NCT04998604

Sanofi-Aventis Recherche & Développement

Dupilumab (SAR231893) - LPS16747

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

15OCT2024

Statistical Analysis Plan

Final Version 1.0

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List of Abbreviations

ACQ-7	Asthma Control Questionnaire-7 Item
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
ATC	Anatomical Therapeutic Chemical
BD	Bronchodilator
BID	Twice a Day
BMI	Body Mass Index
CI	Confidence Interval
CRS	Chronic Rhinosinusitis
CS	Compound Symmetry
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EE	Eastern Europe
EQ VAS	EuroQol Visual Analogue Scale
FEF	Forced Expiratory Flow
FeNO	Fractional exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
HCRU	Health-care Resource Utilization
HLT	High Level Term
HLGT	High Level Group Term
HR	Heart Rate
HRQoL	Health Related Quality of Life
IAD	Internal Airflow Distribution
IcEv	Intercurrent Event
ICS	Inhaled Corticosteroids
IGA-Change	Investigator Global Assessment of Change
IGA-Control	Investigator Global Assessment of Control
IGA-Severity	Investigator Global Assessment of Severity
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IM	Intramuscular
IMP	Investigational Medicinal Product
INCS	Intranasal Corticosteroid Sprays
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IV	Intravenous
iV/Q	Image-based ventilation/perfusion
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-Acting Beta Agonists

LLT	Lowest Level Term
LTRA	Leukotriene Receptor Antagonists
LS	Least Square
MAR	Missing At Random
MCID	Minimal Clinically Important Difference
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MFNS	Mometasone Furoate Nasal Spray
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
NC	Nasal Congestion
NIMP	Non-Investigational Medicinal Product
NP	Nasal Polyp
NPIF	Nasal Peak Inspiratory Flow
NPS	Nasal Polyp Score
PGI-Change	Patient Global Impression of Change
PGI-Control	Patient Global Impression of Control
PCSA	Potentially Clinically Significant Abnormalities
ppb	Parts Per Billion
PRO	Patient-Reported Outcomes
PT	Preferred Term
Q1	First Quartile
Q2W	Every 2 Weeks
Q3	Third Quartile
QoL	Quality of Life
QD	Once Daily
ROW	Rest of World
SABA	Short-Acting Beta Agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCS	Systemic Corticosteroids
SD	Standard Deviation
SE	Standard Error
SNOT-22	Sino-Nasal Outcome Test-22
SoA	Schedule of Activites
SOC	System Organ Class
ROW	Rest of the World
TEAE	Treatment-Emergent Adverse Events
TLFs	Tables, Listings, Figures
TSS	Total Symptom Score
TOEP	Homogeneous Toeplitz
TOEPH	Heterogeneous Toeplitz
ULN	Upper Limit of Normal
UN	Unstructured
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
VAS	Visual Analogue Scale
WHO-DD	World Health Organization-Drug Dictionary

WOCF	Worst Observation Carried Forward
WPAI	Work Productivity and Activity Impairment Questionnaire

Document History – Changes compared to previous version of SAP

Version	Date	Changes

1. Introduction

This document provides the detailed statistical methodology for the analysis of data from Sanofi-Aventis Recherche & Développement study LPS16747. The table, listing and figure shells supporting the statistical analysis plan (SAP) can be found in a separate SAP shell document.

The analyses described herein are based on the Amended Clinical Trial protocol, Version 3.0, dated 14th May 2024. Any changes or revisions to the planned analysis described in this document will be made prior to database lock.

2. Study Objectives, Endpoints and Estimands

The study objectives and corresponding endpoints are shown in the Table 2-1. The summary of estimands for main objectives are shown in Table 2-2.

Table 2-1 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

Objectives	Endpoints
• 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 Week24 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] • 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

Objectives	Endpoints
• To evaluate the efficacy of dupilumab on improving health status at Weeks 24 compared to omalizumab	• [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]

Objectives	Endpoints
• [redacted]	• [redacted]
• [redacted]	• [redacted]
	• [redacted]
	• [redacted]
	• [redacted]

Table 2-2 Summary of estimands for main objectives

Endpoint Category (estimand)	**Estimands**			
	Endpoint(s)[a]	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: 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)	ITT	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 post-baseline value on or before the time of surgery or SCS use will be used to impute missing values (for participants whose post-baseline values are all missing, the baseline will be used to impute. Hypothetical strategy). • Discontinuation of study intervention due to COVID-19 pandemic [b] (IcEv1), off-study intervention data will be set as missing (hypothetical strategy). • Discontinuation of study intervention not due to COVID-19 pandemic (IcEv2), all data collected following schedule after the study intervention discontinuation will be used in the analysis (treatment policy strategy).	Analysis of Covariance (ANCOVA) model with treatment group, stratification factors, and corresponding baseline measurement as covariates. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule. For missing data, a multiple imputation approach will be used to impute missing Week 24 values, and this multiple imputation will use all participants excluding those who have undergone surgery/SCS use on or before Week 24.

Endpoint Category (estimand)	Estimands			
	Endpoint(s)[a]	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
	Change from baseline to Week 24 in University of Pennsylvania Smell Identification Test (UPSIT)	ITT	Same as above	Same as above
Secondary objective: To evaluate the efficacy of dupilumab in CRSwNP symptoms and lung function at Week 24 compared to omalizumab				
Secondary endpoints	Change from baseline to Week 24 in the loss of smell score, the NC score, and TSS of the CRSwNP Nasal Symptom Diary	ITT	Same as the primary endpoint	The same ANCOVA as for the primary estimand (primary objective), with the baseline values corresponding to the outcome variables

a Select secondary endpoints that are not included in this table will be handled with a similar analysis according to the endpoint type (ie, continuous, binary, time-to-event) but without formal testing (ie, nominal p-value provided for descriptive purpose only). The other secondary or tertiary/exploratory endpoints are listed in Section 8.2.

b The COVID-19 pandemic is unexpected and will eventually be over. The objective of the present study is to evaluate the treatment effect in absence of the pandemic and therefore the data collected after study intervention discontinuation due to pandemic will be set to missing.

3. Investigational Plan

3.1. Overall Study Design and Plan

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 patients with severe CRSwNP and comorbid asthma.

Approximately 422 participants (211 per group) will be randomized in a 1:1 ratio to receive either dupilumab or omalizumab. Randomization will be stratified by prior surgery (Yes/No), ICS doses (low versus medium/high dose ICS), presence of AERD (Yes/No) and region (Eastern Europe [EE] versus Rest of World [ROW]). No more than 50% participants should be on low ICS dose, and no more than 35% participants should be from EE countries. 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.

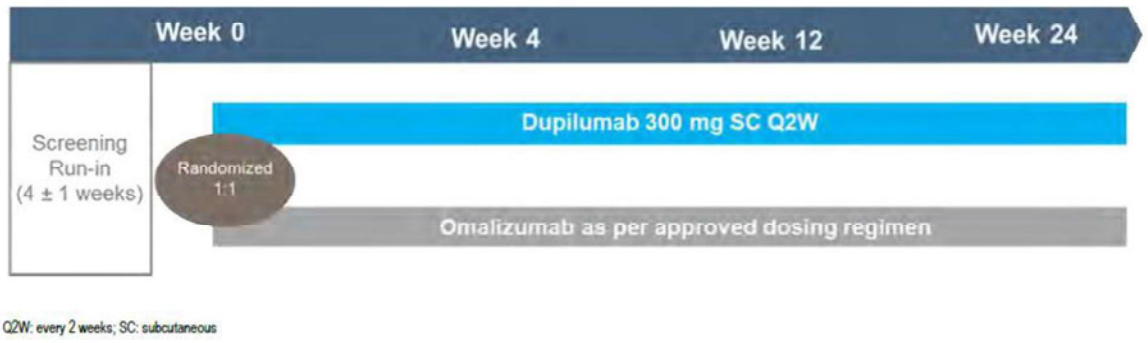
Study duration per participant will be 40 weeks.

The study will comprise 3 periods:

- Screening and run-in period (up to 4 weeks):
  - 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 4 weeks to determine participant's eligibility and for run-in/standardization of background INCS (mometasone furoate nasal spray [MFNS]) prior to randomization. All participants will receive MFNS, 2 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 (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) $\geqslant$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, intravenous [IV], intramuscular [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 stable doses of asthma background therapy.
- Follow-up period: up to 12 weeks after the last IMP dose 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).

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.

Figure 3-1 Study plan



The study analysis will be conducted in two steps. A primary database lock will be performed when all randomized participants will have completed the Week 24 visit or will have discontinued the study. The database will be updated at the end of the study for all participants to include the post-treatment follow-up information and updates for the events previously ongoing at the time of the primary lock. The CSR will include analyses from both the primary database lock and the final database lock.

3.2. Study Endpoints

The study objectives and corresponding endpoints are shown in the Table 2-1.

3.3. Study Interventions

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 3-1 Overview of study interventions administered

ARM name	Dupilumab	Omalizumab	Placebo of Dupilumab
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

ARM name	Dupilumab	Omalizumab	Placebo of Dupilumab
Dosage level(s)	One injection of 300 mg Q2W	75 to 600 mg Q2W/Q4W according to the dosing table	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 patient kit box. Both glass prefilled syringe and box will be labeled as required per country requirement	Each dose of omalizumab will be supplied as 1 prefilled syringe packed in a patient 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 patient kit box. Both glass prefilled syringe and box will be labeled as required per country requirement
Current name(s) or alias(es)	Dupixent	Xolair	Not applicable

IMP: investigational medicinal product; NIMP: non-investigational 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

Non-investigational medical products (NIMP)

- Intranasal corticosteroid background therapy

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

- 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 4 weeks 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.
- 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 end of study, 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 end of study, or modify the treatment based on medical judgment.

3.4. Dose Adjustment/Modifications

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

4. General Statistical Considerations

4.1. Sample Size

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 conditions 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 at the 2-sided 5% alpha level.

[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]

4.2. Randomization, Stratification, and Blinding

Randomization will be stratified by prior surgery, ICS doses (low versus medium/high dose ICS), presence of AERD and region (EE versus ROW). No more than 50% participants should be on low ICS dose, and no more than 35% participants should be from EE countries.

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 Interactive Response Technology [IRT]). A participant cannot be randomized more than once in the study.

4.3. Analysis Set

Participants exposed to Investigational Medicinal Product (IMP) before or without being randomized will not be considered randomized, will not be included in any analysis set and will be reported in listings under a study intervention group named “not randomized but treated”. However, if these participants experienced any safety event, they would be documented separately in the Clinical Study Report (CSR).

Participants randomized but not treated will be included in all efficacy analyses. These participants will be analyzed for efficacy analyses according to the study intervention group to which they are allocated by the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

4.3.1. Screened Analysis Set

The Screened analysis set includes all participants who sign the Informed Consent Form (ICF).

4.3.2. Intent-to-Treat (ITT) Analysis Set

The Intent-to-Treat (ITT) analysis set consists of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not). Participants in the ITT analysis set will be analyzed according to the study intervention group allocated by randomization. This analysis population will be applied to all efficacy analyses.

4.3.3. Safety Analysis Set

The Safety analysis set includes all randomized participants who received at least 1 dose of IMP. Participants will be analyzed according to the study intervention they actually received. Randomized participants for whom it is unclear whether the study medication was taken will be included in the safety analysis set as randomized. For participants receiving more than one IMP during the study (ie, omalizumab and dupilumab), the actual study intervention group will be based on the first study intervention received.

4.4. Reporting Conventions

Statistical analysis will be performed using SAS® Version 9.4 or higher.

Standardized and validated SAS macros will be used to set-up table, listing, figure (TLF) formats (headers/footers and tabulation format) and tabulate the summaries. All tables and listings will be independently validated using double programming; all figures will be independently validated manually.

4.4.1. Study Intervention Labels

The following study intervention labels will be used in the TLFs:

Table 4-1 Study intervention labels

Study intervention order	Study intervention group	Study intervention label
1	Omalizumab 150/75 mg	Omalizumab 75 to 600 mg q2w/q4w
2	Dupilumab 300 mg q2w	Dupilumab 300 mg q2w
3*	Total	Total

*Total column will only be presented for disposition, demographics, prior medication, medical/disease history, and baseline characteristics tables.

4.4.2. Visit Naming Conventions

The electronic Case Report Form (eCRF) visit label will be used to classify the assessments.

4.4.3. Visit Windows

The visit windows as defined in Section 15.5 will be applied to all endpoints.

4.4.4. Unscheduled Visits

Unscheduled visit measurements will be used in the analysis on efficacy variables and will be included in the by visit summaries for the safety variables if they are re-allocated to scheduled visits according to the visit window definitions in Section 15.5.

4.4.5. Display of Data Summary and Analysis

Continuous variables will be summarized using descriptive statistics, including the following: number of participants (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum for each study intervention group.

All mean, Q1, Q3 and median values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value. Minimum and maximum will be formatted to the same number of decimal places as the measured value.

95% confidence intervals (CI) will be two-sided and displayed to the same level of precision as the statistic they relate to. If an estimate or a CI is not estimable, it will be presented as ‘NE’. If neither an estimate, nor its CI are estimable, it will be presented as simply ‘NE’, not displaying ‘NE’ twice.

The p-values will be two-sided and will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as ‘<0.001’. If a p-value is greater than 0.999 it will be reported as ‘>0.999’.

Categorical and ordinal data will be summarized using the counts and percentages. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. The percentages on the other rows will be based on the number of non-missing observations for demographics, and baseline characteristics. Unless otherwise specified, the denominator for all other percentages will be the number of participants in that study intervention within the specific analysis set of interest. All percentages will be rounded to one decimal place. The number and percentage of responses

will be presented in the form xx (xx.x), where the percentage is in the parentheses. When the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0), unless otherwise specified.

All listings will be sorted for presentation in order of assigned study intervention arm, study center number, participant number and date of procedure or event.

4.4.6. Baseline, Study Day, and Duration Derivations

For assessments to be completed daily during the screening period (ie, CRSwNP nasal symptom diary, NPIF, and ADSD), the baseline value will be calculated by averaging the data collected/recorded from Day -6 to Day 1 (for ADSD: from Day -7 to Day -1). If less than 4 measurements are available between Day -6 and Day 1 (for ADSD: between Day -7 and Day -1), the most recent 4 measurements will be used for the calculation; if finally, less than 4 measurements are available, it will be considered as missing.

For all other efficacy parameters, the baseline value is generally defined as the last available valid (non-missing) value up to and including the day of first administration of IMP. For participants randomized but not treated, the baseline value is defined as the last available value up to and including the day of randomization.

For all safety parameters, the baseline value is generally defined as the last available valid (non-missing) value up to and including the date of first dose of IMP.

If multiple valid values of a variable (efficacy or safety) exist within a same day (and the recorded times of measurement do not enable to identify which of them is the last assessment), the value measured during the scheduled visit will be used as Baseline in the analysis. If none of those values were assessed during a scheduled visit, then all these measurements will be used for the analysis and the average will be calculated to derive the baseline value.

Baseline safety and efficacy results are presented in the safety and efficacy analyses.

The safety reference date (denoted as Day 1) for the calculation of study day of safety assessments will be the date of first dose of IMP.

- For visit prior to the date of first dose of IMP, study day = assessment date – first dose of IMP.
- For visit at or after the date of first dose of IMP, study day = assessment date – first dose of IMP + 1.

The efficacy reference date (denoted as Day 1) for the calculation of study day of efficacy assessments will also be the date of the first administration of IMP (except for participants randomized but not exposed).

- For visit prior to the first administration of IMP, study day = assessment date – the first administration of IMP.
- For visit at or after the first administration of IMP, study day = assessment date – the first administration of IMP + 1.

Note: For participants randomized but not treated, the efficacy reference date will be the randomization date.

Intervals that are listed and/or tabulated in weeks will be transformed from days to weeks by using (without rounding) the following conversion formula:
WEEKS = DAYS /7

Intervals that are listed and/or tabulated in months will be transformed from days to months by using (without rounding) the following conversion formula:
MONTHS = DAYS /30.4375

4.4.7. Change from Baseline and Percent Change from Baseline

Change from baseline is defined as:

$$\text{Change from baseline} = \text{Value at specific time point} - \text{Baseline value}$$

Percent change from baseline is defined as:

$$\text{Percent change from baseline}(\%) = \frac{\text{Value at specific timepoint} - \text{Baseline value}}{\text{Baseline value}} \times 100\%$$

4.5. Intercurrent Event Types

Table 4-2 specifies the types of Intercurrent events, and associated labels, used to define the estimands (Table 2-2).

Table 4-2 Intercurrent event types

Label	Intercurrent Event Type
NP Surgery or receiving SCS	Undergoing surgery for NP or receiving systemic corticosteroids (SCS) for any reason prior to Week 24
IcEv1 (discontinuation of study intervention due to COVID-19)	Premature study intervention discontinuation due to COVID-19 pandemic before Week 24
IcEv2 (discontinuation of study intervention not due to COVID-19)	Premature study intervention discontinuation not due to COVID-19 pandemic before Week 24

5. Participant Disposition

5.1. Disposition

The participant disposition will be summarized for the ITT analysis set by study intervention group and overall using number and percentage. This section describes participant disposition for both participant study status and the participant analysis sets.

For participant study status, the number and percentage of participants in the following categories will be presented:

- Screened participants
- Screen failure participants
- Participants treated without being randomized
- Randomized participants
- Randomized but not treated participants
- Randomized and treated participants
- Participants who have completed the study intervention period
- Participants who early discontinued the study intervention period and the main reason for study intervention discontinuation. Relationship with COVID-19 will be reported for “Adverse Event” and “Other” reasons
- Participants who completed the study

- Participants who early discontinued the study and the main reason for study discontinuation. Relationship with COVID-19 will be reported for "Other" reasons
- Participants who discontinued the study before Week 24
- Participants who discontinued the study after Week 24 (ie, during post-study intervention follow-up period)
- Participants who had rescue medications for Asthma and/or CRSwNP during the study intervention period:
  - Participants who have completed the study intervention period and had rescue medications for Asthma
  - Participants who did not complete the study intervention period and had rescue medications for Asthma
  - Participants who have completed the study intervention period and had rescue treatment for CRSwNP
  - Participants who did not complete the study intervention period and had rescue medications for CRSwNP
- Final study status

For screened, screen failure, and participants treated without being randomized, percentages will be calculated using the number of screened participants as the denominator for overall only. All other categories of participants will be presented by randomized study intervention group and for overall whilst the percentages will be calculated using the number of randomized participants, within each study intervention group and overall, as denominator. Reasons for study intervention and study discontinuation will be supplied in the disposition table showing number and percentage by study intervention group.

A summary of all the analysis sets for safety and ITT will be summarized for the ITT analysis set by study intervention group and overall using number and percentage.

Participants with permanent study intervention and study discontinuation (early withdrawals) will be identified and described in separate listings (with the reason of discontinuation and the specification in case of other reason).

Additionally, trial impact (disruption) due to COVID-19 will be summarized for the ITT analysis set by study intervention group and overall using number and percentage. Participants for whom at least one of the following events occur during the study will be presented:

- Permanent end of study intervention due to COVID-19 pandemic
- Permanent end of study intervention due to AE related to COVID-19 infection
- Premature end of study due to COVID-19 pandemic
- Critical or major protocol deviation due to COVID-19 pandemic

Some safety (adverse events) analyses will also be repeated on the subgroup of safety participants according to trial impact (disruption) due to COVID-19 pandemic (see Section 9.1).

The disposition of screened participants by country and site will be summarized for the screened analysis set using number and percentage.

A summary table to show participant disposition by visit according to trial impact (disruption) due to COVID-19 pandemic (visit not done, visit partially done on site, visit partially done by phone and visit done but delayed) will be provided overall and by country for the ITT analysis set.

5.2. Protocol Deviations

All critical or major protocol deviations potentially impacting efficacy analyses (including randomization and drug-dispensing irregularities; see Table 5-1), and other major or critical deviations will be summarized overall and according to COVID-19 impact (ie, deviations related to COVID-19 pandemic) for the ITT analysis set by study intervention group using number and percentage.

A listing of participants with at least one critical or major protocol deviations will be provided with comprehensive information related to each deviation identified.

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible participant is randomized, b) a participant is randomized based on an incorrect stratum, c) a participant is randomized twice, or d) in a dynamic randomization scheme the study intervention assignment is, in fact, not random, due to a computer program error.

OR

2. A participant is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a participant at any time in the study is dispensed a different study intervention kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized participant is treated with IMP reserved for randomized participants.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the CSR. If the number of irregularities is large enough to make a tabular summary useful, the critical or major irregularities will be categorized and summarized for the ITT analysis set by study intervention group using number and percentage.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Table 5-1 Randomization and drug dispensing irregularities

Randomization and drug allocation irregularities
• Wrong randomization stratum • IMP kit number actually dispensed to the participant is different from the IMP kit number allocated

6. Demographics and Baseline Characteristics

The demographics, participant characteristics and baseline disease characteristics will be summarized using the ITT analysis set by study intervention group and overall using descriptive statistics or using number and percentage. P-values on the study intervention difference for the demographic and baseline characteristics data will not be calculated. In general, no specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety/efficacy analysis.

6.1. Demographics and Participant Characteristics

The following demographics and participant characteristics will be summarized by study intervention group and overall, for the ITT analysis set:

- Age (years)
- Age categories (≥18 to ≤64, ≥65 to ≤74, ≥75 to ≤84, ≥85 years)
- Gender (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Not Reported, Unknown)
- Baseline body weight (kg)
- Baseline body weight categories (<50, ≥50 to <100 and ≥100 kg)
- Baseline height (cm)
- Baseline body mass index (BMI) (kg/m²) derived as: (Weight in kg)/(Height in meters)²
- Baseline BMI categories (<30, ≥30 kg/m²)
- ICS Dose Level (Low, Medium/High)
- Region (EE, ROW)
- AERD (Yes, No)
- Previous Systemic Corticosteroids Therapy used in the past two years prior to V1 (Yes, No)
- Previous Systemic Corticosteroids Therapy use reason (CRSwNP, Asthma, Others)

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by study intervention group and overall, for the ITT analysis set.

6.2.1. CRSwNP Assessment at Baseline

- NPS
- UPSIT
- CRSwNP Nasal Symptom Diary*:
  - Loss of Smell Score
  - NC Score
  - TSS Score
- SNOT-22
  - Total Score
  - Nasal Domain Score
  - Sleep Domain Score
  - Function Domain Score
- NPIF*
- Rhinosinusitis VAS
- WPAI-CRSwNP scores
  - Percent work time missed
  - Percent impairment while working
  - Percent overall work impairment
  - Percent activity impairment
- PGI-Control
- IGA
  - Severity
  - Control

6.2.2. Asthma Assessment at Baseline

- Spirometry
  - Pre-BD FEV1 (L)
  - Pre-BD percent Predicted FEV1 (%)
  - Pre-BD FVC (L)
  - FEF 25% to 75% (L/s)
  - Percent Predicted FEF 25% to 75% (%)
- ACQ-5 score
- ACQ-7 score
- ADSD* score
- AQLQ score

* average value of the assessment reported during the week prior to first administration of IMP (or randomization for participants not exposed).

6.2.3. Generic Assessment at Baseline

- EQ VAS

6.2.4. Biomarker

- Blood Eosinophils Counts
- Blood Eosinophils counts (10^9/L) in class
  - $<0.3, \geq 0.3$
  - $<0.15, \geq 0.15$
- FeNO
- FeNO in class ($<25, \geq 25$ to $<50, \geq 50$ ppb)
- Total IgE

6.3. Tobacco Usage

The following smoking habits at screening will be summarized by study intervention group and overall:

- Tobacco consumption: status (never, current, former) and amount (cigarette) per day
- Electronic cigarette consumption: status (never, current, former) and amount (mg) per day

6.4. Medical History

6.4.1. General Medical History

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the participant.

Medical and surgical history will be coded to “lowest level term (LLT)”, “preferred term (PT)”, “high level term (HLT)”, “high level group term (HLGT)”, and associated primary “system organ class (SOC)” using the version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of each database lock.

The number and percentage of participants with any medical history will be summarized by study intervention group and overall and for each primary SOC, HLT and PT. SOC will be sorted by internationally agreed order of primary SOC, and HLT and PT will be sorted by alphabetical order. Participants experiencing asthma exacerbations will be further summarized using the LLT level as appropriate within medical history summaries.

Additionally, a separate table will present atopic comorbidities captured in the past and current medical conditions eCRF page by primary SOC, HLT and PT based on the ITT set.

6.4.2. Disease-Specific History

Chronic Rhinosinusitis History
The following CRS history will be summarized by study intervention group and overall, for the ITT analysis set. The number of participants with the specified disease history and the severity of the specified disease history at date of screening visit, 4 weeks ago, and 8 weeks ago (No Symptoms, Mild Symptoms, Moderate Symptoms, Severe Symptoms, and Unknown) will be presented:

- Chronic Rhinosinusitis
- Nasal Congestion
- Posterior Nasal Discharge
- Anterior Nasal Discharge
- Reduction of Smell

Asthma History
For Asthma history, the following information will be summarized by study intervention group and overall:

- Asthma (Yes, No)
- Age at asthma diagnosis (years)
- Age at asthma diagnosis categories (<18, ≥18 to <40, ≥40 years)
- Time since first diagnosis of asthma (years)
- Number of severe asthma exacerbation events within 1 year prior to the study entry
- Number of severe asthma exacerbation events within 1 year prior to the study (0, 1, 2, >2)
- Number of Severe asthma exacerbations that required hospitalization or urgent medical care visit
- Time since last severe asthma exacerbation (months)
- Number of asthma controller medications at study entry

Nasal Polyposis History
For nasal polyposis history, the following information will be summarized by study intervention group and overall:

- Time since first diagnosis of nasal polyposis (years)
- Age of onset of nasal polyposis (years)
- Previous surgery for nasal polyposis (Yes, No)
- Number of previous surgeries for nasal polyposis (0, 1, 2, ⩾3)
- Number of previous surgeries for nasal polyposis by type:
  - Nasal/sinus endoscopy, surgical, with 3 ethmoidectomy, total (anterior and posterior)
  - Nasal/sinus endoscopy, surgical, with maxillary and antrostomy with removal of tissue from maxillary sinus
  - Nasal/sinus endoscopy, surgical, with frontal sinus exploration, with or without removal of tissue from frontal sinus
  - Nasal/sinus endoscopy, surgical, with maxillary antrostomy
  - Nasal/sinus endoscopy, surgical, with sphenoidotomy with removal of tissue from the sphenoid sinus
  - Nasal/sinus endoscopy, surgical, with sphenoidotomy

  - Nasal/sinus endoscopy, surgical, with ethmoidectomy, partial
  - Excision, nasal polyp(s), extensive
  - Excision, nasal polyp(s), simple
  - Excision or destruction (eg, laser), intranasal lesion; internal approach
  - Other
- Time since most recent nasal polyposis surgery (years)
- Eligibility for NP surgery at screening (Yes, No)

Epistaxis History

For Epistaxis event, the following information will be summarized by study intervention group and overall:

- Location of bleed (anterior bleed, posterior blood, both, unknown)
- Nature of bleeding (Blood mixed with secretions after blowing the 4 noses, freely bleeding from the nose, running into the pharynx even if the anterior nares are compressed)
- Episode duration (minutes)
- Frequency of episodes (per week)
- Time of the day does epistaxis usually occur (Morning, Afternoon, evening, night, no particular time)
- Linked to seasonal factor (No, Yes – Spring, summer, autumn, and winter)
- Associated with dry nose (Yes, No)
- Temporally associated with intranasal corticosteroid (INCS) use (Yes, No)
- Associated with intake of anti-coagulants (Yes, No)
- Associated with intake of aspirin (Yes, No)
- Other causes for epistaxis (Yes, No)
- Associated with hypertension (Yes, No)
- Associated with septal abnormalities (Yes, No)
- Associated with blood (coagulation/aggregation) disorders (Yes, No)

AERD

The number and percentage of participants with specified history below will be summarized by study intervention group and overall, for the ITT analysis set:

- History of Respiratory, Nasal and/or Bronchial Symptoms Following the Intake of Aspirin or/and Nonsteroidal Anti-inflammatory Drugs (NSAID)
- History of Aspirin Provocation Test, Either Nasal, Bronchial, or Oral While Having a Positive Clinical History of AERD (No, Yes Negative, Yes Positive)

Comorbidities History

The number and percentage of participants with specified history below will be summarized by study intervention group and overall, for the ITT analysis set:

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Allergic rhinitis
- Allergic conjunctivitis
- Atopic dermatitis
- Ear, nose, throat (ENT) disorder
- Epistaxis
- Aspirin-exacerbated respiratory disease
- Hives
- Eosinophilic esophagitis

- Egg allergy
- Fish allergy
- Milk allergy
- Peanut allergy
- Allergy to nuts
- Shellfish allergy
- Soy allergy

6.5. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be presented for the screened analysis set using number and percentage.

6.6. Other Background Information

Not applicable.

7. Study Interventions and Medications

7.1. Prior and Concomitant Medications

The prior and concomitant medications will be presented for the ITT analysis set for each study intervention group (and overall, for prior medications) using number and percentage. No statistical test for the between-group difference will be performed.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version at the time of each database lock.

Medications will be summarized by study intervention group according to the WHO-DD, considering the first digit of the anatomic category (ATC) class (anatomic category – Level 1) and the first 3 digits of the ATC class (therapeutic category – Level 2), unless otherwise specified. All ATC codes corresponding to a medication will be summarized, and participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, participants may be counted several times for the same medication.

The summaries for prior and concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the dupilumab study intervention group. In case of equal frequency regarding ATCs, alphabetical order will be used.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as described in Section 15.4.3.

A given medication can be classified as a prior medication as well as a concomitant medication.

7.1.1. Prior Medications

Prior medications are those the participant began prior to first IMP intake. Prior medications can be discontinued before first study intervention administration or can be ongoing during the study intervention phase.

The following prior medication summaries will be generated separately by study intervention group and overall:

- Inhaled corticosteroids, in combination with other asthma controllers summarized by medication type (ICS, LABA, Long-Acting Muscarinic Antagonist (LAMA), LTRA, Other) and standardized medication name.
  Note: These medications are recorded in the Asthma controller medication eCRF page and ATC codes will be used to categorize them into ICS (ATC class R03BA), LABA (ATC class R03AC), LAMA (ATC class R03BB), LTRA (ATC class R03DC) or Other.

- Reliever medications for Asthma summarized by medication type (Short-Acting Beta Agonists (SABA), and other) and standardized medication name (see Section 15.14).
  Note: These medications are recorded in the Asthma reliever medication eCRF page.

- Systemic Corticosteroids by reason (Asthma, CRSwNP, and others)
  Note: These medications are recorded in the systemic corticosteroid medication eCRF page

- Other prior medications.
  Note: These medications are recorded in the Other medications eCRF page.

The prior prohibited medications will also be presented by prohibited medication category as defined in deviation and standardized medication name (see Section 15.14).

7.1.2. Concomitant Medications

Concomitant medications are any treatments received by the participant concomitantly to the IMP, starting from the 1st administration of IMP to the date of last administration + 98.

The following concomitant medications summaries will be generated separately by study intervention group:

- Inhaled corticosteroids in combination with other controllers summarized by medication type (ICS, LABA, LAMA, LTRA, Other) and standardized medication name.
  Note: These medications are recorded in the asthma controller medication eCRF page and ATC codes will be used to categorize them into ICS (ATC class R03BA), LABA (ATC class R03AC), LAMA (ATC class R03BB), LTRA (ATC class R03DC) or Other.

- Reliever (rescue) medications for Asthma summarized by medication type (SABA, and other) and standardized medication name (see Section 15.14).
  Note: These medications are recorded in the asthma reliever medication eCRF page
  .
- Rescue treatment for CRSwNP
  Note: These medications are recorded in the rescue treatment for CRSwNP eCRF page.

- Systemic Corticosteroids by reason (Asthma, CRSwNP, and others)
  Note: These medications are recorded in the systemic corticosteroid medication eCRF page

- Other concomitant medications.
  Note: These medications are recorded in the other medications eCRF page.

The concomitant prohibited medications will also be presented by prohibited medication category as defined in deviation and standardized medication name (see Section 15.14).

7.1.3. Post-treatment Medications

Post-treatment medications are those the participant took (continued or initiated) in the period running from the 15th day after the last administration of IMP or the day after the participant switches to commercialized dupilumab or other logic treatment up to the end of the study. Post-treatment medications will not be summarized or presented in the CSR.

7.2. Intranasal Corticosteroid

Intranasal corticosteroid medications taken 1 year prior to screening will be summarized by study intervention group sorted by standardized medication name. The total daily dosage will be summarized descriptively by standardized medication name and by unit. The MFNS controller medication at randomization will be summarized by total daily dosage.

7.3. Study Interventions

The extent of IMP exposure and compliance will be assessed and summarized by actual study intervention group, for the safety analysis set.

7.3.1 Extent of Exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of IMP exposure is defined as last IMP administration dose date – first IMP administration dose date + 14 days, regardless of unplanned intermittent discontinuations.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, Q1, Q3, minimum and maximum). In addition, duration of IMP exposure will also be summarized categorically by numbers and percentages for each of the following categories:

- >0 and ≤2 weeks
- >2 and ≤4 weeks
- >4 and ≤8 weeks
- >8 and ≤12 weeks
- >12 and ≤16 weeks
- >16 and ≤20 weeks
- >20 and ≤24 weeks
- >24 weeks

and cumulatively according to the following categories:

- ⩾1 day
- >2 weeks
- >4 weeks
- >8 weeks
- >12 weeks
- >16 weeks
- >20 weeks
- >24 weeks

Additionally, the sum of the duration of IMP (total) exposure for all participants will be summarized by study intervention group and will be expressed in participant years.

7.3.2 Study Intervention Compliance and Modifications

A given administration will be considered non-compliant if the participant did not take the planned dose of study intervention as required by protocol (ie, a syringe not fully injected is considered as a non-compliant administration). No imputation will be made for missing or incomplete data.

Percentage of compliance for a participant will be defined as the number of administrations that the participant was compliant (planned dose fully injected) divided by the total number of administrations that the participant was planned to take during the study intervention period.

$$\text{Percentage of compliance (\%)} = \left[\frac{\text{Total number of compliant administrations during the study intervention period}}{\text{Number of planned administrations during the study intervention period}}\right] \times 100\%$$

Percentage of compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, Q1, Q3, minimum and maximum). In addition, the percentage of compliance will be presented by the specific ranges:

- <80%
- ≥80 %

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 within the intended therapeutic interval (planned study intervention period), adjusted according to the tested drug. Cases of symptomatic overdoses will constitute AESIs and will be listed as such.

Dose modification of IMP for an individual participant is not allowed and therefore no summary of dose modifications will be provided.

8. Efficacy Analysis

All efficacy analyses will be performed on the ITT analysis set.

Participants will be analyzed for efficacy according to the study intervention group to which they are allocated by the IVRS according to the randomization schedule at the randomization visit (as randomized), irrespective of the study intervention actually received.

For the two primary endpoints,

- The null statistical hypothesis tested is that there is no mean treatment difference between dupilumab and omalizumab.
- The alternative statistical hypothesis tested is that there is a mean treatment difference between dupilumab and omalizumab. 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 conditions is met:
  - p1 ⩽ p2 ⩽0.05 and both endpoints are in favor of dupilumab, or,
  - p1 ⩽0.025 and is in favor of dupilumab irrespective of the value of p2.

For the secondary efficacy endpoints, the null statistical hypothesis is same as primary endpoints. The alternative statistical hypothesis is that dupilumab is superior to omalizumab at the 2-sided 5% alpha level.

Summary statistics with 95% CI by study intervention group will be provided.

All efficacy measurements collected during the study will be considered for analyses, including those obtained after IMP discontinuation except off-study intervention data if study intervention discontinuation was due to the COVID-19 pandemic and except data after NP surgery or SCS uses. For more details, refer to Table 2-2.

All daily assessments (ie, CRSwNP nasal symptom diary, NPIF) will be analyzed as monthly averages, calculated from the 28 days immediately preceding (and including) the theoretical expected day of the study visit calculated from the efficacy reference date.

ADSD will be analyzed at each timepoint as 30 days averages for the day immediately preceding the study visit, including the day of the visit as these data are collected only for each of the 30 days prior the visit.

The other efficacy parameters (NPS, UPSIT, spirometry, FeNO, ACQ-7, AQLQ(S), EQ-5D, VAS, PGI-Control/Change, IGA-Severity/Control/Change, WPAI-chronic rhinosinusitis and HCRU) will not use any of these approach since they are collected/measured a single time before or the day of the visit.

Line plots for change from baseline will be presented by study intervention group, displaying the least square (LS) mean and SE at each visit. These plots will be provided for the primary and secondary/exploratory continuous endpoints.

When applicable, inferential tests will be performed at all scheduled visits: The adjusted LS mean in change from baseline of each study intervention group, the LS mean difference between the dupilumab and omalizumab groups, and the corresponding SEs and 95% CIs will be provided. The p-value corresponding to the LS mean difference will be provided at Week 24 only.

8.1. Primary Efficacy Endpoint

The 2 primary endpoints are change from baseline in NPS and UPSIT at Week 24 assessed for dupilumab versus omalizumab.

8.1.1. Primary Analysis

Change from baseline in NPS and UPSIT at Week 24 will be analyzed on the ITT population in this ANCOVA model, and study intervention (dupilumab, omalizumab), corresponding baseline value, prior surgery (Yes/No), ICS doses (low versus medium/high dose ICS), presence of AERD (Yes/No) and region (EE versus ROW) will be included as covariates.

The adjusted LS means in change from baseline of each study intervention group, the LS mean difference between the dupilumab and omalizumab groups, and the corresponding SEs and 95% CI of the differences generated from the ANCOVA models will be combined using Rubin's formula and presented in a statistical table for the ITT population.

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 not be included (ie, set to missing) but will be assumed missing at random, and will be imputed by MI.

For participants who undergo surgery for NP or receive SCS for any reason during the study, data collected post-surgery or post SCS will be set to missing, and the worst post-baseline 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 the treatment without being rescued by surgery or receiving SCS, an MI approach will be used to impute missing Week 24 value by using all participants excluding those who have undergone surgery/SCS use on or before Week 24 under an assumption of missing at random (MAR). Under this assumption, each missing score will be imputed 50 times and incorporated with non-missing data to form 50 complete datasets. Each dataset will include the efficacy assessment at Baseline, all scheduled post-baseline visits, as well as relevant covariates specified below to support the analysis. Following steps will be conducted for this analysis. The number of imputations (50) will be informally verified by replicating sets of 50 imputations and checking whether the combined results are stable. If not stable, the number of imputations will be increased and informally checked as above, until stable estimates are obtained.

- Use the Markov chain Monte Carlo (MCMC) method to impute for intermittent missing values to create 50 datasets with monotone missing pattern. The seed will be set to 16747. According to the nature of NPS and UPSIT, minimum and maximum values will be specified in this imputation.

- For each of 50 datasets with monotone missing pattern created from MCMC imputation, use monotone regression method to impute the remaining missing value up to Week 24. In the imputation regression model, corresponding prior surgery (Yes/No), ICS doses (low versus medium/high dose ICS), presence of AERD and region (EE versus ROW), study intervention, and baseline value of the response variable will be included as covariates.

Each of the 50 imputed datasets will be merged with the one dataset imputed by WOCF approach. Change from baseline in NPS and UPSIT at Week 24 can be calculated with non-missing score or imputed score for every single participant in all datasets. Repeatedly perform ANCOVA modeling for each of 50 datasets with full imputation for missing values.

8.1.2. Assumption Testing

No assumption testing will be performed.

8.1.3. Missing Data Handling

A hybrid method of the WOCF and the MI will be used. See Section 8.1.1 for details.

8.1.4. Subgroup Analysis

Subgroup analyses will be conducted for the two primary endpoints in the following subgroups:

- Age categories (≥18 to ≤64, ≥65 years)
- Gender (Male, Female)
- Baseline body weight categories (<70, ≥70 to <90, ≥90 kg)
- Baseline BMI categories <30, ≥30 kg/m²))
- ICS Dose Level (Low, Medium/High)
- Region (EE, ROW)
- AERD (Yes, No)
- Prior NP surgery (Yes, No)
- Age of onset of asthma (<18, ≥18 to <40, ≥40 years)

- Number of severe asthma exacerbation events (0, ≥1) within 1 year prior to the study
- Smoking history (Former, Never)
- SCS use during the past 2 years prior to V1 (Yes, No)
- FeNO in class (<25, ≥25 to 50, ≥50 ppb)
- Blood Eosinophils counts (10^9/L) in class
  - <0.3, ≥ 0.3
  - <0.15, ≥0.15

In these subgroup analyses, nominal p-value will be provided for descriptive purpose only. If the sample size is not large enough, a subgroup may be combined in the analysis.

Results will also be illustrated with forest plots.

8.1.5. Sensitivity Analysis

For all sensitivity approaches, for patients who undergo surgery for NP or receive SCS for any reason, data collected post-surgery or post SCS will be set to missing. For any participants discontinuing the study intervention due to the COVID-19 pandemic, off-study intervention data will not be included (ie, set to missing) but will be assumed MAR.

A sensitivity analysis on the primary endpoint of change from baseline up to week 24 will be analyzed on the ITT population using a MMRM. The MMRM model will include study intervention (dupilumab, omalizumab), prior surgery (Yes/No), ICS doses (low versus medium/high dose ICS), presence of AERD and region (EE versus ROW), visit (up to Week 24), study intervention by visit interaction, corresponding baseline value, and baseline-by-visit interaction as covariates.

An unstructured correlation matrix will be used to model the within-participant errors covariances. The Kenward-Roger approximation (ddfm=kr) will be used to estimate the denominator of degrees of freedom. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. The adjusted LS mean in change from baseline of each study intervention group, the LS means difference between the dupilumab and Omalizumab groups, and the corresponding SEs and 95% CI will be provided at all scheduled visits. The p-value corresponding to the LS mean difference will be provided at Week 24 only.

If the MMRM model under unstructured correlation matrix fails to achieve convergence due to complexity of model specification, different covariance structures will be used according to the following order till convergence is achieved:

1. Heterogeneous Toeplitz (TOEPH)
2. Homogeneous Toeplitz (TOEP)
3. First-Order Autoregressive [AR(1)]
4. Compound Symmetry (CS)

8.1.6. Supplementary Analyses

As a supplementary analysis, the primary analysis will be repeated for the ITT population but instead of removing all data after surgery and SCS, only the data after surgery will be set to missing and imputed by Worst Observation Carried Forward (WOCF). Other conditions remain unchanged.

8.1.7. Impact of COVID-19 Pandemic

During the COVID-19 pandemic, a business continuity plan (BCP) was put in place to minimize the impact of the clinic visit interruptions and ensure IMP treatment continuity and data collection. Direct to participant delivery of IMP from the site(s) and home injection(s) done by qualified site personnel and/or healthcare professionals for study drug administration were made available, where allowed by local regulations and approved by the participant, as planned per protocol. IMP permanent discontinuation due to COVID-19 pandemic is therefore expected to be minimum. Patient-reported outcome data are not expected to be missing as they can be completed at the participant's home on his/her electronic devices. Site(s) can update/correct the schedule of completion if visit is rescheduled/delayed – unless site staff cannot access vendor platform to update scheduled dates.

Data missing due to the COVID-19 pandemic are likely to be MAR. Therefore, the primary analysis using a hybrid method of the WOCF and the MI can adequately address this type of missing data. Participant disposition summaries by visit according to trial impact (disruption) due to COVID-19 overall and by country are already mentioned in Section 5.1 of this SAP.

8.2. Secondary and Tertiary/Exploratory Efficacy Endpoints

The differences will be assessed between dupilumab and omalizumab in the efficacy endpoints.

The secondary and tertiary efficacy endpoints associated with "Change from baseline" unless otherwise noted will be analyzed using the ANCOVA model in the same fashion as for the analysis of the primary endpoints (see Table 2-2). The ANCOVA model will also be performed for the change from baseline to all post-baseline visits for the continuous measurements.

The adjusted LS means in change from baseline of each study intervention group, the LS mean difference between the dupilumab and omalizumab groups, and the corresponding SEs and 95% CI of the differences generated from the 50 ANCOVA models will be combined using Rubin's formula and presented for all endpoints (and p-value corresponding to the LS mean difference provided at Week 24 only).

The efficacy parameters (PGI-Change, IGA-Change, and HCRU) will not use any of these approaches but setting to missing any assessment performed after NP surgery or SCS intake and any off-study intervention data for participants discontinuing the study intervention before Week 24 due to the COVID-19 pandemic.

For the time to event analysis, proportion participants with CRSwNP worsening/acute sinusitis, and annualized rate analysis, the follow up period will be 24-week study intervention period. The 24 week study intervention period is defined from the efficacy reference date to the date of Week 24 actual visit. If participant does not have the week 24 actual visit date, the date will be considered as the earliest date of efficacy reference date + 24 *7, end of study date, last contact date, and death date. For participants with no event, the participant will be censored at Week 24 date as descripted above.

Further definitions of endpoints are included in Section 15.8 to Section 15.12.

8.2.1. Nasal Polyp Score (NPS)

In addition to primary ANCOVA model, the ANCOVA model will be performed for the change from baseline to Week 4, and Week 12. NPS will also be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics.

8.2.2. University of Pennsylvania Smell Identification Test (UPSIT)

In addition to primary ANCOVA model, the ANCOVA model will be performed for the change from baseline to Week 2, Week 4, and Week 12. UPSIT will also be summarized at baseline and each post-baseline visit (Week 2, Week 4, Week 12, and Week 24) through descriptive statistics.

8.2.3. CRSwNP Nasal Symptom Diary

In addition to ANCOVA model, the average Loss of smell score, NC score, and TSS, will be summarized at baseline and each month (Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24) through descriptive statistics. ANCOVA model will be performed for all post-baseline visits.

8.2.4. Spirometry

In addition to ANCOVA model, Pre-BD FEV1 (L), FVC(L), and FEF 25% to 75% (L/s) will be summarized at baseline and each post-baseline visit (Week 2, Week 4, Week 8, Week 12, Week 16, and Week 24) through descriptive statistics of actual values and change from baseline. ANCOVA model will be performed for all post-baseline visits.

8.2.5. Sino-Nasal Outcome Test-22-Items (SNOT-22)

In addition to ANCOVA model, SNOT-22 total score, nasal domain score, sleep domain score, and function domain score will be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics. ANCOVA model will be performed for all post-baseline visits.

8.2.6. Asthma Control Questionnaire 7-iterm Version (ACQ-7)

In addition to ANCOVA model, the ACQ-7 global score will be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics. ANCOVA model will be performed for all post-baseline visits.

8.2.7. Nasal Peak Inspiratory Flow (NPIF)

In addition to ANCOVA model, the average NPIF will be summarized at baseline and each month (Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24) through descriptive statistics. ANCOVA model will be performed for all post-baseline visits.

8.2.8. Rhinosinusitis Severity Visual Analogue Scale (rhinosinusitis VAS)

In addition to ANCOVA model, VAS will be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics. ANCOVA model will be performed for all post-baseline visits.

8.2.9. Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S])

In addition to ANCOVA model, AQLQ will be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics.

8.2.10. Asthma Daytime Symptom Diary (ADSD)

For ADSD, only the overall score will be presented/assessed, and it will be calculated using the average from the 6 items. ADSD score will be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics. The ANCOVA model will also be performed for the change from baseline to Week 4, Week 12, and Week 24.

8.2.11. Fractional Exhaled Nitric Oxide

In addition to ANCOVA model, FeNO will be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics. ANCOVA model will be performed for all post-baseline visits.

8.2.12. EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Questionnaire (EQ 5D)

In addition to ANCOVA model, EQ VAS will be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics. ANCOVA model will be performed for all post-baseline visits.

8.2.13. Work Productivity and Activity Impairment Questionnaire: Chronic Rhinosinusitis (WPAI)

The ANCOVA will be performed for the WPAI-CRSwNP concept scores (percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment). All individual scores should be assessed in employed participants only, except Percent activity impairment (from question 6) which is not related to work.

The WPAI- CRSwNP concept scores will also be summarized at baseline and each post-baseline visit (ie, Week 4, Week 12, and Week 24) through descriptive statistics. ANCOVA model will be performed for all post-baseline visits.

In addition, the number and percentage of participants currently employed (yes/no) will be presented at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) alongside with the number of participants evaluated at those visits.

8.2.14. Investigator Global Assessment (Severity, Control, Change) in CRSwNP

The number and percentage of participants with each score for IGA-Severity, and IGA-Control will be presented at baseline and each post-baseline visit (Week 4, Week 12, and Week 24). IGA-Change will be summarized at each post-baseline visit (Week 4, Week 12, and Week 24).

The ANCOVA model will also be performed for the change from baseline to Week 4, Week 12, and Week 24 for IGA-Severity, and IGA-Control. IGA-Severity, and IGA-Control will also be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics.

8.2.15. Patient Global Impression of Control and Change in CRSwNP

The number and percentage of participants with each score for PGI-Control will be presented at baseline and each post-baseline visit (Week 4, Week 12, and Week 24). PGI-Change will be summarized at each post-baseline visit (Week 4, Week 12, and Week 24).

The ANCOVA model will also be performed for the change from baseline to Week 4, Week 12, and Week 24 for PGI-Control. PGI-Control will also be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics.

8.2.16. Cumulative Number of Health-Care Resource Utilization (HCRU)

Cumulative number of HCRU will be summarized at baseline and each post-baseline visit (Week 4, Week 12, and Week 24) through descriptive statistics.

8.2.17. Cumulative Number of Missed Days of Work

Cumulative number of missed days of work recorded in the severe asthma exacerbation events eCRF page will also be summarized.

8.2.18. Time to Assessment and Other Exploratory Analyses

Time from Randomization will be considered as Time from efficacy reference date.

Time to first recurrence of nasal polyps will be analyzed.
Recurrence of NP is defined as

- NPS increases from baseline >=1 and SNOT-22 total score increases from baseline >=8.9
  Or
- Clinical intervention: a need for planned NP surgery, or SCS use for NP.

The data will be analyzed by the Cox proportional hazards regression model. The model will include the event as the dependent variable, study intervention (dupilumab, omalizumab), prior surgery (Yes/No), ICS doses (low versus medium/high dose ICS), presence of AERD and region (EE versus ROW) as covariates. Hazard ratio and corresponding 95% CI and p-values will be estimated for dupilumab 300 mg q2w versus omalizumab. Kaplan-Meier methodology will be used to estimate the distribution function of time to first recurrence of nasal polyps and median time to recurrence will be presented along with a 95% confidence interval. The Kaplan-Meier plot will also be provided.

Time to first SCS burst for Asthma, time to first SCS burst for NP, time to need for nasal surgery, and time to asthma worsening*, will be analyzed in the same fashion as time to first recurrence of NP.
*Worsening of asthma symptoms that require initiation with rescue therapy.

The number and percentage of participants with CRSwNP worsening**/acute sinusitis during the 24-Week study intervention period will be summarized. Statistical comparisons will be made to compare the proportion of events between the study intervention groups, using the Cochran-Mantel-Haenszel test stratified by prior surgery (Yes/No), ICS doses (low versus medium/high dose ICS), presence of AERD and region (EE versus ROW). The corresponding odds ratios, 95% CI, and P-value will be reported.
**Worsening of any CRS symptoms that require initiation with rescue therapy.
The annualized rate of SCS course* will be analyzed using a generalized linear model assuming a negative binomial distribution with study intervention, prior surgery (Yes/No), ICS doses (low versus medium/high dose ICS), presence of AERD (Yes/No) and region (EE versus ROW) as covariates. The time at risk for a participant is defined as the duration of 24-week study intervention period in days and the log(time at risk in years) will be used as the offset variable in the model. The SAS procedure GLIMMIX will be used for analysis. If the model fails to achieve convergence, different estimation algorithms will be applied following the order: RSPL (default)- > LAPLACE-> QUAD. If the issue still exists, other handling may be considered. The adjustment will be added to the footnote of the corresponding outputs.

Study intervention group ratio of rate will be presented together with 95% confidence interval and two-sided p-value.
*A course of SCS is considered continuous if treatment is separated by less than 7 days.

The annualized rate of severe asthma exacerbations will also be analyzed same approach as SCS course.

8.2.19. Multiplicity Issues

Significance is only possible at the p=0.05 level for each key secondary and secondary endpoint in the hierarchy if both comparisons have p<0.05 for the primary endpoints.

The following key secondary endpoints and the selected secondary endpoints will be included in the multiplicity adjustment scheme and tested in the following order:

1. Change from baseline to Week 24 in the loss of smell score of the CRSwNP Nasal Symptom Diary
2. Change from baseline to Week 24 in the NC score of the CRSwNP Nasal Symptom Diary
3. Change from baseline to Week 24 in TSS derived from the CRSwNP Nasal Symptom Diary

This fixed hierarchical approach will ensure a strong control of the overall Type-I error rate at the 0.05 level.

Additional endpoints (secondary or tertiary) that are not included in the hierarchical testing procedure will not be formally tested (ie, nominal p-value provided for descriptive purpose only).

9. Safety Analysis

All safety results will be summarized using the safety analysis set by actual study intervention group.

The observation periods include:

- The pre-treatment period is defined as the time from the signed informed consent date up to first administration of the IMP.
- The treatment-emergent period is defined as the time from the first administration of the IMP (on Day 1) to the last administration of the IMP + 98 days and up to the end of the study follow-up.*

The post-treatment period is defined as the time starting 1 day after the end of the treatment-emergent period up to the end of the study follow-up.

*The participant may switch to commercialized dupilumab/omalizumab or other biologic treatment after the end of the study follow-up.

9.1. Adverse Events

The adverse event categories include:

- **Pre-treatment adverse events** are adverse events that developed or worsened or became serious during the pre-treatment period.
- **Treatment-emergent adverse events (TEAEs)** are adverse events that developed or worsened or became serious during the treatment-emergent period.
- **Post-treatment adverse events** are adverse events that developed or worsened or became serious during the post-treatment period. AEs categorized as post-treatment AEs will not be summarized.

The primary focus of AE reporting will be on TEAEs. Pre-treatment AEs will be summarized separately.

All AEs will be coded by LLT, PT, HLT, HLGT, and associated primary SOC using the version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

Adverse events will be recorded from the time of signed informed consent until the end of the study or the resolution/stabilization of all SAE and AESI.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, or treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment-emergent unless there is definitive information to determine it is pre-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 15.4.5.

AEs will be summarized by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of primary SOC and then alphabetically for the other levels, for each study intervention group using number and percentage of participants experiencing an adverse event. Multiple occurrences of the same event in the same participant will be counted only once in the tables within an observation period (pre-treatment period or TEAE period). The denominator for computation of percentages will be the safety analysis set within each study intervention group. Participants experiencing asthma exacerbations will be further summarized using the LLT level as appropriate within adverse event summaries.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent). For that purpose, the table of all TEAEs presented by primary SOC and PT (sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs in the dupilumab group) will define the presentation order for all other summaries unless otherwise specified. In case of equal frequency regarding PTs, alphabetical order will be used.

On top of the analysis planned below, all TEAEs, all treatment-emergent SAEs, TEAEs leading to permanent study intervention discontinuation and TEAEs leading to death will be summarized by study intervention group and repeated on the subgroups of safety participants according to trial impact (disruption) due to COVID-19 pandemic.

Overview summary of the number and percentages of participants within the following categories will be provided by study intervention group:

- Any TEAE
- Any study intervention related TEAE
- Any severe TEAE
- Any serious TEAE
- Any TEAE leading to permanent study intervention discontinuation
- Any TEAE of special interest
- Any serious TEAE of special interest
- Any TEAE leading to death

The overview summary for TEAEs will be provided on the safety analysis set and will be repeated on the subgroups of safety participants according to trial impact (disruption) due to COVID-19 pandemic.

Additionally, an overview of pre-treatment AEs will be presented using similar categories including:

- Any AE
- Any Severe AE
- Any Serious AE
- Any AESI
- Any Serious AESI
- Any AE leading to death

Individual listings (AEs, SAEs, TEAEs leading to permanent study intervention discontinuation, AEs leading to death, AESI and all AEs in treated but not randomized participants (where such participants are recorded in the study)) will be provided to support the summary tables based on the safety set. All AEs for participants receiving more than one IMP during the study will also be listed separately.

Additionally, any defect in the IMP will be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines. Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess

whether the quality issue must be reported together with an AE or SAE. No analysis of these data is foreseen. Reporting of these information falls beyond the scope of this SAP.

9.1.1. Incidence of Adverse Events

The following TEAE summaries will be generated for the safety analysis set, for each study intervention group.

- All TEAEs presented by primary SOC, HLGT, HLT, and PT, showing the number and percentage of participants with at least 1 TEAE
- All TEAEs presented by primary SOC, showing number and percentage of participants with at least 1 TEAE, sorted by the internationally agreed primary SOC order
- All TEAEs presented by PT, showing number and percentage of participants with at least 1 TEAE, sorted by decreasing incidence of PT in the dupilumab group
- All pre-treatment AE presented by primary SOC and PT, showing number and percentage of participants with at least 1 pre-treatment AE
- All TEAEs presented by primary SOC and PT, showing number and percentage of participants with at least 1 TEAE
- All treatment-emergent COVID-19 related adverse events presented by primary SOC and PT, showing number and percentage of participants with at least 1 treatment-emergent COVID-19 related AE
- Common TEAEs (PTs with an incidence $\geqslant$5% in any study intervention group) by primary SOC, HLGT, HLT, and PT

Search criteria for COVID-19 related AE will be provided by SANOFI.

9.1.2. Relationship of Adverse Events to Study Intervention

The following TEAE summary will be generated.

- All TEAEs by relationship, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 TEAE

9.1.3. Severity of Adverse Event

The following TEAE summary will be generated.

- All TEAEs by maximal severity, presented by primary SOC and PT, showing the number and percentage of participants with at least 1 TEAE by severity (ie, mild, moderate, severe).

9.1.4. Serious Adverse Events

The following TEAE summaries will be generated.

- All serious TEAEs presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 serious TEAE.
- All serious TEAEs by relationship, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 serious TEAE.

9.1.5. Adverse Events Leading to Permanent Study Intervention Discontinuation

The following TEAE summary will be generated.

- All TEAEs leading to permanent study intervention discontinuation, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 TEAE leading to permanent study intervention discontinuation.

9.1.6. Adverse Events Leading to Study Discontinuation

Not applicable.

9.1.7. Adverse Events of Special Interest (AESIs)

As defined in Section 15.6, AESIs include:

- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Keratitis
- Any severe type of conjunctivitis or blepharitis
- Significant Alanine Aminotransferase (ALT) elevation:
  - ALT >5 x Upper limit of normal (ULN) in participants with baseline ALT ⩽2 x ULN; or
  - ALT >8 x ULN if baseline ALT >2 x ULN.
- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a 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
- 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.

The following TEAE summaries will be generated.

- All TEAEs of Special Interest, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 TEAE of Special Interest.
- All serious TEAEs of Special Interest, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 serious TEAE of Special Interest.

9.1.8. Adverse Events Leading to Death

The following TEAE summary will be generated.

- All TEAEs leading to death (death as an outcome on the eCRF form “Adverse Event” as reported by Investigator), presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 TEAE leading to death.

9.1.9. Death

The following summaries of deaths will be generated.

- Number and percentage of participants who died during the trial by study period (ie, on study, pre-treatment, TEAE period, and post-treatment period).
- Number and percentage of participants who died during the trial by cause of death.
- Number and percentage of non-randomized but treated participants or randomized but not treated participants who died (where such participants are recorded in the study).

A listing of all participants who died during the study will be provided.

9.2. Clinical Laboratory Evaluations

The laboratory tests will be performed by the local laboratories except the serum total IgE level and eosinophils that will be done in a central laboratory. The Investigator will review the laboratory report, document this review, and record any clinically relevant findings/changes occurring during the study in the AE section of the CRF.

The following laboratory tests will be performed:

- Hematology: blood eosinophil count.
- Biomarker: Serum total IgE and allergen-specific IgE.
- Highly sensitive serum human chorionic gonadotropin pregnancy at screening visit (urine or serum pregnancy test as required by the local regulations at other time points) (as needed for women of childbearing potential).
- Hepatitis screening covering hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (total HBcAb) including IgM HBcAb; hepatitis C virus antibodies (HCVAb). In case of results showing HBsAg (negative), and HBcAb (positive), a hepatitis B virus (HBV) deoxyribonucleic acid (DNA) testing will be performed 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 HCVAb (positive), a hepatitis C virus (HCV) ribonucleic acid (RNA) testing may be performed to rule out a false positivity, if the Investigator believes the participant is a false positive.
- Human Immunodeficiency Virus (HIV) screening (Anti-HIV-1 and HIV-2 antibodies).
- Tuberculosis testing would only be performed on a country-by-country basis according to the routine clinical practice and the local guidelines or if required by Regulatory Authorities or Ethics Committees.

Additional laboratory tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations; any clinically significant abnormal lab values will be included in the adverse event analyses. These additional laboratory tests will be displayed in a separate listing.

Eosinophil counts will be summarized by visit (baseline, Week 4, Week 12 and Week 24) using descriptive statistics of actual values and change from baseline. Same analysis will be done for total IgE counts and allergen-specific IgE counts.

9.3. Vital Sign Measurements

Vital signs: heart rate (HR), sitting systolic (SBP) and diastolic blood pressure (DBP), temperature and respiratory rate, will be collected at screening visit, at baseline visit (Day 1) before receiving the IMP and then at all subsequent visits.

The vital sign results will be summarized using descriptive statistics for each visit or study assessment (baseline, and each-post-baseline time point).

The Potentially Clinically Significant Abnormalities (PCSA) at any time during the TEAE period will be summarized using number and percentage. The PCSA are provided in Section 15.7.

All measurements collected during the TEAE period, including values from unscheduled visits, will be considered for the PCSA summaries. The summaries will include participants who have at least 1 assessment performed during the TEAE period. When a PCSA definition involves a change from baseline value, participants must also have a baseline value to be included in the summaries.

A listing of participants with at least 1 post-baseline PCSA will be provided and will display the participant's full profile (all participant's results) over time of all vital sign parameters.

Individual data listings will include the following flags:

- Baseline values will be flagged "B",
- Parameter values reaching a PCSA limit will be flagged (+, or - depending of the direction).

9.4. Physical Examination

There will be a physical examination at screening visit, at baseline visit (Day 1) before receiving the IMP and then at week 24 visit to examine and assess any abnormalities that may be present, as indicated by the participant's medical history. It will include, at a minimum, assessments of the skin, nasal cavities, eyes and ears, cardiovascular, respiratory, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Body weight will also be measured at screening, baseline and then at week 4, week 12 and week 24 whereas height will be measured at screening only. The weight will be summarized the same way as vital sign parameters, including PCSA description.

Any new or worsening finding will be reported as a new adverse event.

No analysis is planned for physical examinations.

9.5. Electrocardiogram

12-lead ECG will be obtained at screening visit. A summary of ECG overall interpretation at screening (abnormal/normal) will be presented for the safety analysis set.

9.6. Other Safety Data

Not applicable.

10. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

11. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

12. Interim Analysis

Not applicable.

13. Changes in the Planned Analysis

13.1. Sino-Nasal Outcome Test-22-Items (SNOT-22)

The definition of the domain score in the protocol has been changed in the SAP to use the average score of the items from each domain in order to have the same range across the domains according to the most recent publication.

13.2. Time from Randomization Endpoints

Time from Randomization will be considered as Time from efficacy reference date due to the efficacy baseline is defined based on the first administration of IMP (or randomization) for participants not exposed).

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15. Appendices

15.1. Summary of Statistical Analyses

Table 15-1.1 Summary of statistical analyses

Endpoint	Analysis Set	Primary analysis	Supportive analysis	Subgroup analysis	Estimands
Primary endpoint					
To evaluate the efficacy of dupilumab compared to omalizumab in reducing the polyp size and improving sense of smell	ITT	ANCOVA (missing data handled using a hybrid method of the WOCF and the MI)	Sensitivity analyses: MMRM (missing data handled through the MMRM model only, no additional imputation performed)	Yes	Yes
Secondary endpoints					
Continuous variables	ITT	Same approach as primary endpoint	No	No	Yes (only for selected secondary endpoints included in the hierarchical testing procedure)
Tertiary/Exploratory endpoints					
Selected Continuous variables	ITT	Same approach as primary endpoint	No	No	No
Event type variables	ITT	Cox model	No	No	No
Annualized rate of events	ITT	Negative Binomial	No	No	No
Categorical variables	ITT	Summary statistics only	No	No	No

Table 15-2.2 Summary of selected endpoints interpretation

Endpoint	Range	Interpretation
Change from baseline to Week 24 in Nasal Polyp Score (NPS)	0-8	A reduced score indicates improvement. Higher scores indicate more extensive or severe nasal polyps (sum of the right and left scores; average of 2 independent raters) 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 The following scores are used to evaluate the improvement of nasal polyps: Much improved: ≥22-point decrease Improved: ≥8.9-point and <22-point decrease No change: <8.9-point decrease and <8.9-point increase Worse: ≥8.9-point and <12-point increase Much worse: ≥12-point increase
	0-40	Higher scores indicate better olfactory function
Change from baseline to Week 24 in the loss of smell score of the CRSwNP Nasal Symptom Diary	0-3	A reduced score indicates improvement. 0 = No symptoms 1 = Mild symptoms 2 = Moderate symptoms 3 = Severe symptoms

Endpoint	Range	Interpretation
Change from baseline to Week 24 in the nasal congestion (NC) score of the CRSwNP Nasal Symptom Diary	0-3	A reduced score indicates improvement. 0 = No symptoms 1 = Mild symptoms 2 = Moderate symptoms 3 = Severe symptoms
Change from baseline to Week 24 in TSS derived from the CRSwNP Nasal Symptom Diary	0-9	A reduced score indicates improvement. (sum of NC, LoS, and average of anterior and posterior rhinorrhea, Higher scores indicate more severe symptoms)
Change from baseline to Week 24 in 22-Item Sino-nasal Outcome Test (SNOT-22) total score	0-110	Lower is better Higher scores indicate greater impacts of CRS (chronic rhinosinusitis) on HRQoL (sum of the 22 items) 0 = No problem 1 = Very mild problem 2 = Mild or slight problem 3 = Moderate problem 4 = Severe problem 5 = Problem as bad as it can be
Change from baseline to Week 24 in rhinosinusitis visual analogue (VAS)	0-10	Higher scores indicate more severe CRS Severity categories: 0–3 = mild, >3–7 = moderate, >7–10 = severe 0 = Not troublesome to 10 = Worst thinkable troublesome (sic)
Change from baseline to Week 24 in Investigator Global Assessment of Severity (IGA-Severity)	1-4	The scales range from 1 (no disease) to 4 (severe). Higher scores on the items denote greater severity.

Endpoint	Range	Interpretation
Change from baseline to Week 24 in Investigator Global Assessment of Control (IGA-Control)	1-5	The scales range from 1 (Not controlled at all) to 5 (completely controlled). Lower score on the items denote greater severity.
Summary at Week 24 in Investigator Global Assessment of Change (IGA-Change)	1-7	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).

15.2. Schedule of Study Procedures

Procedure	Screening /run-in (up to 4 weeks 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	×																
Inclusion and exclusion criteria	×	×															Recheck clinical status before Randomization and/or first dose of study intervention
Demography	×																Including race and ethnicity
Full physical Examination [e]	×	×												×	×		
Body weight (kg) and height (cm)	×	×		×				×						×	×		Height will be measured only at screening visit
Vital signs	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×		Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius)
Medical/ Surgical history (includes substance usage)	×	×															Substances: tobacco usage collected at screening; alcohol usage will be collected in case of ALT increase.
Past and current medical conditions [f]	×	×															It will also include atopic comorbidities (eg, AD) and asthma diagnosis

Procedure	Screening /run-in (up to 4 weeks 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**			
Spirometry (pre-bronchodilator FEV1, FVC, FEF 25% to 75%) [g]	×	×	×	×		×		×		×				×	×		Central reading
Nasal Endoscopy [h]	×	×		×				×						×	×		Central reading
FeNO		×	×	×		×		×		×				×	×		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)	×	×						×						×	×		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]	×																HBs Ag, HBs Ab, total HBc Ab, HCV Ab, HIV screen (Anti HIV-1 and HIV-2 Abs), TB test, (local laboratory)
Laboratory assessment		×		×				×						×	×		Eosinophils count done by central laboratory
12-lead ECG	×																Performed and assessed locally

Procedure	Screening /run-in (up to 4 weeks 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**			
Serum total IgE, allergen-specific IgE	×	×												×	×		Done by the central laboratory
Randomization		×															
IWRS	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×		
IMP preparation and administration [j]		×	×	×	×	×	×	×	×	×	×	×	×				At site, by the unblinded healthcare professional only following instructions provided in the pharmacy manual.
NIMP: background therapy for CRSwNP and asthma diary	×	<==========												==========>	×		Diary for both MFNS and asthma background therapy
Dispense or download eDiary [k]	×	<==========												==========>	×		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	×	<==========												==========>	×	×	Relevant prior medication at screening visit. Record rescue therapy if applicable.

Procedure	Screening /run-in (up to 4 weeks 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**			
Record planned surgery for NP, SCS use, and other rescue medication use [l]	×	< ========== >													×		
Smell test (UPSIT)		×	×	×				×						×	×		Collect baseline value ahead of first dose of IMP
Nasal Peak Inspiratory Flow (NPIF)	×	< ===== daily morning (AM) up to Week 24 ===== >													×		eDiary on eDevice [k]
Clinical Outcomes Assessment Measures and Resource Use [m]																	
22-item sino-nasal outcome test (SNOT-22)		×		×				×						×	×		ePRO on eDevice
Asthma Daytime/ Symptom Diary (ADSD)	×	×		×				×						×	×		Completed by the participant daily for 30 days prior to W4, W12, and W24. eDevice [k]
CRSwNP nasal symptom diary	×	< ========== >													×		eDiary on eDevice [k]
ACQ-7 [n]	×	×		×				×						×	×		ePRO on eDevice
AQLQ(S)		×		×				×						×	×		ePRO on eDevice
EQ-5D		×		×				×						×	×		ePRO on eDevice
Rhinosinusitis VAS		×		×				×						×	×		ePRO on eDevice

Procedure	Screening /run-in (up to 4 weeks 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**			
WPAI-chronic rhinosinusitis		×		×				×						×	×		ePRO on eDevice
HCRU		×		×				×						×	×		Investigator assessment at site (from eCRF)
Patient global impression of control (PGI-Control)		×		×				×						×	×		Participant assessment/ eDevice
Patient global impression of change (PGI-Change)		×		×				×						×	×		Participant assessment/ eDevice
Investigator Global Assessment of Severity (IGA-Severity) and Control (IGA-Control)		×		×				×						×	×		Investigator assessment at site (from eCRF)
Investigator Global Assessment of Change (IGA-Change)				×				×						×	×		Investigator assessment at site (from eCRF)
AE/SAE, TEAE, and AESI review	×	< ========== >													×	×	

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-3L: EuroQol-5 Dimensions; -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: non-investigational medicinal product; NP: nasal polyps; NPS: nasal polyp score; NPIF: Nasal Peak Inspiratory Flow; 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;, WPAI: Work Productivity and Activity Impairment; WOCBP: woman of childbearing potential.

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 running period window prior to Day 1(V2) is respected. These patients do not need to sign a new consent form and be allocated a new patient number within this same window. 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 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. For spirometry the Investigator will assess the eligibility based on the FEV1 local values from V1 and V 2 before randomization (the results from central reading will not be available on the same day). Further details on the procedure will be provided in a separate instruction manual.

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 and enter the result in the eCRF. 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.

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. HIV viral load test for participants with HIV history only. 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.

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 patient 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 up to Week 24), 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, the PROs should be completed by the participant in the electronic PRO device before seeing the physician, in the following order: daily symptoms of NC, loss of smell and rhinorrhea, SNOT-22, rhinosinusitis VAS, ACQ-7, AQLQ, WPAI-chronic rhinosinusitis, EQ-5D, Patient Global Impression of Control, and Patient Global Impression of Change.

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.

15.3. Missing Efficacy Data

Asthma Daytime Symptom Diary (ADSD)

Global score to be calculated if

- There are at least 4 items (out of 6) available at each day. At least 4 days of data is needed to calculate the average.

Asthma Control Questionnaire (ACQ-7)

- Based on the manual of ACQ, any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing score, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. For instance, answer to question 5 is missing at Visit 4, and all questions are completed at Visit 3. Then the question 5 score at Visit 4 is interpolated as: (sum of score at Visit 4/sum of scores excluding question 5 at Visit 3) × score of question 5 at Visit 3. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

Asthma Quality of Life Questionnaire (AQLQ)

- To have a valid overall score, it is not acceptable to have more than three missing responses or more than one missing response per domain. For responses with more than acceptable amount of missing value(s), the overall score will be considered as missing. For responses with amount of missing value(s) within accept range, the missing score will be interpolated using the previous completions of the questionnaire following the similar algorithm used for ACQ. AQLQ domain missing score will be imputed by mean of global score.

SNOT-22

The global score is the sum of response to each of the 22 questions. For responses with some item scores are missing, the global score will be imputed as mean of the completed scores× 22, providing at least 50% of items have been completed. If more than 50% of items are missing, the global score is set to missing.

The score for each domain is the average of response to each question in that domain. For responses with some item scores are missing, the domain score will be imputed as mean of the completed items in that domain, providing at least 50% of items in that domain have been completed. If more than 50% of items in a domain are missing, the score for that domain is set to missing.

15.4. Missing Safety Data

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

15.4.1. Handling of Missing Age

If age is missing but year of birth is collected, then age will be derived as year of informed consent signed minus year of birth.

15.4.2. Handling of Computation of Study intervention duration if investigational medicinal product end of treatment date is missing

For the calculation of the study intervention duration, the date of the last dose of IMP is equal to the date of last administration reported on the eCRF "Treatment status" page. If this date is missing, the last available administration date in the "Exposure" form will be used.

The last dose intake should be clearly identified in the eCRF and should not be approximated by the last returned package date.

15.4.3. Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant and post-treatment medication.

15.4.4. Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to study intervention or after the study intervention period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

15.4.5. Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as TEAEs. The exposure duration should be kept as missing.
The last dose intake should be clearly identified in the eCRF and should not be approximated by the last returned package date.

15.4.6. Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of related adverse events, but no imputation should be done at the data level.

15.4.7. Handling of missing severity/grades of adverse events

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

15.4.8. Handling of potentially clinically significant abnormalities

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

15.5. Visit Windows

The analysis window below "[in brackets]" will be applied to post-baseline measurements to allocate them to a scheduled visit for the parameter (see Section 15.2 for details of scheduled visits).

Table 15-3 Analyses window definition

Scheduled visit Post-baseline	**Targeted study day*** **	**FeNO/ Spirometry**	**Vital Sign (excluding body weight)**	**UPSIT**	**Diary data** (CRSwNP nasal symptom diary, NPIF)	**All other parameters**
Week 2 (Visit 3)	15	[2,21]	[2,21]	[2,21]		
Week 4 (Visit 4)	29	[22, 42]	[22, 42]	[22, 56]	[2, 29]	[2, 56]
Week 8 (Visit 6)	57	[43, 70]	[43, 70]		[30, 57]	
Week 12 (Visit 8)	85	[71, 98]	[71, 98]	[57, 126]	[58, 85]	[57, 126]
Week 16 (Visit 10)	113	[99, 140]	[99, 126]		[86, 113]	
Week 20 (Visit 12)	141		[127, 154]		[114, 141]	
Week 24 (Visit 14)	169	[141, ∞]	[155, ∞]	[127, ∞]	[142, 169]	[127, ∞]

** For ADSD parameters, each post-baseline assessment will be allocated to a scheduled visit, taking into account **the day of the corresponding actual visit on site**. For other parameters (daily collected or collected once per visit) each post-baseline assessment will be allocated to a scheduled visit, taking into account **the day of the assessment**.

After applying the above time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. In case of equality, the last measurement will be used. Re-allocated scheduled visits (ie, visit numbers) should be sequential if ordered by the date of measurement.

If there is no measurement available for a given parameter in an analysis window data, is considered missing for the corresponding visit.

15.6.Search Criteria for AESI

Table 15-4 Search criteria for AESI

AESI	Only SMQ (Y/N)	Name or Code	Additional Search Criteria
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms).	N	CMQ10641	
Anaphylactic reactions.	Y	CMQsn00021	includes anaphylactic reaction narrow SMQ terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not.
Systemic hypersensitivity reactions.	Y	CMQsn00214	SMQ hypersensitivity narrow search and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events
Helmintic infections	N	CMQ10544	HLGT Helmithic disorders
Keratitis	N	CMQ10642	Keratitis_manually selected
Any severe type of conjunctivitis or blepharitis	N	CMQ10498	"Severe" ticked in Adverse Events eCRF page
	N	CMQ10497	"Severe" ticked in Adverse Events eCRF page
Significant ALT elevation	N	CMQ00029	"AESI" answered Yes on AE eCRF as reported by the investigator
Pregnancy	Y		"Pregnancy" or "Partner Pregnancy" checked in eCRF form "Pregnancy"
Symptomatic overdose	N		Symptomatic Overdose is answered Yes, with Overdose of IMP/NIMP answered Yes on AE eCRF.

15.7.Potentially Clinically Significant Abnormalities (PCSA) Criteria

Table 15-5 Potentially Clinically Significant Abnormalities Criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007

15.8.Nasal Polyp Score

The NPS is assessed by central video recordings of nasal endoscopy. The score (NPS) is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. NPS is graded based on poly size described below.

- 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 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 and enter the result in the eCRF. Thus, the patient 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 central reading from Visit 2 onward will be made available to the site after the end of study.

The adjudication for V1 will not be required if both readers score ineligible (total NPS score less than 5 or at least one side less than 2, in which case the patient will be considered as ineligible) or both readers score eligible (total NPS score of 5 or more and at least 2 in each side, in which case the patient will be considered as eligible). Unreadable scores (bad quality videos) at V1 even from one reader should have endoscopy redone as soon as possible (requiring patient to come back at site). In the case the two readers differ on eligibility for the study, an adjudicator will read the endoscopy again independently. The total NPS score and each side score to determine eligibility will be based on the average of the adjudicator and one of the two readers whose total NPS score is closer to the adjudicator's reading (in the case that the two readers' scores are different but equidistant from the adjudicator's score, the reader with the higher score will be used in the calculation). In the special case that the two readers give different eligibility opinions but the total NPS scores are the same (the only possibility of the total NPS score for such a case is 5), eligibility will follow the adjudicator's opinion.

For V2 and onward (excluding V1), if the total NPS scores assigned by two independent readers differ less than or equal to 1, the total NPS score for analysis for this endoscopy will be the average of the two readings; if they differ more than 1, an adjudicator will read the endoscopy again independently, and the total NPS score for analysis will be the average of the total NPS scores by the adjudicator and one of the two readers whose total NPS score is closer to the adjudicator's reading (in the case that the two readers' total NPS scores are equidistant from the adjudicator's total NPS score, the higher score will be used in the calculation). If the endoscopy is scored unreadable by both readers, the analysis score will be set to missing. If one and only one of the two readers score unreadable, the endoscopy will be read again independently by the adjudicator. Then the average of the two available readings (if the adjudicator gives a readable score) or missing value (if the adjudicator scores it as unreadable) will be set as the total NPS score for analysis.

For the analysis of primary endpoint, central reading of V2 will be used as the baseline. In the scenario that V2 central reading scores are missing, V1 central reading will be used instead and adjudication will be required if the total NPS scores by the two readers at V1 differ more than 1 and the adjudication has not been performed. Calculations of the analysis score for such V1 readings will follow the aforementioned approach for V2 and onward.

15.9.Participant-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.

15.10. Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS)/European Respiratory Society (ERS) (59) 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. Spirometry data will be provided by CLARIO.

15.11. 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.

15.12. Patient-Reported Outcomes (PROs)

<u>CRSwNP nasal symptom diary including nasal congestion/obstruction, loss of smell, and total symptom score</u>

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. 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.

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.

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. 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 (60). 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 domain scores are presented as the average item score per domain with higher score representing higher burden.

Asthma 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

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

Asthma Control Questionnaire-7 (ACQ-7) collects participants assessment of their asthma during the previous week based on 6 questions on a 7-point scale (0 = no impairment to 6 = maximum impairment) and a scoring of the FEV1% predicted by clinic staff, also on a 7-point scale.

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 study intervention.

The ACQ-7 has 7 questions:
The first 5 items assess the most common asthma symptoms:

1. frequency in past week awoken by asthma during the night
2. severity of asthma symptoms in the morning
3. limitation of daily activities due to asthma

4. shortness of breath due to asthma
5. Frequency of wheezing
6. Short-acting bronchodilator use
7. FEV1 % predicted

The first 6 items will be used directly according to the result recorded on the 7-point scale (0 = no impairment to 6 = maximum impairment).

For item 7, the Percent predicted FEV1 value will be used and converted into the same 7-point scale, according to the following table:

FEV1% predicted	Score
> 95% predicted	0
95 - 90%	1
89 - 80%	2
79 - 70%	3
69 - 60%	4
59 - 50%	5
< 50% predicted	6

A global score is calculated: the questions are equally weighted and the ACQ-7 score is the mean of the 7 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. 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.

Asthma Control Questionnaire items 1 to 6 should be completed by the participant, , the local read values of pre-bronchodilator FEV1 will be completed by the investigator.
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 of pre-bronchodilator FEV1 will be used.

Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S])

AQLQ[S] was designed as a self-administered patient-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)
  - 6 - Chest Tightness
  - 8 - Short of Breath
  - 10 - Wheeze
  - 12 - Coughing
  - 14 - Chest Heaviness

16 - Clear Your Throat
18 - Difficulty Breathing Out
20 - Wake Up with Asthma Symptoms
22 - Heavy Breathing
24 - Woken at Night
29 - Interference with a Good Night
30 - Fighting for Air

- Activity limitation (11 items)
  1 - Strenuous Activities
  2 - Moderate Activities
  3 - Social Activities
  4 - Work/School-Related Activities
  5 - Sleeping
  11 - Avoid Cigarette Smoke
  19 - Avoid Dust
  25 - Avoid Weather Pollution Outside
  28 - Avoid Strong Smells or Perfume
  31 - Overall Range of Activities
  32 - All the Activities
- Emotional function (5 items)
  7 - Having Asthma
  13 - Frustrated
  15 - The Need to Use Medication
  21 - Asthma Medication Not Available
  27 - Getting Out of Breath
- Environmental Stimuli (4 items)
  9 - Exposure to Cigarette Smoke
  17 - Exposure to Dust
  23 - Weather or Air Pollution Outside
  26 - Exposure to Strong Smells

The overall AQLQ[S] score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. 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.

To have a valid overall score, it is not acceptable to have more than three missing responses or more than one missing response per domain. For the symptoms and activity limitation domain score, only one missing value per domain is acceptable. For the emotional function and environmental stimuli domain scores, no missing value is acceptable. For responses with more than acceptable amount of missing value(s), the overall or the domain score will be considered as missing. For responses with amount of missing value(s) within accept range, the missing score will be interpolated using the previous completions of the questionnaire following the similar algorithm used for ACQ.A global score is calculated ranging from 1 to 7. 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) +12 is 0.5 (30).

The AQLQ (S) + 12 questionnaire data will be directly provided by CLARIO

Work Productivity and Activity Impairment Questionnaire: Chronic Rhinosinusitis

The WPAI Questionnaire is designed to assess the impact of a disease on patient' s productivity. The WPAI is a 6-item, validated questionnaire to measure impairments in work and activities over a 7-day recall period, The following WPAI- CRSwNP questionnaire scores will be investigated:

- Percent Work Time missed calculated as:

$$\left(\frac{\text{Number of hours Missed [Q2]}}{(\text{Number of hours Missed [Q2]}) + (\text{Hours Actually Worked [Q4]})}\right) \times \mathbf{100}$$

- Percent impairment while working calculated as:

$$\left(\frac{\text{Problem Affecting Productivity [Q5]}}{10}\right) \times \mathbf{100}$$

- Percent overall work impairment calculated as:

$$\Big(\text{Percent work time missed} + \big((1\text{- percent work time missed}) \times \text{Percent impairment while working}\big)\Big) \times \mathbf{100}$$

- Percent Activity impairment calculated as:

$$\left(\frac{\text{Asthma Affecting Regular Daily Activity [Q6]}}{10}\right) \times \mathbf{100}$$

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

The 5-level version of EQ-5D is a standardized patient reported outcome 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'. 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 $\geqslant$8 points is considered clinically important, and the scores can also be compared with population norm scores which ranges from 70.4 to 83.3.

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'

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).

Cumulative number of health-care resource utilization (HCRU)

A questionnaire about HCRU and productivity (missed workdays) will be collected by the Investigator for all participants at the time points specified in the schedule of activities (SoA) (see Section 15.2) through eCRF.

15.13. Biomarkers

Whole blood biomarkers: Blood eosinophil count, IgE counts and allergen-specific IgE will be measured as per schedule of study procedures.

Fractional exhaled nitric oxide (FeNO) will be analyzed using a NIOX instrument using a flow rate of 50 mL/s,and reported in ppb. This assessment should be conducted prior to spirometry and the participant should refrain from eating and drinking for at least 1 hour prior to the procedure.

15.14. Rescue and Prohibited Medications

Rescue Medications for Asthma

Rescue medications (ie, reliever medications) will be identified from the "Asthma Reliever Medication" eCRF page (SABA, other). Systemic corticosteroids will be collected in Systemic corticosteroids eCRF page.

In the table summary, rescue medications will be categorized into SABA (ATC class R03AC), or Other.

Rescue medication for CRSwNP

The following rescue medications may be used:

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

Rescue medications and surgical intervention for CRSwNP will be collected in Rescue treatment for CRSwNP eCRF page.

Prohibited Medications

Treatment with the following medications is considered as prohibited 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 an asthma exacerbation and are not allowed to be used for other conditions from 1 month or at least 5 half-lives prior to Visit 1, whichever is longer, or during the screening and run-in period or the randomized intervention period
- Short term courses ($\leqslant$2 weeks) of SCS (oral or parenteral) are prohibited only between Visit 1 and Visit 2 and they are allowed as rescue to treat an asthma exacerbation 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

16. SIGNATURE PAGE

Client:	**SANOFI**
Protocol Number:	LPS16747

Document Description:	Final Statistical Analysis Plan
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