS) report will flag rescreened participants.

Nasal endoscopy can be repeated once during screening (at the latest 1 week before randomization) in case of not meeting eligibility criteria as per the Investigator discretion.

5.5 CRITERIA FOR TEMPORARY DELAYING SCREENING/RANDOMIZATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 9 (Section 10.9) should be considered for screening/randomization.

6 STUDY INTERVENTION

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.

6.1 STUDY INTERVENTION(S) ADMINISTERED

All participants will randomly receive either dupilumab or omalizumab during the treatment period. In some cases, placebo injections may be used to preserve the blinding given the differences in dose regimens between dupilumab and omalizumab.

Table 2 - Overview of study interventions administered

ARM name	Dupilumab	Omalizumab	Placebo of Dupilumab and Omalizumab
Intervention name	Dupilumab 300 mg	Omalizumab 150 mg or Omalizumab 75 mg	Placebo*
Type	Biological	Biological	Other
Dose formulation	Dupilumab 300 mg: A 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in 2 mL	Omalizumab 150 mg: A 150 mg/mL omalizumab solution in a prefilled syringe to deliver 150 mg in a 1 mL injection or Omalizumab 75 mg: A 150 mg/mL omalizumab solution in a prefilled syringe to deliver 75 mg in a 0.5 mL injection	Dupilumab placebo will be supplied as an identical formulation to the active formulation without dupilumab, in a prefilled syringe to deliver placebo 2 mL
Unit dose strength(s)	300 mg	150 mg or 75 mg	0 mg
Dosage level(s)	One injection of 300 mg Q2W	75 to 600 mg Q2W/Q4W according to the dosing table (see Figure 2)	As needed to blind number of active dupilumab and omalizumab injections
Route of administration	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Active comparator	Placebo (to blind the number of active dupilumab and omalizumab injections)
IMP and NIMP	IMP	IMP	IMP
Packaging and labeling	Each dose of dupilumab will be supplied as 1 glass prefilled syringe packed in a participant kit box. Both glass prefilled syringe and box will be labeled as	Each dose of omalizumab will be supplied as 1 prefilled syringe packed in a participant kit box (commercial box). The commercial box will be labeled as required per country requirement	Each dose of placebo will be supplied as 1 glass prefilled syringe packed in a participant kit box. Both glass prefilled syringe and box will be labeled as required per country requirement

ARM name	Dupilumab	Omalizumab	Placebo of Dupilumab and Omalizumab
	required per country requirement		
Current name(s) or alias(es)	Dupixent	Xolair	Not applicable

IMP: investigational medicinal product; NIMP: noninvestigational medicinal product; Q2W: every 2 weeks; Q4W: every 4 weeks
*An algorithm will be used to randomly lower the number of placebo injection in some cases for the participants randomized in the dupilumab arm

Investigational medicinal Products

The IMP will be administered every 14±3 days (Q2W) during the 24-week intervention period (with the last IMP administration at Week 22), as per the instruction provided in the pharmacy manual.

The IMP will be administered at site following clinical procedures and blood collection. When operationally feasible and if treating physician determines that is appropriate and safe, administration of IMP at study participant's home by qualified and trained healthcare professionals as well as direct to participant shipment may be arranged. These approaches will only be implemented if allowed by local regulations, approved labeling and agreed by the treating physician, while ensuring blinding measures are maintained. 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 as per the instructions provided in the pharmacy manual.

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: Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.9).

Non investigational medicinal Product(s)

Background therapies and rescue therapies will be supplied by the Sponsor's local affiliate as locally required or by the sites. Reimbursement will be provided when deemed necessary and as per country regulation.

Intranasal corticosteroid background therapy

Throughout the study, the participant will use a diary to record daily use of MFNS 50 µg/actuation Nasal Spray, suspension.

Before study entry, treatment with intranasal mometasone ≥200 µg QD or equivalent of another INCS is required for 1 month prior to Visit 1. After Visit 1 only MFNS is allowed for a better standardization of background medication.

Screening/Run-in period

After Visit 1 (screening visit), once the eligibility for study entry has been confirmed, all participants will enter a run-in period of 28 days where they will receive MFNS:

- Two actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg) starting at Visit 1. If the participants are unable to tolerate the BID regimen or this dose is not approved in specific countries, they will follow a QD regimen (total daily dose of 200 µg).
- Participant's MFNS dose will be stabilized during the run-in period.

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

Participant who receive rescue medication including INCS drops or systemic (oral, IV, IM) steroids between Visit 1 and Visit 2 will not be randomized, but they can be rescreened.

Randomized IMP intervention period

During the randomized intervention period, all participants will continue on the stable dose of MFNS.

Post-treatment period (ie, follow-up period)

Upon completing the randomized intervention period (or following early discontinuation of IMP), participants can continue treatment with the stable dose of MFNS maintained over the randomized intervention period until the EOS, or modify treatment based on medical judgment.

Asthma background therapy

Screening/Run-in period

Participants should be on a stable dose of low, medium or high dose ICS in combination with a second controller medication (eg, LABA, LTRA) ≥1 month prior to screening visit and during the screening and run-in period.

Participants requiring a third controller for their asthma will be considered eligible for this study, also, at a stable dose ≥1 month prior to screening visit and during the screening and run-in period.

- Formulation and route(s) of administration: as per label.
- Dose regimen: as prescribed.

Randomized IMP intervention period

The asthma background therapy should be maintained on a stable dose during the study intervention period.

An asthma background therapy diary will be provided to collect information related to NIMP use.

Post-treatment period (ie, follow-up period)

Upon completing the randomized IMP intervention period (or following early discontinuation of IMP), participants can continue treatment with the stable dose of ICS maintained over the randomized intervention period until the EOS, or modify the treatment based on medical judgment.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Storage and handling

1. The Investigator or designee must confirm appropriate temperature conditions (dupilumab, omalizumab, and placebo to be maintained between +2°C to +8°C) have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.
2. Only participants enrolled in the study may receive IMP and only authorized healthcare professionals may supply or administer IMP. At the study site, all IMP 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 authorized unblinded site staff.
3. The Investigator, institution, or the unblinded site staff (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.2.2 Responsibilities

Any quality issue noticed with the receipt or use of an IMP (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 may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

- The randomized intervention kit number list is generated centrally by Sanofi. The IMPs are packaged in accordance with this list.

- The randomization and intervention allocation are performed centrally by Interactive Response Technology (IRT). The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.
- Participants will be randomized in a 1:1 ratio to dupilumab and omalizumab treatment arms.
- Randomization will be stratified by prior surgery, ICS doses (low versus medium/high dose ICS), presence of AERD and region (EE versus ROW).
- Participant's dose and dosing frequency will be based on serum total IgE levels and body weight measured before starting study intervention (see Figure 2).
- At Visit 1 (screening visit), the Investigator or designee will contact the IRT to receive the participant number. Participants who are rescreened are required to sign a new ICF. 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.
- IMP will be dispensed by an unblinded authorized personnel at the time points specified in the Schedule of Activities (SoA) (see Section 1.3).

Methods of blinding

- Dupilumab 300 mg (2 mL of solution for injection per prefilled syringe), omalizumab 150 mg (1 mL of solution for injection per prefilled syringe), and omalizumab 75 mg (0.5 mL of solution for injection per prefilled syringe) prefilled syringes are visually different (for appearance and filled volume of solution). Dupilumab placebo (identical formulation to the active formulation without dupilumab) will be provided in the prefilled syringes of 2 mL solution to blind the number of active dupilumab or omalizumab injections between the IMP intervention groups.
- Kits will be labeled with a treatment kit number. Treatment kits will not be blinded due to the different prefilled syringe characteristics, and different volume size (2 mL versus 1 mL versus 0.5 mL) of the dose level of omalizumab/dupilumab that will be used according different body weight and IgE levels.
- Investigators will remain blinded to each participant's assigned IMP group throughout the course of the study. In order to maintain this blind, unblinded study site personnel will be responsible for the dispensation and administration of IMPs and will endeavor to ensure that there are no differences in time taken to dispense following randomization. This third party will instruct the participant to avoid discussing the dosing frequency, or packaging of the IMP with the Investigator.
- To minimize the risk of potential bias, the unblinded study site personnel who are responsible for reconstituting and/or administering study drug will not be permitted to conduct any safety or efficacy evaluations. Each center will identify an individual (eg, pharmacist) responsible for IMP administration procedures. This individual will

prepare the IMP for each participant prior to administration. An individual not involved with evaluating the participant must be identified to administer the IMP.

- In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.
- All participants will wear an eye sleep mask during IMP administration to minimize the risk of unblinding.
- The following individuals/groups will be blinded to treatment assignment throughout the study: participants, the designated evaluating physician(s) and study nurses, the central image readers, and the Sponsor and Sponsor's agents. The following are exceptions to the blinding: IWRS service provider, unblinded study site personnel, and bioanalytical laboratory personnel. To minimize risk of potential bias arising from access to laboratory results that could potentially unblind treatment assignments (eg, free IgE levels), access to these results will be restricted to the site and the Sponsor until study completion. Treatment assignment may be unblinded to the personnel analyzing the data from the intervention period when all data through Week 24 are in the database and the data have been cleaned and verified.

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 IMP assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's IMP assignment unless this could delay emergency treatment of the participant. If a participant's IMP 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 from IMP administration.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE for the purpose of expedited regulatory reporting (see Section 8.3.2). Sponsor staff involved in the conduct of the study will remain blinded to the participant intervention assignment.

6.4 STUDY INTERVENTION COMPLIANCE

- When participants are dosed at the site, they will receive IMP directly from the unblinded site personnel. The date and time of each dose administered at the site will be recorded in the source documents and recorded in the eCRF.
- Measures taken to ensure and document intervention compliance and accountability include:

- Proper recording of intervention kit number as required on appropriate eCRF page for accounting purposes.
- The unblinded site personnel tracks intervention accountability/compliance, by counting the number of used intervention kits and fills in the appropriate page (Intervention Log Form).
- The Investigator or his/her delegate records the dosing information on the appropriate page(s) of the eCRF (record kit number and injection site).
- The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and intervention log forms.

6.5 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 Sponsor Representative should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Prohibited medications

The following concomitant treatments are not permitted during the screening, run-in, and the randomized intervention periods:

- 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; and nasal spray using Exhalation Delivery System such as Xhance.
- Long term courses (>2 weeks) of SCS. Systemic corticosteroids can only be used to treat severe asthma exacerbation and are not allowed to be used for other conditions from 1 month or at least 5 half-lives prior to Visit 1, whichever is longer, or during the screening and run-in period or the randomized intervention period.
- Short term courses (≤2 weeks) of SCS (oral or parenteral) are prohibited only between Visit 1 and Visit 2 and they are allowed as rescue treatment after Visit 2.
- Live, attenuated vaccines. Examples include, but are not limited to Bacillus Calmette-Guérin (BCG), chickenpox (varicella), FluMist-influenza, intranasal influenza, 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), and yellow fever.

- Bronchial thermoplasty.
- IVIG therapy.
- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with dose stabled 1 month prior to Visit 1).
- Use of asthma relievers other than salbutamol/albuterol or levosalbutamol/levalbuterol is not recommended during the study period. In case of use in exceptional circumstances (eg, prescribed by a physician not participating in the study), it will be documented in the participant's file and reported in the eCRF.
- Other investigational drugs.
- Other mAbs (biological immunomodulators), including but not limited to anti-IL-5 and anti- tumor necrosis factor, etc.
- During the screening period, the following treatments for chronic rhinosinusitis (CRS) are not allowed: antifungals, and antibiotics.

Participants who receive any of the prohibited treatments, or are treated with systemic (oral, IV, or IM) corticosteroids, or undergo surgery between Visit 1 and Visit 2 will not be randomized. However, they may be rescreened following the procedures described in the protocol.

6.5.2 Permitted concomitant medication

The following treatments are allowed:

- MFNS during the run-in period and throughout the whole study.
- Intranasal normal saline.
- Single topical decongestants administration (eg, oxymetazoline hydrochloride to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic (eg, lidocaine are allowed before endoscopy).
- Administration of antibiotics for a concurrent infection is allowed during the study except during screening period (reason for and duration of treatment should be documented in the eCRF).
- Short-acting beta-2 agonists (SABA), LABA, and long-acting muscarinic antagonists (LAMA). Nebulizer solutions maybe used as an alternative delivery method.
- Methylxanthines (eg, theophylline, aminophylline).
- ICS.
- 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 and dose stable for 1 month prior to Visit 1 is permitted.
- SCS (to treat severe asthma exacerbation or in case of CRSwNP worsening).

6.5.3 Rescue medicine for CRSwNP

The following rescue medications may be used:

1. Nasal lavage with saline and/or systemic antibiotics (up to 2 weeks in case of acute infection).
2. Short course SCS (prednisone or prednisolone up to 2 weeks).
3. Sino-nasal surgery for NP.

Participants receiving rescue treatment other than surgery during the study should continue on study drug unless the Investigator decides to withdraw the study intervention. Before starting treatment with SCS, participants should come to the study site for the clinical assessments including endoscopy and PROs.

For participants who undergo or are planned for surgery for NP, the Investigator may decide to continue the IMP up to the time of surgery or end of treatment (EOT), whichever comes first. At the time of surgery participants will be permanently discontinued from the IMP and assessed as soon as possible using the procedures scheduled for the EOT visit.

6.5.3.1 Rescue medications for asthma

Short-acting beta-2 agonists (SABA) may be used as rescue medication during the study if needed. Nebulizer solutions maybe used as an alternative delivery method. Systemic corticosteroids are also allowed after Visit 2 to treat severe exacerbations.

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the participants in a diary/peak expiratory flow meter. Each participant should be reminded that salbutamol/albuterol or levosalbutamol/levalbuterol should be used only as needed for symptoms, not on a regular basis or prophylactically.

6.6 DOSE MODIFICATION

No dose modification is allowed during the conduct of the study. Omalizumab should be discontinued in participants who experience a severe hypersensitivity reaction.

6.7 INTERVENTION AFTER THE END OF THE STUDY

Sponsor will not be responsible for intervention after the EOS. Intervention after the EOS will be at the discretion of Investigator or treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for efficacy and safety. See the SoA (Section 1.3) 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.

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets the condition outlined in the algorithm "increase of alanine aminotransferase (ALT)" (Appendix 6, Section 10.6) or if the Investigator believes that it is in best interest of the participant.

Regular monitoring of liver function is not required in this study since no safety concerns with respect to hepatobiliary disorders have been identified with dupilumab/omalizumab treatment. (Appendix 6, Section 10.6) provides adequate guidance on the management of elevated ALT, in a proactive manner in order to support participating investigators should any events be reported during routine clinical care.

Participants must be permanently withdrawn from the IMP for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative is considered to be 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 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.
- If the participant misses 2 consecutive IMP doses.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- If the randomization code is broken at the request of the Investigator.
- Pregnancy.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Section 10.10).
- Diagnosis of a malignancy during the study, excluding carcinoma in situ of the cervix, or 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 10.11).

- Serum ALT >3 × upper limit of normal (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).

If a clinically significant finding is identified after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Handling of participants after definitive intervention discontinuation

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.

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

For participants who discontinue the study intervention prematurely (prior to completing the 24-week intervention period), the early study discontinuation (ESD) visit will be performed as soon as possible with all the assessments scheduled for the EOT visit, to assure a complete clinical assessment in close temporal proximity to the premature termination of study intervention is available.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure scheduled for the last dosing day with the IMP.

Under exceptional circumstances when a participant cannot come to the site for a scheduled visit, a phone contact can be made. During the phone contact, at least information about AEs, concomitant medication, and the status of CRSwNP should be collected.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 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: Contingency Measures for a regional or national emergency that is declared by a governmental agency, Section 10.9). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary intervention discontinuation decided by the Investigator corresponds to at least 1 dose not administered to the participant. Following a temporary interruption or missed dose, the treatment should be reinitiated at the next scheduled administration, maintaining the planned dose.

If 2 consecutive IMP doses have been missed, the study intervention will be definitively discontinued (see Section 7.1.1). Investigator must contact the participant to instruct not to take any subsequent injection.

7.1.2.1 Rechallenge

Reinitiation 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 in the occurrence of the concerned 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: Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.9).

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, compliance, or administrative 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 (Section 1.3) 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 participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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, and the Investigator must document this in the site study records.

- All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF 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 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 site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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.
- If a participant continues to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Patient-reported outcome questionnaires should be completed by the participants before the consultation and/or clinical tests in a quiet place (at home in electronic PRO/electronic device [eDevice] and at study site). The questionnaires should be completed by the participants themselves, independently from their physician, the study nurse, or any other medical personnel, and without any help from friends or relatives. Participants will be instructed on the use of the eDevice and eDiary. During the study, the PROs should be completed by the participant in the electronic PRO device before seeing the physician, electronic PRO will be completed by participant in the following order for the visits during Intervention Period: CRSwNP Morning Diary, NPIF Morning Diary (completed by participant at home or after visit, between 04:00 in the morning and 12:30 in the afternoon); SNOT-22, Rhinosinusitis VAS, PGI-Control, PGI-Change, WPAI, ACQ-7, AQLQ, EuroQol-5 dimensions 5 Level (EQ-5D-5L) (when participant at site), ADSD evening questionnaire (completed by participant at home daily between V1 and V2 and 30 days before the next confirmed visit, between 05:00 in the afternoon and before 11:59 in the evening).
- The total volume of blood required for all assessments as per protocol is expected to be within the recommended safe limit for human in clinical trials by the local Institutional Review Boards (IRBs) and Ethics Committees.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9: Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.9).

8.1 EFFICACY ASSESSMENTS

8.1.1 Nasal polyp score

The NPS (54, 55) is assessed by central video recordings of nasal endoscopy. The score (NPS) is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. The NP is graded based on polyp size described in Table 3.

Table 3 - 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 after all other efficacy assessments have been completed and before the administration of IMP. It must be preceded by local administration of anesthetic drugs in combination with a decongestant.

Standard video sequences will be downloaded and 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 Visit 2, only the Visit 1 central reading will be made available to the site. In addition, at Visit 2 the Investigator will perform the nasal endoscopy to confirm eligibility score. Thus, the participant is considered eligible based on a Visit 1 central reading followed by a Visit 2 local reading NPS score of 5 or more and at least 2 each side. The final results of central reading from Visit 2 onward will be made available to the site after the EOS.

Nasal endoscopy can be repeated once per time point (for quality or safety issues). Nasal endoscopy can be repeated once during screening (at the latest 1 week before randomization) in case of not meeting eligibility criteria as per the Investigator discretion.

For the analysis of primary endpoint, central reading of Visit 2 will be used for comparison with Week 24 reading. The sites will remove participant-identifying information from the imaging data header prior to sending the imaging data to the central reader.

Nasal endoscopy will be performed at the time points specified in the SoA (see Section 1.3).

8.1.2 University of Pennsylvania Smell Identification Test (UPSIT)

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

The test consists of 4 booklets, each containing 10 odorants with 1 odorant per page. The test-time is about 15 minutes. The stimuli are embedded in 10 to 50 (mu) diameter plastic microcapsules on brown strips at the bottom of each page. Above each odorant strip is a multiple choice question with 4 alternative words to describe the odor. The participant will be asked to release the odorant

by rubbing the brown-strip with the tip of a pencil and to indicate which of 4 words best describes the odor. Thus, each participant receives a score out of 40 possible correct answers. The final score will be recorded in the eCRF. The odorants of the UPSIT test utilized in this study will consider the cultural differences.

The 40-odorant UPSIT is used in over 1500 clinics and laboratories throughout the US, Canada, South America, and Europe, and has been administered to nearly 200 000 people since its development in the early 1980s. A particular strength of this test is that it provides an olfactory diagnosis based on comparing the participant test score with normative data, providing a percentile score of an individual relative to his or her age-matched normal group. Furthermore, a clinician can distinguish participants with a normal sense of smell ("normosmia") from those with different levels of reduction ("mild, moderate, and severe microsmia") or loss ("anosmia") (56).

The Investigator will administer, score, and complete the UPSIT at the time points specified in the SoA (see Section 1.3).

8.1.3 Nasal Peak Inspiratory Flow (NPIF)

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

At Visit 1 participants will be issued an NPIF meter for recording morning (AM) NPIF. Participants will be instructed on the use of the device, and written instructions on the use of the NPIF meter will be provided to the participants. In addition, the Investigator will instruct the participants on how to record the following variables in the eDiary.

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

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

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

The nasal flow is expressed in liter per minute, and consecutive measurements are performed.

Taking the best of 3 outcomes with less than 10% variation is considered to be the best means of expression of the result (56).

Participants will record the NPIF values in the eDiary at the time points specified in the SoA (see Section 1.3).

8.1.4 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS)/European Respiratory Society (ERS) (57) recommendations will be used. Spirometry should be performed in accordance with these recommendations.

Spirometry will be performed before IMP administration and after withholding the standard of care asthma treatment as described in Table 4. Forced expiratory volume in 1 second, FVC, and FEF at 25% to 75% of forced vital capacity (FEF 25-75) will be determined at the designated treatment visits.

Table 4 - Washout period of asthma controllers and rescue medication before lung function assessments

Drug/Medication name	Washout period
Oral Xanthine derivatives	72 hours
Long-acting beta agonists (LABA) (eg, salmeterol)	24 hours
Long-acting muscarinic antagonist (LAMA) (eg, Tiotropium)	48 hours
Inhaled corticosteroids (ICS)/LABA	24 hours
Ultralong ICS/LABA combinations	48 hours
Inhaled and/or nebulized short-acting beta-2 agonists (SABAs) (eg, salbutamol)	6 hours
Inhaled and/or nebulized short-acting muscarinic antagonist (SAMA) (eg, ipratropium)	8 hours
SABA/SAMA combination	8 hours
Inhaled and/or nebulized corticosteroids	12 hours

At all specified visits (as per SoA, Section 1.3), spirometry should be performed before IMP administration, in the morning, if possible. The spirometer provided by the service provider should be used and standard spirometric techniques, including calibration, will be used to perform spirometry at all specified visits and, whenever possible, the same person should perform the measurements. Afternoon/evening is allowable in the exceptional circumstance when morning spirometry cannot be performed. Spirometry should be done at approximately the same time at each specified visit (as per SoA [Section 1.3]) throughout the study.

Pulmonary function tests will be measured in the sitting position if possible. If the testing was made with the participant in another position, this should be noted in the spirometry report. For any participant, the position should be consistent throughout the study.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at each specified visit. The acceptability criteria must be applied before the repeatability criteria.

Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a participant fails to provide repeatable maneuvers, an explanation should be recorded in the eCRF.

At least 2 acceptable curves must be obtained.

The largest FEV1 should be recorded after the data from all of the acceptable curves have been examined, even if they do not come from the same curve.

The spirometer must be calibrated following the principles of the ATS/ERS guidelines prior to spirometry. The calibration records should be kept in a reviewable log. It is preferred that the equipment that is used to calibrate the spirometer (ie, 3 L syringe) be subjected to a validated calibration according to the manufacturer's specifications.

8.1.5 Severe asthma exacerbation

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

- Use of SCS for ≥3 days; or
- Hospitalization or emergency room visit because of asthma, requiring SCS.

8.1.6 Patient-reported outcome (PRO) questionnaires

8.1.6.1 CRSwNP nasal symptom diary including nasal congestion/obstruction, loss of smell, and total symptom score

The Nasal Symptom Diary is designed to assess the severity of CRS nasal symptoms on a daily basis. These symptoms include NC/obstruction, loss of smell, anterior rhinorrhea, and posterior rhinorrhea (2). Each of the individual items of the diary are scored from 0 ("No symptoms") to 3 ("Severe symptoms - symptoms that are hard to tolerate, cause interference with activities, or daily living"). Higher scores on the items of the individual symptoms denote greater symptom severity (see Table 5).

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

Table 5 - Nasal symptom score

Response scale	Response choices
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 psychometric properties of NC as an individual item, including validity, reliability and ability to detect changes have been demonstrated in adult participants 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.

The electronic PRO collected in an eDevice is used for daily recording of participant's answers to the questionnaires. This eDevice will be dispensed at Visit 1 (screening visit), including instructions for use. Participants will be instructed on the use of the eDevice. Recorded information will be downloaded from this device daily. At EOT visit, the eDevice will be downloaded and returned to the site. On a regular basis, the site staff should review on the vendor's website the information downloaded from participants' eDevice. They should particularly check status of the disease reviewing as well as compliance to background/rescue therapy and overall electronic PRO compliance. The site should follow-up with the participant as appropriate.

The CRSwNP Nasal Symptom Diary will be administered electronically. Participants will complete the Nasal Symptom Diary at the time points specified in the SoA (Section 1.3).

8.1.6.2 Sino-Nasal Outcome Test-22-Items (SNOT-22)

The SNOT-22 is a PRO questionnaire designed to assess the impact of CRS on patients' HRQoL (58). The SNOT-22 has 22 items covering symptoms, social/emotional impact, productivity, and sleep consequences of CRS. The recall period is past 2 weeks. Each item is rated on a 6-point Likert scale response option, ranging from 0 ('No problem') to 5 ('Problem as bad as it can be'). A global score ranging from 0 to 110 is calculated by summing the responses to all items; higher score indicates greater rhinosinusitis-related health burden. The questionnaire is an easy, valid, and reliable tool. The minimally important difference that is the smallest change in SNOT-22 score that can be detected by a participant was found to be 8.9 points (58). The SNOT-22 is categorized into 5 domains, these include: Nasal (Items 1, 2, 3, 4, 5, 6, 7, and 12); Ear/Facial (Items 8, 9, 10, and 11); Sleep (Items 13, 14, 15, and 16); Function (Items 17, 18, and 19); Emotion (Items 20, 21, and 22). The score of each domain is the sum of response to each question in that domain.

Participants will complete the SNOT-22 at the time points specified in the SoA (Section 1.3).

8.1.6.3 Rhinosinusitis Severity Visual Analogue Scale (rhinosinusitis VAS)

The rhinosinusitis severity VAS is used to evaluate the overall severity of the rhinosinusitis. It is a recommended scale to determine the patient's disease severity and to guide the treatment for CRS. The participant is asked to answer the following question: "How troublesome are your symptoms of your rhinosinusitis" on a 10 cm VAS from 0 ('not troublesome') to 10 ('worst thinkable troublesome'). Based on their score on the VAS, the severity of rhinosinusitis can be divided into 3 categories as follows:

- Mild = VAS 0 to 3
- Moderate = VAS >3 to 7

- Severe = VAS >7 to 10

Participants will complete the rhinosinusitis severity VAS at the time points specified in the SoA (Section 1.3).

8.1.6.4 Asthma Daytime Symptom Diary (ADSD)

The ADSD is a PRO measure developed by the PRO Consortium' Asthma Working Group. Both instruments have been designed to measure asthma symptoms in adult and adolescent (12 years of age and older) patients diagnosed with mild to severe asthma. The ADSD assesses asthma severity based on patient self-report of asthma core symptoms, ie, difficulty breathing; wheezing; shortness of breath; chest tightness; chest pain; and cough. Participants are asked to complete the ADSD every night before they go to bed, thinking about their asthma symptoms today, from when they got up this morning until now.

It has demonstrated adequate evidence of content validity and cross-sectional measurement properties in asthma patients (ie, internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of asthma. It is composed of 6 items rated using an 11-point numeric rating scale that ranges from 0 = None to 10 = As bad as you can imagine.

Participants will record their daytime asthma symptoms in an eDiary, once in the evening.

Participants will complete the ADSD at the time points specified in the SoA (see Section 1.3).

8.1.6.5 Work Productivity and Activity Impairment Questionnaire: Chronic Rhinosinusitis Version 2.0

The WPAI Questionnaire is designed to assess the impact of a disease on patient's productivity (59). The WPAI is a 6-item, validated questionnaire to measure impairments in work and activities over a 7-day recall period, and yields 4 types of scores:

1. Absenteeism (work time missed)
2. Presenteeism (impairment at work/reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment/absenteeism plus presenteeism)
4. Activity Impairment.

The WPAI Specific Health Problem version 2.0 will be used; the term "Problem" in the questions will be replaced by chronic rhinosinusitis (WPAI-chronic rhinosinusitis).

The WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Participants will complete the WPAI-chronic rhinosinusitis in an eDiary at the time points specified in the SoA (see Section 1.3).

8.1.6.6 Asthma Control Questionnaire 7-item version (ACQ-7)

The ACQ was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment (60).

The ACQ-7 has 7 questions, with the first 5 items assessing the most common asthma symptoms:

1. Frequency in past week awoken by asthma during the night
2. Severity of asthma symptoms in the morning
3. Limitation of daily activities due to asthma
4. Shortness of breath due to asthma
5. Frequency of wheezing

Plus short-acting bronchodilator use and FEV1 (pre-bronchodilator use, % and % predicted use).

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

Clinic staff score of the FEV1% predicted is also on a 7-point scale.

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

Participants will complete the ACQ-7 at the time points specified in the SoA (see Section 1.3).

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

At screening visit, ACQ-5 scores (sum of the responses to the first 5 questions) will be derived from ACQ-7.

8.1.6.7 Asthma quality of life questionnaire with standardized activities (self-administered)

Asthma Quality of Life Questionnaire with Standardized Activities Self-Administered (AQLQ[S]) - was designed as a self-administered participant reported outcome to measure the functional impairments that are most troublesome to adolescents ≥12 years of age and adults as a result of their asthma.

The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains.

The domains and the number of items in each domain are as follows:

- Symptoms (12 items)
- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental Stimuli (4 items)

A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life. The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (participant interviews), and sensitive to change. The MCID for AQLQ(S) is 0.5 (61).

Participants will complete the AQLQ(S) at the time points specified in the SoA (see Section 1.3).

8.1.6.8 Cumulative number of health-care resource utilization (HCRU)

A questionnaire about health-care resource utilization (HCRU) and productivity (missed workdays) will be collected by the Investigator for all participants at the time points specified in the SoA (see Section 1.3) through eCRF.

8.1.6.9 EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Questionnaire (EQ-5D)

The 5-level version of EQ-5D is a standardized PRO to provide a simple, generic measure of health for clinical and economic appraisal.

The EQ-5D consists of 2 parts: the descriptive system and the EQ VAS. The EuroQol-5 Dimensions-5 Levels descriptive system is comprised of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). These dimensions have 5 levels of perceived problems: “no problem”, “slight problems”, “moderate problems”, “severe problems” and “extreme problems ” (62). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions.

The EQ VAS records the respondent’s self-rated health on a vertical, VAS which ranges from “best imaginable health state (100)” to “worst imaginable health state (0)”. This provides a simple measure of general health status, and in which a change of ≥8 points is considered clinically important (63), and the scores can also be compared with population norm scores which ranges from 70.4 to 83.3 (64).

8.1.6.10 Patient Global Impression of Control and Change in CRSwNP

The PGI-Control is a 1-item questionnaire that asks participants to provide the overall self-assessment of their CRSwNP control on a 5-point scale during the past 7 days. Response options range from 1=“Not controlled at all” to 5=“completely controlled”.

The PGI-Change is a 1-item questionnaire that asks the participant to provide the overall self-assessment of change in their CRSwNP on a 7-point scale compared to just before the participant started taking the study intervention. The response choices range from 1="Very Much Improved" to 7="Very Much Worse"

8.1.6.11 Investigator Global Assessment (Severity, Control, Change) in CRSwNP

The Investigator Global Assessments are 1-item questionnaires that asks the Investigator to assess the current a) severity (IGA-Severity) and b) control (IGA-Control) of the patient's CRSwNP. The scales range from 1 (no disease) to 4 (severe), and 1 (Not controlled at all) to 5 (completely controlled), respectively.

The Investigator Global Assessment of Change (IGA-Change) of CRSwNP is a 1-item questionnaire that asks the Investigator to provide the overall assessment of change in the patient's CRSwNP on a 7-point scale compared to just before the initiation of the study intervention. The scale ranges from 1 (very much improved) to 7 (very much worse).

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the skin, nasal cavities, eyes and ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Height and weight will also be measured and recorded. Height (cm) will be only measured at baseline. Weight (kg) will be measured at the time points specified in the SoA (Section 1.3).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- Body temperature (degrees Celsius), heart rate (beats per minute), respiratory rate (breaths per minute), and blood pressure (mmHg) will be assessed.
- Blood pressure and pulse measurements will be assessed 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) 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 on the eCRF.

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained locally as outlined in the SoA (see Section 1.3) for screening purpose.

8.2.4 Clinical safety laboratory assessments

- 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 laboratory tests, pregnancy, and other screening tests will be performed by the local laboratories according to routine clinical practice at site and country level. Considering this, any leftover blood sample will not be used for any other research purposes related to the study (re-analyses) or for future exploratory use (secondary use).
- A central laboratory will be used to assess the serum total IgE levels and eosinophils.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, 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 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such 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 notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments 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 or dose modification), then the results must be recorded in the eCRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events 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 (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3).

All SAEs and adverse event of special interest (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 AE or SAE 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

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading 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 AEs, SAEs, and AESIs (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 a 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, IRBs/Independent Ethics Committees (IECs), and Investigators.

- Adverse events that are considered expected will be specified in the reference safety information (Investigator's Brochure for dupilumab and Summary of Product Characteristics).
- Suspected unexpected serious adverse reactions (SUSARs) are reported 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 a 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 Investigator's Brochure 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 and female partners of male participants will be collected after the start of study intervention and until the outcome has been determined.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- In the event of pregnancy in a female participant, the IMP should be permanently discontinued.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner 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. While the Investigator is not obligated to actively seek this information in former study participants /pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention.

8.3.6 Adverse event of special interest

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

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described in Section 10.3 even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the eCRF. Adverse event of special interests for this study include:

- Anaphylactic reactions (Appendix 10 [Section 10.10])
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in the study with IMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial will be qualified as an SAE only if it fulfills one of the seriousness criteria.
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Significant ALT elevation
  - ALT >5 × ULN in participants with baseline ALT ≤2 × ULN;

    OR
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- 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 verbatim and symptoms, if any, entered on separate AE forms.

- An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the 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.

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator/unblinded site personnel 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.

8.4 TREATMENT OF OVERDOSE

Overdose is an AESI (defined in Section 8.3.6) in this study. No antidote is available for dupilumab or omalizumab. The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Provide symptomatic care.
2. Contact the medical monitor immediately.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities until dupilumab or omalizumab can no longer be detected systemically.
4. Obtain a plasma sample for PK analysis as soon as possible if requested by the medical monitor (determined on a case-by-case basis).
5. Document appropriately in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

Pharmacokinetic parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

Whole blood biomarkers: Blood eosinophil count, IgE counts and allergan-specific IgE will be measured at the time points mentioned in the SoA (Section 1.3).

Fractional exhaled nitric oxide levels: FeNO test should be conducted prior to spirometry and following a fasting of ≥1 hour. Further details on the procedure for measuring FeNO will be provided in a separate instruction manual. Fractional exhaled nitric oxide levels will be measured at the time points mentioned in the SoA (Section 1.3).

8.9 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed.

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

The WPAI-chronic rhinosinusitis and the HCRU questionnaires are described in Section 8.1.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The null statistical hypothesis is there is no treatment difference between dupilumab and omalizumab for both primary endpoints. The alternative statistical hypothesis for the 2 primary endpoints is that dupilumab 300 mg Q2W is superior to omalizumab on at least one of the 2 primary endpoints.

Assuming that the resulting 2-sided p-values for the 2 primary endpoints, ordered from lower to higher, are p1 and p2, the alternative hypothesis will be considered to have been met if either of the condition is met:

- $p1 \leq p2 \leq 0.05$ and both endpoints are in favor of dupilumab, or,
- $p1 \leq 0.025$ and is in favor of dupilumab irrespective of the value of p2.

The alternative statistical hypothesis for each of the secondary efficacy endpoints is also that dupilumab 300 mg Q2W is superior to omalizumab. A multiplicity control procedure will be provided in SAP to test the multiple hypotheses to control the familywise Type I error rate at two-sided 0.05 level.

9.2 SAMPLE SIZE DETERMINATION

[redacted]

Considering the multiplicity testing procedure described above, this sample size will provide [redacted]

The original sample size of 422 was estimated to power the key secondary endpoint, change from baseline in pre-BD FEV1 at Week 24, at [redacted]. By downgrading this endpoint to an exploratory endpoint and with a minimum total sample size of 320 participants (160 participants per arm), the estimated power for NPS and UPSIT are about [redacted].

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 6):

Table 6 - Populations for analyses

Population	Description
Screened	All participants who sign the informed consent form
Randomized	Randomized participants consist of all participants with a treatment kit number allocated and recorded in the Interactive Web Response System (IWRS) database, regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered as randomized and will not be included in any efficacy population. Data from these participants will be summarized separately.
Intent-to-treat (ITT)	The analysis population for the efficacy endpoints will be the ITT population: all randomized participants will be included in the ITT population and analyzed according to the treatment group allocated by randomization.
Safety (As-treated)	All randomized participants who take at least 1 dose of study intervention will be the safety population. Participants will be analyzed according to the intervention they actually received.

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be developed and finalized prior to the database lock 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 key secondary endpoints.

9.4.1 General considerations

A multiplicity control procedure and the whole list of secondary endpoints to be tested in the hierarchical order will be specified in the SAP.

The baseline value is generally defined as the last available value before randomization. For endpoints collected on the daily basis in the screening period, baseline value is defined as the average of the scores in the 7 days prior to randomization. If fewer than 4 measurements are collected during the 7 days, the average of the most recent 4 prior to randomization during the screening period will serve as the baseline.

All efficacy analyses will be performed on the intent-to-treat (ITT) population, unless otherwise noted. All safety analyses will be performed on the safety population.

9.4.2 Primary endpoints

The 2 primary endpoints are change from baseline in NPS and UPSIT at Week 24 assessed for dupilumab 300 mg Q2W versus omalizumab. The primary estimand for the 2 primary endpoints is the hypothetical/treatment policy strategy as described below.

Table 7 - Summary of primary estimand for the primary endpoints

Endpoint Category (estimand)	Estimands			
	Endpoints	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary objectives: To evaluate the efficacy of dupilumab compared to omalizumab in reducing the polyp size and improving sense of smell				
2 primary endpoints (treatment policy /hypothetical strategy)	Change from baseline to Week 24 in nasal polyp score (NPS) Change from baseline to Week 24 in University of Pennsylvania Smell Identification Test (UPSIT)	Intent-to-treat (ITT) population	The intercurrent events will be handled as follows: • Undergoing surgery for NP or receiving systemic corticosteroids (SCS) for any reason prior to Week 24: data after surgery or SCS use will be set to missing, and the worst postbaseline value on or before the time of surgery or SCS use will be used to impute missing values (for participants whose postbaseline values are all missing, the baseline will be used to impute hypothetical strategy) • Discontinuing the study intervention due to coronavirus disease 2019 (COVID-19) pandemic: off-study intervention data will be set to missing (hypothetical strategy) • Discontinuing the study intervention not due to COVID-19 pandemic: all data collected after treatment discontinuation will be used in the analysis (treatment policy strategy). 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/SCS use on or before Week 24.	Analysis of Covariance (ANCOVA) model with treatment group, stratification factors, and corresponding baseline measurement as covariates is used. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule.

Each of the 2 primary endpoints will be analyzed using a hybrid method of the WOCF and the MI. For participants discontinuing the study intervention before Week 24 not due to the COVID-19 pandemic, off-study intervention efficacy assessments measured up to Week 24 will

be included in this analysis. In contrast, for any participants discontinuing the study intervention due to the COVID-19 pandemic, off-study intervention data will be set to missing.

For participants who undergo surgery for NP or receive SCS for any reason during the study, data collected postsurgery or post SCS will be set to missing, and the worst postbaseline value on or before the time of surgery or SCS intake will be used to impute missing Week 24 value (for participants whose post baseline values are all missing, the baseline will be used to impute). For participants who discontinue without being rescued by surgery or receiving SCS, an MI approach will be used to impute missing Week 24 value. This MI will use all participants who have not been rescued by surgery or receiving SCS by Week 24. The data collected after treatment discontinuation will be included in the analysis. Each of the imputed complete data will be analyzed by fitting an ANCOVA model with corresponding baseline value, treatment group, and stratification factors as the covariates. Statistical inference on treatment comparisons for the 2 primary endpoints at Week 24 will be derived from the ANCOVA model. Descriptive statistics including number of participants, mean, standard deviation, and LS means will be provided. In addition, difference in LS means and the corresponding 95% CIs will be provided along with the p-values.

The sensitivity analysis for the 2 primary endpoints may be performed, and details will be provided in the SAP.

9.4.3 Secondary endpoints

Differences will be assessed between dupilumab and omalizumab in the following secondary efficacy endpoints, and the list of the selected secondary endpoints to be tested in the hierarchy will be provided in SAP. In addition, the primary estimand and details about the intercurrent events strategy and missing data handling will be presented in SAP as well:

Key secondary endpoints:

- Change from baseline to Week 24 in the loss of smell score of the CRSwNP Nasal Symptom Diary.
- Change from baseline to Week 24 in the NC score of the CRSwNP Nasal Symptom Diary.

Secondary endpoints:

- Change from baseline to Week 24 in TSS derived from the CRSwNP Nasal Symptom Diary.
- Change from baseline to Week 24 in SNOT-22 total score.
- Change from baseline to Week 24 in SNOT-22 nasal domain score.
- Change from baseline to Week 24 in NPIF.
- Change from baseline to Week 24 in rhinosinusitis VAS.

The change from baseline in the above continuous endpoints to Week 24 will be analyzed using the hybrid method of the WOCF and the MI with ANCOVA model in the same fashion as for the 2 primary endpoints.

The frequency of TEAE, SAE, and AESI will be used to evaluate the safety of dupilumab and omalizumab.

9.4.4 Tertiary/exploratory endpoints

Analysis of exploratory endpoints will be described in the SAP which will be finalized before database lock. No formal testing will be performed.

9.4.5 Other safety analyses

All safety analyses will be performed on the safety population. The summary of safety results will be presented by treatment group.

Analyses of Adverse Events

Treatment-emergent adverse event frequency tables will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) (sorted by internationally agreed order), MedDRA high level group term (HLGT)and preferred term (PT), the number (n) and percentage (%) of participants experiencing an AE. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages is the safety population within each treatment group. Proportion of participants with at least one TEAE, serious TEAE, TEAE leading to death, and TEAE leading to permanent treatment discontinuation will be tabulated by treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the study drug. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

The frequency of the AESIs and other AE groupings will be tabulated by treatment group. The AESIs and other AE groupings definitions and the method to identify them will be specified in the SAP.

Analyses of laboratory and vital signs parameters

Results and change from baseline for the laboratory and vital signs parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of participants, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

9.4.6 Other analyses

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

9.5 INTERIM ANALYSES

Not applicable.

9.6 DATA MONITORING COMMITTEE (DMC)

No DMC is planned for this study.

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-GCP Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - [GDPR])
- The protocol, protocol amendments, ICF, Investigator Brochure, 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.
- 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 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 health-care 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (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 to the participant or his/her legally authorized representative and answer all questions regarding 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, Health Insurance Portability and Accountability Act (HIPAA) requirements, 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples or new extra samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory 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. A separate consent will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate consent.

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

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (General Data Protection Regulation).

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 these data are required by regulatory agencies (eg, on afro American population for the Food and Drug Administration or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- 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, when applicable, 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 local data protection law. 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.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data are intended to be used for the whole drug development program from collection to reimbursement.
- Personal data of professionals will be retained by Sanofi for up to twenty-five (25) years, unless further retention is required by applicable regulations. 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 - 46 avenue de la Grande Armee-75017-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

There will be no study committees.

10.1.6 Dissemination of clinical study data and results

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

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, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months, respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

In addition, results from clinical trials in patients 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 vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. 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: vivli.org.

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on the eCRF 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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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)
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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.
- 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: source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory reports, notes, memoranda, pharmacy dispensing records, recorded data from automated instruments etc. Data downloaded from the local laboratories, pharmacy dispensing records, spirometry, ECG, patient diaries, electronic PROs/eDevice will be considered source data.

10.1.9 Study and site start and closure

The first act of recruitment is the first participant screened and will be the study start date.

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 subject and should assure appropriate subject 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 laboratory tests detailed in Table 8 will be performed by the local laboratories except the serum total IgE level and eosinophils that will be done in a central laboratory.
- The result of each laboratory test must be entered into the eCRF.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing (serum at screening visit and then urine or serum as required by the local regulations) should be conducted as mentioned in the SoA (Section 1.3).
- Pregnancy testing 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 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.

Table 8 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Eosinophils
Biomarker	Serum total IgE levels
Other screening tests	• Highly sensitive serum hCG pregnancy test (as needed for WOCBP)[a] at screening visit (urine or serum pregnancy test as required by the local regulations at other time points) • Serology[b]: HBs Ag, HBs Ab, total HBc Ab, HCV Ab; HIV screen (Anti-HIV-1 and HIV-2 antibodies) • Tuberculosis test[c] • All study-required laboratory assessments will be performed by the local laboratories, with an exception of serum total IgE levels and eosinophils.

HBc Ab: hepatitis B core antibody; HBs Ab: hepatitis B surface antibody; HBs Ag: hepatitis B surface antigen; HBV: hepatitis B virus; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HCV Ab: hepatitis C virus antibodies; HIV: human immunodeficiency virus; IgE: immunoglobulin E; IEC: Independent Ethics Committee; IRB: Institutional Review Board; WOCBP: women of childbearing potential
NOTES:

a After screening local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

b In case of results showing HBs Ag (negative), HBs Ab (negative) and HBc Ab (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the Investigator believes the participant is a false positive, or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the participant is a false positive.

c Tuberculosis testing will be performed on a country-by-country basis according to the routine clinical practice and the local guidelines if required by the regulatory authorities or ethics committees or if TB is suspected by the investigator.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results (IgE levels) that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 APPENDIX 3: ADVERSE EVENTS: 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 AE is an AE 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 events, 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 home dosing diary.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) 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.
- Protocol defined asthma exacerbation events are collected as efficacy endpoints via the "Asthma Exacerbation Events" form. These events should not be reported as AEs unless they fulfill a seriousness criterion.
- New conditions 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.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

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 detained (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 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) which 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 in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 in the CRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.

- 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 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- 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 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's representative. 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's representative**.**

- The Investigator may change his/her opinion of causality in light of follow-up information and send a 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's representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- 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) in order 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 off-line 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 off-line, 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 protocol.

SAE reporting to Sponsor via paper CRF

- Facsimile transmission of the SAE paper CRF 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 CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the protocol.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 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), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
     - 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.

CONTRACEPTION GUIDANCE:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below Table 9.

Table 9 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the women of child bearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
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.*

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies to male participants who receive study intervention (dupilumab or omalizumab).
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
  The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

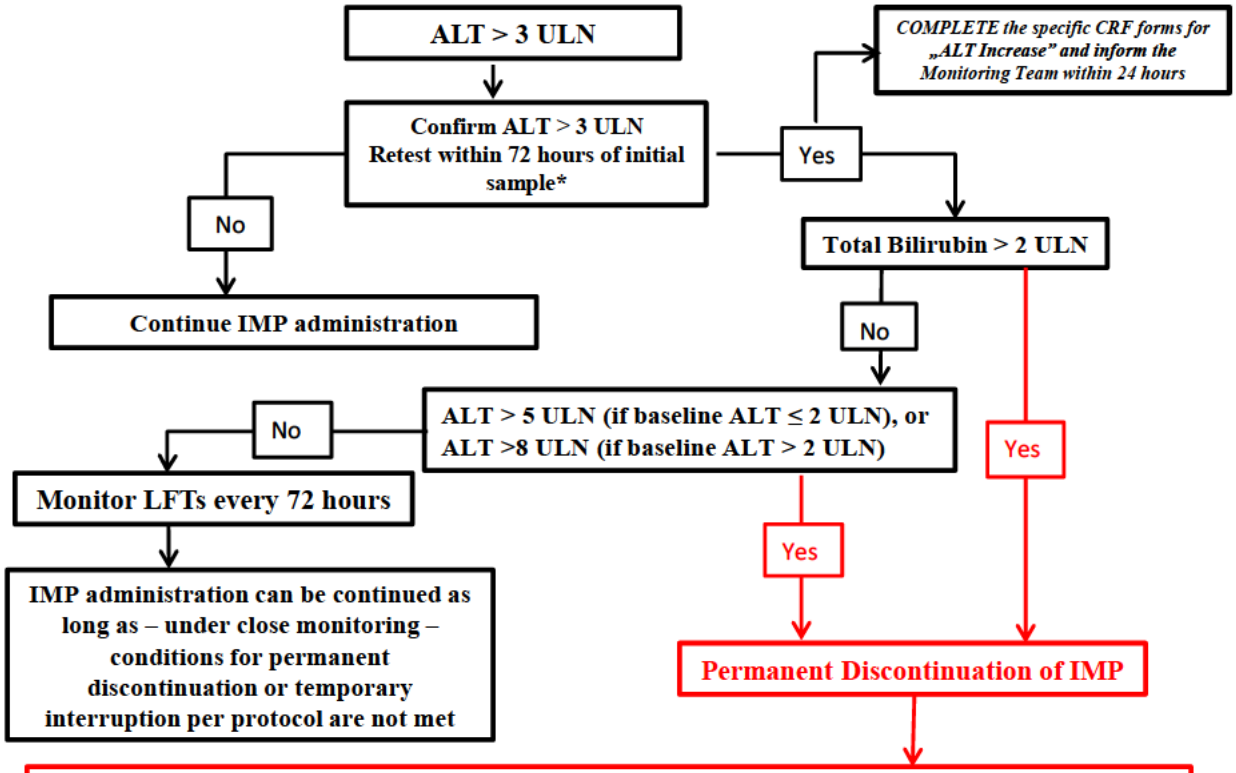
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant 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. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- 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.

10.5 APPENDIX 5: GENETICS

Not applicable.

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

INCREASE IN ALT



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

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

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

Note:

"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 10.3 for guidance on safety reporting.

Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.8 APPENDIX 8: OMALIZUMAB DOSING TABLE

Figure 2 - Omalizumab dosing table

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Bodyweight							
		>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	> 125-150 kg
		Dose (mg)							
30 - 100	Every 4 Weeks	75	150	150	150	150	150	300	300
>100 - 200		150	300	300	300	300	300	450	600
>200 - 300		225	300	300	450	450	450	600	375
>300 - 400		300	450	450	450	600	600	450	525
>400 - 500		450	450	600	600	375	375	525	600
>500 - 600		450	600	600	375	450	450	600	
>600 - 700		450	600	375	450	450	525		
>700 - 800	Every 2 Weeks	300	375	450	450	525	600		
>800 - 900		300	375	450	525	600			
>900 - 1000		375	450	525	600				
>1000 - 1100		375	450	600					
>1100 - 1200		450	525	600					
>1200 - 1300		450	525						
>1300 - 1500		525	600						

Insufficient Data to Recommend a Dose

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

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

For European countries contingency measures are currently only applicable for the COVID-19 pandemic.

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, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below and in Sections 5.5, 6.1, 7.1.2, 7.1.2.1, 8.0, 9.4.6, and 10.1.3 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.

Section 5.5: CRITERIA FOR TEMPORARILY DELAYING SCREENING/RANDOMIZATION

Temporary delay of screening/randomization may be considered by the sponsor, in case of any public health emergency, and the site is unable to adequately follow protocol mandated procedures, in order to ensure participants' safety. Implementation of such mechanisms may differ country-by-country, depending on the country-specific regulations and local business continuity plans.

Section 6.1: STUDY INTERVENTION(S) ADMINISTERED

If on-site visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the administration of IMP where allowed by local regulations, local label, and approved by the participant.

Section 7.1.2: 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.

Temporary intervention discontinuation decided by the Investigator corresponds to at least 1 dose not administered to the participant. Following a temporary interruption or missed dose, the treatment should be reinitiated at the next scheduled administration, maintaining the planned dose.

If 2 consecutive IMP doses have been missed, the study intervention will be definitively discontinued (see Section 7.1.1). Investigator must contact the participant to instruct not to take any subsequent injection.

Section 7.1.2.1: RECHALLENGE

During a regional or national emergency declared by a governmental agency, reinitiation of IMP can only occur once the Investigator has determined, according to his/her best judgment, that the contribution of the IMPs to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

Section 8: STUDY ASSESSMENTS AND PROCEDURES

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

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

- If on-site visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the administration of IMP and collection of possible safety data, PROs, and participants' diary.
- If on-site 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 and phone call visits may be scheduled for collection of safety data.
- Implementation of above mechanisms may differ country-by-country, depending on the country-specific regulations and local business continuity plans. Additionally, no waivers to deviate from protocol enrollment criteria due to any regional or national emergency (or public health emergency) will be granted.
- All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to regional or national emergency (or public health emergency) and will remain in effect only for the duration of the public health emergency.

Section 9.4.6: OTHER ANALYSES

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.

Section 10.1.3: INFORMED CONSENT PROCESS

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).

10.10 APPENDIX 10: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death" (65).

Clinical criteria for diagnosing anaphylaxis

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

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

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

10.11 APPENDIX 11: LIST OF OPPORTUNISTIC INFECTION

- 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 candidiasis
- 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
- Non-TB mycobacteria
- Pneumocystis pneumonia

This list is indicative and not exhaustive.

10.12 APPENDIX 12: DIAGNOSISOF NERD IN CRSWNP PATIENTS (± diagnosed asthma)

QUESTION 1 - ***Have you ever had respiratory, nasal and/or bronchial, symptoms following the intake of aspirin or/and non-steroidal anti-inflammatory drugs (NSAID)?***

- **NO, I usually take aspirin or NSAID drugs** → the patient has not NERD.
- **NO, I don't take aspirin or NSAID drugs** → the patient unlikely has NERD but cannot be totally ruled out.
- **YES, only to one drug** → the patient likely has NERD. However, a potential IgE-mediated allergy to a specific NSAID should be further investigated
- **YES, to 2 or more drugs** → the patient most likely has NERD.

QUESTION 2 - ***While having a positive clinical history of NERD, have you ever undergone an aspirin provocation test, either nasal, bronchial, or oral?***

- **NO** → conclusion can be only obtained from clinical history.
- **YES, negative** → the patient unlikely has NERD but cannot be totally ruled out.
- **YES, positive** → confirms the patient has NERD.

DIAGNOSIS OF NERD:

- **Conditional**: only based on clinical history (question 1)
- **Strong**: based in both clinical history and provocation test (questions 1 and 2).

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10.13 APPENDIX 13: ABBREVIATIONS

ACQ-5:	Asthma Control Questionnaire-5 item
ACQ-7:	Asthma Control Questionnaire-7 item
AD:	atopic dermatitis
ADR:	adverse drug reaction
ADSD:	Asthma Daytime Symptom Diary
AE:	adverse event
AERD:	aspirin-exacerbated respiratory disease

AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AQLQ:	Asthma Quality of Life Questionnaire
AQLQ(S):	Asthma Quality of Life Questionnaire with Standardized Activities
ATS:	American Thoracic Society
BID:	twice a day
CFR:	Code of Federal Regulations
CI:	confidence interval
COPD:	chronic obstructive pulmonary disease
COVID-19:	Coronavirus Disease 2019
CRF:	case report form
CRS:	chronic rhinosinusitis
CRSwNP:	chronic rhinosinusitis with nasal polyps
CSU:	chronic spontaneous urticaria
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
eDevice:	electronic device
EE:	Eastern European
EoE:	eosinophilic esophagitis
EOS:	end of study
EOT:	end of treatment
EQ VAS:	EuroQol Visual Analogue Scale
EQ-5D-5L:	EuroQol-5 Dimensions 5 Level
ERS:	European Respiratory Society
EU:	European Union
FEF:	forced expiratory flow
FeNO:	fractional exhaled nitric oxide
FESS:	functional endoscopic sinus surgery
FEV1:	forced expiratory volume in 1 second
FSH:	follicle stimulating hormone
FVC:	forced vital capacity
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
H2H:	head-to-head
HBc Ab:	hepatitis B core antibody
HBs Ab:	hepatitis B surface antibody
HBs Ag:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCRU:	health-care resource utilization
HCV:	hepatitis C virus
HCV Ab:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
HLGT:	high level group term
HRQoL:	health related quality of life
HRT:	hormonal replacement therapy

ICF:	informed consent form
ICH:	International Council for Harmonisation
ICS:	inhaled corticosteroids
IEC:	Independent Ethics Committees
IGA-Change:	Investigator Global Assessment of Change
IGA-Control:	Investigator Global Assessment of Control
IGA-Severity:	Investigator Global Assessment of Severity
IgE:	Immunoglobulin E
IL:	interleukin
IM:	intramuscular
IMP:	investigational medicinal product
INCS:	intranasal corticosteroid sprays
IRB:	Institutional Review Board
IRT:	Interactive Response Technology
ITT:	intent-to-treat
IV:	intravenous
IVIG:	intravenous immunoglobulin
IWRS:	Interactive Web Response System
LABA:	long-acting beta-2 adrenergic receptor
LS:	least squares
LTRA:	leukotriene receptor antagonists
mAb:	monoclonal antibody
MCID:	minimal clinically important difference
MedDRA:	Medical Dictionary for Regulatory Activities
MFNS:	mometasone furoate nasal spray
MI:	multiple imputation
NC:	nasal congestion
NIMP:	noninvestigational medicinal product
NPIF:	Nasal Peak Inspiratory Flow
NPS:	nasal polyp score
NSAID-ERD:	Non-Steroidal Anti-Inflammatory Drug Exacerbated Respiratory Disease
PGI-Change:	Patient Global Impression of Change
PGI-Control:	Patient Global Impression of Control
PK:	pharmacokinetic
PN:	prurigo nodularis
PRO:	patient-reported outcome
Q2W:	every 2 weeks
Q4W:	every 4 weeks
QD:	once daily
ROW:	rest of the world
SABA:	short-acting beta-2 agonists
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SCS:	systemic corticosteroids
SNOT-22:	Sino-Nasal Outcome Test-22

SoA:	Schedule of Activities
SUSAR:	suspected unexpected serious adverse reaction
TB:	tuberculosis
TEAE:	treatment emergent adverse event
Th2:	T-helper Type 2 cell
TSS:	total symptom score
ULN:	upper limit of normal
UPSIT:	University of Pennsylvania Smell Identification Test
US:	United States
VAS:	Visual Analogue Scale
WOCBP:	woman of childbearing potential
WOCF:	worst observation carried forward
WPAI:	Work Productivity and Activity Impairment Questionnaire

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

Amended protocol 02 (13 December 2022)

This amended protocol (amendment 02) is considered to be non-substantial based on the criteria set forth in Article 2(2)(13) of the Regulation No 536/2014 of the European Parliament and the Council of the European Union [because it does not significantly impact the safety or rights of the participants and/or the reliability and robustness of the data generated in the clinical trial].

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to provide more flexibility in the trial eligibility assessments.

Additionally, minor clarifications and updates have been implemented across the document.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2.2 Background	Text is updated to reflect mepolizumab is approved for treatment of CRSwNP.	Text is updated to reflect current status of mepolizumab.
Section 1.1 Synopsis Section 4.1 Overall design	Study duration is updated to 38 weeks.	To ensure consistency within protocol sections.
Section 1.1 Synopsis Section 4.1 Overall design Section 6.3 Measures to minimize bias: randomization and blinding	Following text is deleted No more than 50% participants should be on low ICS dose, and no more than 35% participants should be from EE countries.	This information is simply deleted from protocol as it is part of IWRS specification.
Section 1.1 Synopsis	Intranasal corticosteroid background therapy is clarified.	To clarify that prior to the study entry, equivalent INCS could be used,

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Study intervention(s) administered		whereas during the study only mometasone can be used.
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities (SOA) Section 4.1 Overall design Section 6.1 Study intervention(s) administered	Screening/run-in period is changed from 4 weeks±1 week to 28±3 days.	To ensure consistency within protocol sections.
Section 1.3 Schedule of Activities (SOA)	Following changes are done to the study procedures Spirometry (pre-bronchodilator FEV1, FVC, FEF 25% to 75%) is removed from Screening/run-in period and footnote "g" is updated to remove instruction regarding eligibility based on spirometry. Timepoint for Nasal Peak Inspiratory Flow and CRSwNP nasal symptom diary collection is clarified. Collection timepoint for Asthma Daytime/ Symptom Diary is clarified. Footnote "h", "i", "k" and "m" are updated.	These changes are made to provide further guidance on study procedures and allow more flexibility in eligibility criteria.
Section 10.2 Appendix 2 clinical laboratory tests Table 8	Table 8 updated to reflect changes done in SOA Footnote "i"	
Section 2 Introduction	Approved treatment indications for dupilumab are added.	To provide upto date information.
Section 2.3 Benefit/Risk assessment	The section is updated with latest data.	
Section 5.1 Inclusion criteria	The eligibility criteria 02 is updated to clarify that eligibility is based on Visit 1 endoscopic bilateral NPS central reading followed by a Visit 2 local reading.	To ensure consistency with Section 8.1.1.
Section 5.1 Inclusion criteria Section 5.2 Exclusion criteria	The eligibility criteria 03 is updated. The eligibility criteria 16 is updated.	To facilitate participant recruitment.
Section 5.1 Inclusion criteria Section 5.2 Exclusion criteria	The eligibility criteria 04 is removed. The eligibility criteria 14 is updated.	To provide more flexibility in the trial eligibility assessments.
Section 5.2 Exclusion criteria	The eligibility criteria 07 is updated.	To provide guidance on TB testing.
Section 5.2 Exclusion criteria	The eligibility criteria 19 and 20 have been modified to avoid overlapping between them and to clarify wash out periods.	To ensure consistency with other Dupilumab studies.
Section 5.4 Screen failures	Rescreening procedure added.	To facilitate participant recruitment.
Section 6.5.1 Prohibited medications	The term "severe" is added for use of systemic corticosteroids to treat asthma exacerbation. Text is updated to clarify that short term courses	To ensure consistency within protocol sections.

Section # and Name	Description of Change	Brief Rationale
	of SCS is not limited to use as rescue treatment for asthma exacerbation.	
Section 6.5.2 Permitted concomitant medication Section 6.5.3.1 Rescue medications for asthma	Text is updated to specify that antibiotics are allowed to treat infection irrespective of causality to CRS exacerbations except during screening period. The term “Short courses” from short courses of systemic corticosteroids is removed.	To ensure consistency between allowed and prohibited medications sections.
Section 7.1.1 Definitive discontinuation	Following reason for permanent discontinuation of IMP is removed • If the participant is treated with the specific prohibited medications mentioned in Section 6.5.1. Study completion date and early discontinuation visit are replaced by EOT and ESD visit, respectively for handling of participants after definitive intervention discontinuation.	To ensure consistency with other Dupilumab Phase 4 studies.
Section 8 Study assessments and procedures Section 8.1.1 Nasal Polyp score	Reference to study reference manual is deleted.	Study reference manual is not available.
Section 8 Study assessments and procedures	The order of electronic PRO at the visits during the Intervention Period is updated.	To ensure consistency with eCOA set up.
Section 8.1.1 Nasal Polyp score	The text is updated to allow retesting of nasal endoscopy once during screening in case of not meeting eligibility criteria as per the Investigator discretion.	To facilitate participant recruitment.
Section 8.1.4 Spirometry	The information regarding recording result of FEV1 (% of predicted normal), FVC, and FEF 25-75 in eCRF is deleted.	To ensure consistency with the centralized spirometry data collection procedure.
Section 8.1.4 Spirometry	This section is updated as per removal of inclusion criteria 4.	To ensure consistency within protocol sections.
Section 8.1.6.2 Sino-Nasal Outcome Test-22 Items (SNOT-22)	The text is updated for the domain score calculation.	To ensure consistency with SAP.
Section 9.1 Statistical hypotheses Section 9.4.2 Primary endpoints	The criterion for alternative hypothesis is updated. Intercurrent event(s) handling for study intervention discontinuation due to COVID-19 is added.	To have a more accurate description.
Section 9.1 Statistical hypotheses	Reference to multiplicity control procedure in SAP is added	To clarify that the multiplicity control strategy will be specified in SAP.
Section 9.3 Populations for analyses Table 6	Definition for Safety (as-treated) population updated to include randomized.	To have a more accurate description of the populations.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.1 General considerations	Criteria for meeting primary endpoints is deleted.	To remove the duplicate information from Section 9.1.
Appendix 3 Section 10.3.1 Definition of AE	Following statement added Protocol defined asthma exacerbation events are collected as efficacy endpoints via the "Asthma Exacerbation Events" form". These events should not be reported as AEs unless they fulfill a seriousness criterion.	To clarify that asthma exacerbation is not an AE.
Throughout the text	Following sections are updated Section 6.3-Measures to minimize bias: Randomization and Blinding Section 8.3.5- Pregnancy Appendix 1 Section 10.1.4-Data protection Appendix 1 Section 10.1.6-Dissemination of clinical study data and results Appendix 1 Section 10.1.9-Study and site start and closure Appendix 9-Contingency Measures for a regional or national emergency that is declared by a governmental agency Appendix 3 Section 10.3.1- Definition of AE unsolicited and solicited AE added Following sections are deleted as they are not applicable Section 8.3.6- Cardiovascular and death events Section 8.3.7- Disease related events and/or disease-related outcomes not qualifying as AEs or SAEs	To follow recent template instructions.
Throughout the text	Minor grammatical, editorial, and/or administrative changes.	To improve the readability and/or clarity of the protocol.

Amended protocol 01 (10 June 2021)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study].

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to fulfill the condition raised by agencies from EU member states participating to VHP.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion criteria	Additional wording on EC 10 to exclude patients with infections receiving symptomatic treatment. E 10: Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antifungals **or receiving only symptomatic treatment (e.g influenza or COVID 19)** within 2 weeks before Visit 1(screening visit) or during the screening and run-in period.	To provide clarification on EC 10 as per Regulatory Agency request

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