NCT05049122

STATISTICAL ANALYSIS PLAN

Protocol title:	**A single-arm, 52-weeks, phase 4 study to assess the efficacy and safety of dupilumab in patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) who are not adequately controlled with existing therapies**
Protocol number:	**LPS16872**
Compound number (INN/Trademark):	**SAR231893 (dupilumab/Dupixent®)**
Study phase:	**Phase 4**
Short title:	**Dupilumab in Japanese patients with chronic rhinosinusitis with nasal polyposis (SINUS-M52)**
Statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study LPS16872 is based on the protocol version 1 dated 11-May-2021. There are no major changes to the statistical analysis features in this SAP compared to those in the protocol.

This SAP will be finalized before efficacy review.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	22NOV2022	Not Applicable	Original version

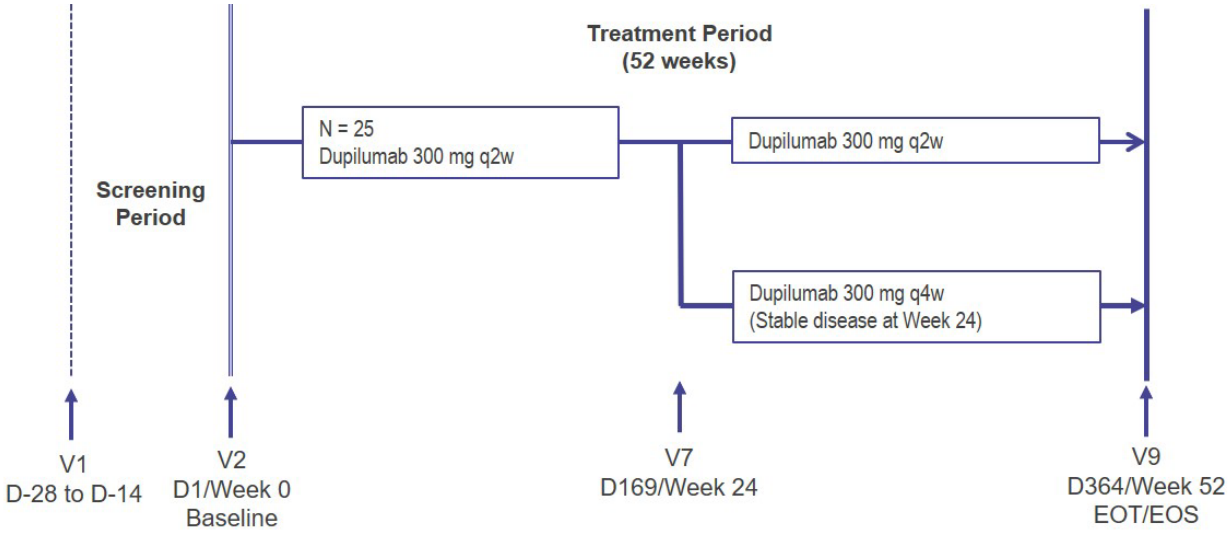
1 INTRODUCTION

1.1 STUDY DESIGN

This is a 52-week, Phase 4, open-label, single-arm, multicenter study to assess the efficacy and safety of dupilumab as monotherapy without concomitant intranasal corticosteroid (INCS) in approximately 25 participants 18 years and older with chronic rhinosinusitis with nasal polyposis (CRSwNP) not adequately controlled with existing therapies.

After a screening phase of 2 to 4 weeks, participants will be treated with dupilumab 300 mg q2w without concomitant administration of INCS for approximately 24 weeks. For participants who have stable disease, the dosing interval can be changed from q2w to q4w at the discretion of the Investigator at Week 24. Participants who change from q2w to q4w will not be permitted to return to the q2w regimen during this study and will receive the q4w regimen until Week 48. Other participants will receive the q2w regimen up to Week 50. The participants will be followed up to Week 52.

Figure 1 - Graphical study design



Study analysis will be conducted after study completion.

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of 24-week treatment with dupilumab 300 mg every 2 weeks (q2w) to reduce nasal polyp score (NPS) in participants with chronic rhinosinusitis with nasal polyposis (CRSwNP) who do not use concomitant intranasal corticosteroid (INCS)	• Proportion of participants with NPS improvement from baseline ≥1 at Week 24
Secondary	
• To assess the efficacy of 24-week treatment with dupilumab 300 mg q2w on other efficacy endpoints in participants with CRSwNP who do not use concomitant INCS	**Key secondary efficacy endpoints:** • Change from baseline to Week 24 in bilateral NPS • Change from baseline to Week 24 in nasal congestion/obstruction (NC) symptom severity score using the CRSwNP nasal symptom diary • Change from baseline to Week 24 in opacification of sinuses assessed by computerized tomography (CT) scan using the Lund Mackay (LMK) score **Other secondary efficacy endpoints:** • Change from baseline to Week 24: - Total symptom score (TSS), a composite score derived from the nasal symptom diary (includes nasal congestion, loss of sense of smell, anterior and posterior rhinorrhea) - Loss of smell symptom severity score using the nasal symptom diary - Visual analogue scale for rhinosinusitis
• To evaluate the safety of 24-week treatment with dupilumab in participants with CRSwNP	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to treatment discontinuation
Tertiary/Exploratory	
• To assess the efficacy of 52-week treatment with dupilumab under different dosing regimens to participants with CRSwNP who do not use concomitant INCS	• Proportion of participants with NPS improvement from baseline ≥1 at Week 52 • Change from baseline to Week 52 in bilateral NPS • Change from baseline to Week 52 in NC symptom severity score using the CRSwNP nasal symptom diary • Change from baseline to Week 52 in opacification of sinuses assessed by CT scan using the LMK score • Change from baseline to Week 52 in TSS
• To evaluate the safety of 52-week treatment with dupilumab in participants with CRSwNP	• Incidence of TEAEs, TESAEs, and TEAEs leading to treatment discontinuation

Abbreviations: CRSwNP: chronic rhinosinusitis with nasal polyposis; CT: computerized tomography; INCS: intranasal corticosteroid; LMK: Lund Mackay; NC: nasal congestion/obstruction; NPS: nasal polyp score; q2w: every 2 weeks; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse events, TSS: total symptom score

1.2.1 Estimands

Primary estimand definitions for main endpoints are summarized below in Table 3. More details are provided in Section 4.

Table 3 - Summary of primary estimand for main endpoints

	Estimands			
Endpoint Category	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy (The missing data handling)**	**Population-level summary (Analysis method)**
Primary objective: To assess the efficacy of 24-week treatment with dupilumab 300 mg every 2 weeks (q2w) to reduce nasal polyp score (NPS) in participants with chronic rhinosinusitis with nasal polyposis (CRSwNP) who do not use concomitant intranasal corticosteroid (INCS)				
Primary endpoint:	Proportion of participants with NPS improvement from baseline ≥1 at Week 24	PP	The intercurrent events will be handled as follows: • Undergoing surgery for NP or receiving SCS for any reason will be considered nonresponders for time points after undergoing surgery or receiving SCS. (composite strategy) In addition, the missing data imputation rules are as follows: Patients having missing data at Week 24 will be considered nonresponders..	The number of participants and percentage with 95% continuity corrected Wilson confidence interval (CI). No additional imputation necessary.
Primary endpoint (Supplymentary analysis)	Proportion of participants with NPS improvement from baseline ≥1 at Week 24	mITT	The intercurrent events will be handled as follows: • Undergoing surgery for NP or receiving SCS for any reason for CRSwNP will be considered nonresponders for time points after undergoing surgery or receiving SCS. • Receiving intranasal corticosteroids (INCS) for CRSwNP up to Week 24 : Participants will be considered as non-responders (composite strategy). In addition, the missing data imputation rules are as follows: Patients having missing data at Week 24 will be considered nonresponders.	The number of participants and percentage with 95% continuity corrected Wilson confidence interval (CI). No additional imputation necessary.
Secondary objective: To assess the efficacy of 24-week treatment with dupilumab 300 mg q2w on other efficacy endpoints in participants with CRSwNP who do not use concomitant INCS				

	Estimands			
Endpoint Category	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy (The missing data handling)**	**Population-level summary (Analysis method)**
Key secondary endpoints	Change from baseline to Week 24: • Bilateral NPS • NC symptom severity score • LMK score	PP	The intercurrent events will be handled as follows: • Taking rescue medications or undergo surgery prior to Week 24: data will be set to missing after the medication usage, and the participant's worst postbaseline value on or before the time of the medication usage or surgery will be used to impute the missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute) (hypothetical strategy) • Discontinuing the treatment prematurely (Participants who did not take rescue medications or undergo surgery): all data collected after treatment discontinuation will be used in the analysis (treatment policy strategy).	All imputed, complete data will be analyzed by descriptive statistics and 95% CI. The summarized mean changes obtained from each imputed dataset will be combined using Rubin's rule for a single estimate.

	Estimands			
Endpoint Category	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy (The missing data handling)**	**Population-level summary (Analysis method)**
Other secondary efficacy endpoints	• Change from baseline to Week 24: • Total symptom score • Loss of smell symptom severity score Visual analogue scale for rhinosinusitis		In addition, the missing data imputation rules are as follows: • After treatment discontinuation due to lack of efficacy prior to Week 24: WOCF approach will be used to impute the missing Week 24 value if needed • After treatment discontinuation due to reasons other than lack of efficacy prior to Week 24: multiple imputation approach assuming missing at random will be used to impute the missing Week 24 value, and this multiple imputation will use all participants, excluding participants who have taken rescue medications or undergone surgery on or before Week 24 and excluding participants who discontinue due to lack of efficacy on or before Week 24.	

	Estimands			
Endpoint Category	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy (The missing data handling)**	**Population-level summary (Analysis method)**
Key secondary (Supplymentary analysis)	Change from baseline to Week 24: • Bilateral NPS • NC symptom severity score • LMK score	mITT	The intercurrent events will be handled as follows: • Taking rescue medications or undergo surgery for CRSwNP prior to Week 24: data will be set to missing after the medication usage, and the participant's worst postbaseline value on or before the time of the medication usage or surgery will be used to impute the missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute) (hypothetical strategy) • Discontinuing the treatment prematurely (Participants who did not take rescue medications or undergo surgery): all data collected after treatment discontinuation will be used in the analysis (composite policy strategy). In addition, the missing data imputation rules are as follows: • After treatment discontinuation due to lack of efficacy prior to Week 24: WOCF approach will be used to impute the missing Week 24 value if needed After treatment discontinuation due to reasons other than lack of efficacy prior to Week 24: multiple imputation approach assuming missing at random will be used to impute the missing Week 24 value, and this multiple imputation will use all participants, excluding participants who have taken rescue medications or undergone surgery on or before Week 24 and excluding participants who discontinue due to lack of efficacy on or before Week 24.	

	Estimands			
Endpoint Category	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy (The missing data handling)**	**Population-level summary (Analysis method)**
Tertiary/exploratory objective: To assess the efficacy of 52-week treatment with dupilumab under different dosing regimens to participants with CRSwNP who do not use concomitant INCS				
	Proportion of participants with NPS improvement from baseline ≥1 at Week 52	PPE	The intercurrent events will be handled as follows: • Undergoing surgery for NP or receiving SCS for any reason will be considered nonresponders for time points after undergoing surgery or receiving SCS. (composite strategy) In addition, the missing data imputation rules are as follows: Patients having missing data at Week 52 will be considered nonresponders..	Descriptive statistics
	Change from baseline to Week 52 in: • Bilateral NPS • NC symptom severity score • LMK score • TSS score		The intercurrent events will be handled as follows: • Taking rescue medications or undergo surgery for NP prior to Week 52: data will be set to missing after the medication usage, and the participant's worst postbaseline value on or before the time of the medication usage or surgery will be used to impute the missing Week 52 value (for participants whose postbaseline values are all missing, the baseline will be used to impute) (hypothetical strategy) • Discontinuing the treatment(Participants who did not take rescue medications or undergo surgery): all data collected after treatment discontinuation will be used in the analysis (treatment policy strategy).	Descriptive statistics

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2 SAMPLE SIZE DETERMINATION

The EFC14280 study, which was conducted as a pivotal study for Nasal Polyposis, the proportion of responders (NPS improvement from baseline ≥1) at Week 24 was 62.0% in the dupilumab group. Based on this result, the target proportion of responders (NPS improvement from baseline ≥1) at Week 24 in this postmarketing study is at least 50.0% to reflect the similar effect size between EFC14280 and this study.

It is necessary for 20 participants to achieve this response rate (at least 50%) with a 90% probability of success. The sample size was adjusted up to 25 to account for a 20% drop-out rate.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined in Table 4.

Table 4 - Populations for analyses

Population	Description
Screened	All participants who signed the informed consent form (ICF).
Enrolled	The enrolled population includes all participants with a treatment kit number allocated and recorded in the interactive response technology (IRT) database, regardless of whether the treatment kit was used or not. Participants treated without a treatment kit number being allocated will not be considered enrolled and will not be included in any efficacy population.
Intent-to-treat (ITT)	Enrolled population with chronic rhinosinusitis with nasal polyposis (CRSwNP)
Modified ITT (mITT)	All participants in ITT allocated to study intervention administered at least 1 dose of study intervention
Per-protocol (PP)	All participants in mITT allocated to study intervention administered at least 1 dose of study intervention, and who did not receive intranasal corticosteroids (INCS) up to Week 24
Per protocol with extension term (PPE)	All participants in mITT allocated to study intervention administered at least 1 dose of study intervention during the intervention period after Week 24, and who did not receive INCS throughout the study
Safety (SAF)	All participants allocated to study intervention administered at least 1 dose of study intervention before Week 24
Safety for extension term (SAFE)	All participants allocated to study intervention administered at least 1 dose of study intervention during the intervention period after Week 24
Population without trial impact (disruption) due to COVID-19	A Population without trial impact (disruption) due to COVID-19 is defined as any participant in randomized population: - without any critical or major deviation related to COVID-19 - and who didn't permanently discontinue treatment due to COVID-19 - and who didn't permanently discontinue study due to COVID-19.

Abbreviations: CRSwNP: chronic rhinosinusitis with nasal polyposis; ICF: informed consent form; INCS: intranasal corticosteroids; IRT: interactive response technology; ITT: intent-to-treat; mITT: modified ITT; PP: per protocol; PPE: per protocol with extension term; SAF: safety; SAFE: safety for extension term

Efficacy analyses for the treatment period up to Week 24 will be performed using the per protocol (PP) population. Efficacy analyses for the treatment period after Week 24 will be performed using the per protocol with extension term (PPE) population. Additionally, supportive efficacy analyses will be performed using the modified intent-to-treat (mITT) population.

Safety analyses for the treatment period up to Week 24 will be performed using the Safety population, including all participants allocated to study intervention and administered at least one dose of study medication prior to Week 24. Safety analyses for the treatment period after Week 24 will be performed using the Safety for extension term population, including all participants allocated to study intervention administered at least 1 dose of study intervention after Week 24.

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

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

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

Regarding the COVID-19 pandemic, additional summaries by COVID-19 subgroups will be provided to assess the impact of the COVID-19 on treatment effect. Participants impacted by the COVID-19 pandemic are defined as randomized participants with any critical or major deviation related to COVID-19 or who permanently discontinued study intervention or study due to COVID-19.

4 STATISTICAL ANALYSES

The database lock will be performed when all participants have completed their treatment phase. Final analyses in the clinical study report will be based on all data collected up to this database lock.

4.1 GENERAL CONSIDERATIONS

The baseline value of efficacy parameters is defined as the last available value up to enrollment(Visit 2) but prior to the first dose of study medication unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of investigational medicinal product (IMP). The baseline value of the other parameters is defined as the last available value prior to the first dose of IMP if the patient is treated, or the last available value up to enrollment if the patient is not exposed to IMP.

During the treatment term, including efficacy variables after Week 24, continuous variables and binary variables for efficacy by each visit will be summarized using descriptive statistics and frequency tables in the PP and mITT populations. Analyses up to Week 52 will be run using the PPE population, including data through Week 24.

All safety analyses up to Week 24 will be analyzed for the SAF analysis population. Safety data collected during the extension term after Week 24 up to Week 52 will be reported for the SAFE analysis population. Safety analyses for the extension term will be presented by dose regimen group and overall.

Observation period

The observation period will be divided into 2 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **treatment-emergent period** is defined as the period from the first IMP administration to the last visit in the study or the date of treatment discontinuation if discontinued from the study, whichever is earlier.

Dose regimen groups

Dose regimen groups in the extension term after Week 24 will be defined as follows:

- 300 mg q2w group: participants who were administered at least 1 dose of the 300 mg q2w regimen and never experienced q4w administration during the extension term after Week 24
- 300 mg q4w group: participants with stable disease who were administered at least 1 dose of the 300 mg q4w regimen during the extension term after Week 24

Rescue

Participants who have undergone surgery or received SCS for any reasons are considered rescued. NP surgery and SCS use will be determined by the corresponding eCRF pages.

The date of rescue will be the earliest date of having undergone surgery or received SCS for any reason.

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be summarized.

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

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled. The number (%) of screen failures and reasons for screen failures will be provided in the Screened population.

The number (%) of participants in the following categories will be provided:

- Screened participants
- Enrolled participants
- Enrolled but not exposed participants
- Enrolled and exposed participants
- Participants who completed the Week 24 study treatment period as per protocol
- Participants who did not complete the Week 24 study treatment period as per protocol and main reason for permanent treatment discontinuation including due to COVID-19
- Participants with nasal polyp score (NPS) improvement from baseline to both Weeks 16 and 24 is ≥ 2 points.
-
- Participants who decreased treatment to the q4w regimen
  - Participants who completed the Week 52 study treatment period as per protocol
  - Participants who did not complete the Week 52 study treatment period as per protocol and the main reasons for permanent treatment discontinuation including due to COVID-19
  - Participants rescued prior to Week 52 by type of rescue
- Participants who continued the q2w regimen
  - Participants who completed the Week 52 study treatment period as per protocol

- Participants who did not complete the Week 52 study treatment period as per protocol and the main reasons for permanent treatment discontinuation including due to COVID-19
- Participants rescued prior to Week 52 by type of rescue

For all categories of participants (except for the screened categories), percentages will be calculated using the number of enrolled participants as the denominator.

4.3 PRIMARY ENDPOINT ANALYSIS

4.3.1 Definition of endpoints

The primary endpoint is the proportion of responders, defined as the proportion of participants with a nasal polyp score (NPS) improvement from baseline ≥1, at Week 24. Baseline will be the central reading at Visit 2. If a Visit 2 reading is missing, the central reading at Visit 1 will be used.

The NPS is assessed by central video recordings of nasal endoscopy (NE). The NPS is the sum of the right and left nostril scores and is graded based on polyp size as described below in Table 5.

Table 5 - Endoscopic nasal polyp score

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

Nasal endoscopy should be performed at the end of the scheduled visits before the administration of IMP and should be preceded by local administration of anesthetic drugs in combination with a decongestant. NE will be conducted at the Screening Visit (Visit 1), Visit 2, and Visits 4 to 9.

Standard video sequences will be downloaded or sent to a 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 NE to confirm the eligibility score and enter the result in the e-CRF. Thus, the participant will be 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 on each side.

Further details on NE is available in a separate operational manual provided to the sites.

4.3.2 Main analytical approach

The number of participants and percentage with the 95% continuity corrected Wilson confidence interval (CI) will be provided at Week 24 using the PP population.

The main strategy for handling intercurrent events will be a Composite approach, where participants who are rescued (undergo surgery for NP or receive SCS for any reason) will be considered nonresponders for time points after rescue. Participants who have missing data at Week 24 will be considered nonresponders.

The date of rescue will be the earliest date of any intercurrent events that occur.

4.3.3 Sensitivity analysis

There are no sensitivity analyses planned.

4.3.4 Supplementary analyses

The primary endpoint, the proportion of responders, defined as the proportion of participants with a nasal polyp score (NPS) improvement from baseline ≥1, at Week 24 will be analyzed using the mITT population and the following methodologies for intercurrent events:

- **Composite strategy:** Censor participants with INCS use, SCS, and surgery for CRSwNP prior to Week 24 at the earliest date of all intercurrent events. These participants will be categorized as nonresponders at timepoints after the censoring date.

Missing data related to the primary endpoint will be tabulated including by relation to the COVID-19 pandemic. If necessary, additional supplementary analyses will be presented.

4.3.5 Subgroup analyses

The number and percent of responders with NPS improvement from baseline ≥1 at Week 24 will be presented by the following subgroups within the PP analysis population:

- Age group (18-64, 65-74, ≥75 years)
- Gender (Male, Female).

Intercurrent events and missing data will be handled using the same methodology as Estimand 1 Participants who receive INCS are excluded from the PP analysis population. Participants who undergo surgery for NP, receive SCS for any reason, or have missing data will be considered nonresponders for time points after the earliest date of all intercurrent events that occur.

4.4 SECONDARY ENDPOINTS ANALYSIS

4.4.1 Key secondary endpoints

- Change from baseline to Week 24 in bilateral NPS

- Change from baseline to Week 24 in NC symptom severity score using the CRSwNP nasal symptom diary
- Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the LMK score

4.4.1.1 Definition of endpoints

Change from baseline to Week 24 in bilateral NPS is defined as the difference between the central reading NPS at Week 24 and the central reading NPS at Visit 2. If the central reading value at Visit 2 is missing, the central reading value from Visit 1 will be used.

See Section 4.3.1 for additional details regarding NE.

Change from baseline to Week 24 in NC symptom severity score:
On a daily basis from Visit 1 and throughout the study, the participant will use a diary to respond to the morning individual rhinosinusitis symptom questions evaluating symptom severity over the past 24 hours using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms) as described in Table 6 below.

Table 6 - Symptom severity score

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

A NC symptom severity score ≥2 at Visit 1 and a weekly average severity >1 at the time of enrollment (Visit 2) are required and will be provided to the site to determine participant eligibility. The participant must have 4 or more measurements collected within 7 days prior to enrollment; the baseline will be the average of the non-missing measurements.

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For the baseline to EOT/EOS analysis, the average of the symptom severity scores from the most recent 4 weeks before a scheduled visit will be used.

Change from baseline to Week 24 in LMK score

Computerized tomography (CT) scan should be performed anytime during the Screening Period before the first administration of IMP and at Visits 7 and 9 (Weeks 24 and 52). Whenever possible, a cone beam CT scan should be utilized.

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

The LMK system is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side. The osteomeatal complex (OC) is graded as 0 = not occluded or 2 = occluded. Adding the scores of these 6 parameters will derive a maximum score of 12 per side (left and right). The total score of the 2 sides will be used for analysis. This scoring system has been validated in several studies(1)(2)(3).

For participants in whom the OC is missing (because of a previous surgery), the reader should consider the location of the previous OC and provide a score (as if the OC were there).

4.4.1.2 Main analytical approach

Handling of missing data

Each of the 3 key secondary efficacy endpoints will be analyzed using the PP population and a hybrid method of worst observation carried forward (WOCF) and multiple imputation. For participants taking rescue medications or who undergo surgery, their data after the medication usage or surgery will be set to missing, and the worst postbaseline value on or before the time of the medication usage or surgery will be used to impute the missing Week 24 value. Participants who discontinue the treatment prematurely are encouraged to follow the planned clinical visits, and in those participants who did not take rescue medications or undergo surgery, all data collected after treatment discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts to collect the data after treatment discontinuation. For participants who discontinue due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute the missing Week 24 value if needed. For participants who discontinue not due to lack of efficacy, a multiple imputation approach assuming missing at random will be used to impute the missing Week 24 value, and this multiple imputation will use all participants, excluding participants who have taken rescue medications or undergone surgery on or before Week 24 and excluding participants who discontinue due to lack of efficacy on or before Week 24. All of the imputed complete data will be analyzed by descriptive statistics with the 95% CI. The summarized mean changes obtained from each imputed dataset will be combined using Rubin's rule for a single estimate.

The following steps will be used to create the primary imputed datasets:

- Impute any missing baseline values with the mean baseline value of all participants with non-missing baseline data.
- For participants who are rescued (undergo surgery for NP or receive SCS for any reason) or discontinue treatment early due to lack of efficacy:
  - Set all data on or after earliest date of rescue or treatment discontinuation to missing.
  - Replace all missing values with the worst observation prior to the missing data through Week 24, including baseline values.
- For participants who are not rescued, discontinue treatment for reasons other than lack of efficacy, or complete the study:

- Create 1 dataset with monotone missing pattern using the Markov Chain Monte Carlo (MCMC) method including values at all applicable visits through Week 24 in chronological order including baseline.

- For participants having missing data at Week 24 regardless of reason(s), a multiple imputation (MI) approach will be used to impute the missing endpoint value
- Set both datasets together.
- The remaining missing data will be imputed 40 times using the regression method for the monotone pattern with adjustment for values at all applicable visits through Week 24 in chronological order including baseline.
- Applying Rubin's rule to combine analysis results (means and standard errors) from 40 imputations using PROC MIANALYZE for the final estimated mean and 95% CL.

Missing data related to the key secondary endpoints will be tabulated including by relation to the COVID-19 pandemic. If necessary, additional supplementary analyses will be presented.

4.4.1.3 Supplementary analyses

The key secondary endpoint, change from baseline to Week 24 for Bilateral NPS, NC symptom severity score and LMK score will be analyzed using the mITT population and the following methodologies for intercurrent events:

- **Treatment policy strategy:** Discontinuing the treatment prematurely (Participants who did not take rescue medications or undergo surgery): all data collected after treatment discontinuation will be used in the analysis
- **Hypothetical strategy**: Taking rescue medications or undergo surgery for CRSwNP prior to Week 24: data will be set to missing after the medication usage, and the participant's worst postbaseline value on or before the time of the medication usage or surgery will be used to impute the missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute).

4.4.2 Supportive secondary endpoints

- Change from baseline at Week 24: Total symptom score (TSS)
- Change from baseline at Week 24: Loss of smell severity score
- Visual analogue scale for rhinosinusitis

4.4.2.1 Definition of endpoints

Change from baseline at Week 24 in TSS and Loss of smell severity score
TSS is a composite score (ranging between 0 and 9) consisting of the sum of the following symptoms assessed daily in the morning: nasal congestion/obstruction, decreased/loss of sense of smell, and rhinorrhea (average of the non-missing anterior/posterior nasal discharge). At least 2 symptoms scores must be reported to calculate the TSS, otherwise the score will remain missing.

The symptoms scores at baseline and changes from baseline will be calculated using the same approach as for NC as described in Section 4.4.1.1. Baseline is defined as the average of the non-missing 7 days prior to enrollment and requires ≥4 responses. Timepoints will be evaluated using the average symptom severity from the most recent 28 days before each scheduled visit. Participants with fewer than 28 days in between visits will use data from one day after the previous visit through the day of the current visit. At least 50% of days (with a maximum of 28) must be non-missing in order to calculate the average symptom severity.

Change from baseline to Week 24 in reported Visual analogue scale (VAS) for rhinosinusitis
The VAS for rhinosinusitis is used to evaluate the total severity (4) based on the distance (cm) from 0 to a subject's response to the following question:

"How troublesome are your symptoms of your rhinosinusitis?"

The response can be categorized as MILD, MODERATE, and SEVERE based on total severity VAS score [0 (Not troublesome) to 10 cm (Worst thinkable troublesome)]:

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

4.4.2.2 Main analytic approach

The supportive secondary efficacy endpoints (TSS, Loss of smell severity, VAS) will be analyzed using similar methodology as the key secondary endpoints using the PP population. Additionally, the number and percent of participants with VAS scores ≤7 cm will be presented using similar methodology for intercurrent events as the primary endpoint (Estimand 1).

4.5 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS

4.5.1 Tertiary/Exploratory Endpoints

- Proportion of participants with NPS improvement from baseline ≥1 at Week 52
- Change from baseline to Week 52 in bilateral NPS
- Change from baseline to Week 52 in NC symptom severity score using the CRSwNP nasal symptom diary
- Change from baseline to Week 52 in opacification of sinuses assessed by CT scan using the LMK score
- Change from baseline to Week 52 in TSS
- Same as primary and secondary endpoints

4.5.2 Main Analytical approach

4.5.2.1 Proportion of participants with NPS improvement from baseline ≥1 at Week 52

The number of participants and percentage with the 95% continuity corrected Wilson confidence interval (CI) will be provided at Week 52 in the PPE analysis population, similar to the primary endpoint (Estimand 1).

Participants who are rescued (undergo surgery for NP or receive SCS for any reason) will be considered nonresponders for time points after rescue. Participants who have missing data at Week 52 will be considered nonresponders.

4.5.2.2 Change from baseline to Week 52

Descriptive statistics for the exploratory efficacy endpoints (NPS, NC symptom severity score, LMK score, and TSS at Week 52) will be presented by dose regimen group and overall using the PPE analysis population.

4.5.2.3 Same as primary and secondary endpoints

Primary and secondary endpoints up to Week 24 will be summarized each visit. These endpoints after Week 24 up to Week 52 will be summarized each visit by dose regimen group and overall. Imputation will not be used.

4.6 MULTIPLICITY ISSUES

No hypothesis testing will be performed within this study.

4.7 SAFETY ANALYSES

4.7.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the Safety population until Week 24 and the Safety for extension term population after Week24.

If needed, extent of exposure to investigational medicinal product will be summarized for participants experiencing disruption due to COVID-19.

The participants who received COVID-19 vaccines are summarized.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP date – first IMP date

- + 14 days at the time of last IMP for the q2w group and
- + 28 days at the time of last IMP for the q4w regimen,

regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively and categorically: 1 to 2 weeks, 3 to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, 13 to 18 weeks, 19 to 24 weeks, 25 to 30 weeks, 31 to 36 weeks, 37 to 42 weeks, 43 to 48 weeks, 48 to 52 weeks, and >52 weeks. The duration of treatment exposure in weeks will be the duration (in days)/7, rounded to the nearest integer.

Duration of study will be summarized separately and analyzed descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). The duration of study is defined as date of study completion (or discontinuation) – date of first dose of IMP + 1.

Treatment compliance

A given administration will be considered noncompliant if the participant did not take the planned number of doses as required by the protocol.

Percentage of treatment compliance for a participant will be defined as the number of injections (a partial injection will be counted as 1 injection) a participant took divided by the total number of planned injections from the first to the last injection of IMP *100. Number of planned injections is calculated as:

- For q2w participants,
  1 + (last dose date – first dose date + 1)/14, rounded to the nearest integer
- For q4w participants,
  1+ [(Week 24 date – 1) – first dose date + 1)/14 +
  (last dose date – Week 24 date + 1)/28, rounded to the nearest integer

Treatment compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of participants whose compliance is <60, ≥60 and <80, ≥80% and ≤100%, or >100% will be summarized.

4.7.2 Adverse events

General common rules for adverse events

All safety analyses up to Week 24 will be analyzed for the SAF. Safety data collected during the extension term after Week 24 up to Week 52 will be reported for the SAFE. Safety analyses for the extension term will be presented by dose regimen group and overall.

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the latest MedDRA version currently in effect at the time of DBL.

AEs will be categorized as:

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

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

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

An AE with incomplete or missing date/time of onset will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If severity is missing for 1 of the treatment-emergent occurrences of an AE, the severity will be imputed as the maximal severity of the other occurrences. If the severity is missing for all the occurrences, severity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 7.

Table 7 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a],
SMQ/CMQ and PT	By decreasing frequency of SMQs/CMQs and PTs
SOC	By the internationally agreed SOC order
PT	By decreasing frequency of PTs

a The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any severe TEAE
- Any TEAE related to IMP

- Any treatment emergent SAE
- Any treatment emergent SAE related to IMP
- TEAE leading to death
- Any TEAE leading to permanent treatment discontinuation
- Any treatment emergent AE of special interest (AESI)

The AE summaries in Table 8 will be generated with number (%) of participants experiencing at least one event.

Table 8 - Analyses of adverse events

Type of AE	MedDRA levels
Overview	
TEAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
	Primary SOC
	PT
TEAE related to IMP as per Investigator's judgment	Primary SOC, and PT
Treatment emergent SAE	Primary SOC, HGLT, HLT and PT
TEAE leading to permanent discontinuation	Primary SOC, HGLT, HLT and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC, HGLT, HLT and PT
TEAE by maximal intensity	Primary SOC, HGLT, HLT and PT
Pretreatment AE	Primary SOC, HGLT, HLT and PT
Post-treatment AE	Primary SOC, HGLT, HLT and PT
TEAE(s) related to COVID-19	Primary SOC, HGLT, HLT and PT
TEAE(s) occurred within 2 weeks of a COVID-19 vaccine	Primary SOC, HGLT, HLT and PT

a Will include the following AE categories: any AEs, AEs by severity, any related AEs, any serious AEs, any related serious AEs, any AEs leading to death, any AEs leading to permanent IMP discontinuation

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) will be selected for analyses as indicated inTable 9. Number (%) of participants experiencing at least one event will be provided for each event of interest, sorted by decreasing incidence of PTs within each SMQ in the 300 q2w . Tables will be sorted as indicated in Table 7.

Table 9 - Selections for AESIs and other AEs of interest

AESIs [and other AEs of interest]	Selection
AESI	
Anaphylactic reactions	Anaphylactic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries (SMQs)): includes anaphylactic reaction narrow SMQ (20000021) 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	SMQ [20000214] 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
Helminthic infections	CMQ10544 based on HLGT as "Helminthic disorder"
Any severe type of conjunctivitis	CMQ10498 based on PTs (See Section 5.6)a and "Severe" ticked in Adverse Events eCRF page
Any severe type of blepharitis.	CMQ10497 based on HLT as "Lid, lash and lacrimal infections, irritations and inflammations" and "Severe" ticked in Adverse Events eCRF page
Keratitis	CMQ10642 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, herpes ophthalmic, ophthalmic herpes simplex, corneal infection]a
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)b	CMQ10641 based on HLT = Eosinophilic disorders or PT=Eosinophil count increased
Significant ALT elevation	ALT >5 × the ULN in participants with baseline ALT ≤2 × ULN for age; OR ALT >8 × ULN for age if baseline ALT >2 × ULN for age
Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP	"Pregnancy" or "Partner Pregnancy" checked on thePregnancy eCRF page as reported by the investigator
Symptomatic overdose (serious or nonserious) with IMP/NIMP.	Symptomatic Overdose is answered Yes, with Overdose of IMP answered Yes on AE eCRF.
Other selected AE Grouping	
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥ 24 hours or ongoing
Severe or serious infection	Primary SOC = 'Infections and infestations' and with severe or serious status
Parasitic infection	The Infection Type 'Parasitic' was checked on eCRF page "Infection Defined as AESI Complementary Form"
Opportunistic infection	The Infection Type 'Opportunistic' was checked Yes on eCRF page "Infection Defined as AESI Complementary Form"

AESIs [and other AEs of interest]	Selection
Drug-related hepatic disorder	SMQ [20000006] Drug-related hepatic disorders- narrow
Injection site reaction	HLT = 'Injection site reaction'
Suicidal behavior	CMQ10639 based on the following PTs [Completed suicide, Suicidal ideation, Depression suicidal, Suicidal behavior, Suicide attempt][a]
Conjunctivitis (narrow)	CMQ10644 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis][a]
Conjunctivitis (broad)	CMQ10645 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia][a]
Conjunctivitis (FDA)	CMQ10643 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye irritation, Eye inflammation, Giant papillary conjunctivitis][a]

a The list of terms may be adjusted according to MedDRA version changes

b All cases of Eosinophilia will be included in the analysis, where cases associated with clinical symptoms will be further described in the CSR

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables and vital signs will be converted into standard international units and analyzed.

- Hematology:
  - Red blood cells and platelets and coagulation: [hemoglobin, hematocrit, red blood cell count, platelet count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose, total cholesterol, total protein, albumin, creatine phosphokinase
  - Electrolytes: sodium, potassium, chloride
  - Renal function: creatinine, blood urea nitrogen, uric acid.
    Creatinine clearance will be derived with the equation of Cockroft and Gault using weight assessed at the same visit as creatinine. eGFR will be derived using the Modification of the Diet in Renal Disease (MDRD) equation.
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin
  - Pregnancy test: Serum and urine β-human chorionic gonadotropin (all childbearing potential female participants)
- Urinalysis:

  - Urinalysis for quantitative analysis: pH, specific gravity, glucose, protein, blood, ketones, urobilinogen, nitrite by dipstick
- Vital signs:
  - pulse rate, systolic and diastolic blood pressure, weight, respiratory rate, temperature

ECG data are used for screening purposes only.

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

Grading (LLN, ULN) will be derived using local laboratory normal ranges.

Quantitative analyses

For all laboratory variables and vital signs above, descriptive statistics for results and changes from baseline will be provided for each planned visit during the on-treatment period. These analyses will be performed using local measurements, converted into SI units for laboratory variables.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. Parameters with no PCSA criteria defined, similar analyses will be done using the local normal ranges, if applicable.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements.

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

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

Additional analyses for drug-induced liver injury(if applicable)

The following additional analyses will be performed for drug-induced liver injury:

- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.

4.8 OTHER ANALYSES

No other analyses are planned.

4.9 INTERIM ANALYSES

No interim analysis is planned.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE: adverse event
AESIs: adverse events of special interest
CI: confidence interval, confidence interval
CRSwNP: chronic rhinosinusitis with nasal polyps
CT: computerized tomography
HGLT: high level group term, high level group term, high level group term, high level group term
HLT: high level term
INCS: intranasal corticosteroid
ITT: intent-to-treat
LLT: lower-level term
LMK: Lund Mackay
MCMC: Markov Chain Monte Carlo
MedDRA: Medical Dictionary for Regulatory Activities
mITT: modified intent-to-treat
NE: nasal endoscopy
NPS: nasal polyp score
PCSA: potentially clinically significant abnormality
PP: per protocol
PPE: per protocol extension
PT: preferred term
q2w: every 2 weeks
q4w: every 4 weeks
SAF: safety population
SAFE: safety population for extension
SAP: statistical analysis plan
SCS: systemic corticosteroid
SOC: system organ class
TEAE: treatment-emergent adverse event
WHO-DD: World Health Organization-Drug Dictionary
WOCF: worst observation carried forward

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

Protocol Version	Approval Date	Changes	Rationale
1	11-May-2021	4.1 GENERAL CONSIDERATIONS	This is to prevent the case that patient discontinues treatment very

Protocol Version	Approval Date	Changes	Rationale
		Observation period · The treatment-emergent period is defined as the period from the first IMP administration to the last visit in the study **or the date of treatment discontinuation if discontinued from the study, whichever is earlier.**	early, but have a EOS conducted, for example, 24 weeks after the last IMP.
		4.1 GENERAL CONSIDERATIONS *Rescue* Participants who have undergone surgery **or** received SCS for any reasons~~, and/or received selected prohibited medications~~ are considered rescued. NP surgery and SCS use will be determined by the corresponding eCRF pages~~, while selected prohibited medications will be determined based on corresponding WHODD code in EFC14280~~. The date of rescue will be the earliest date of having undergone surgery **or** received SCS for any reason~~, and/or received selected prohibited medications~~. And delete "selected prohibited medications" in the sections related to changes to the above definitions.	For the purpose of consistency with EFC14280, it focus the following data handling. · only surgery for NP or receive SCS triggers non-responder imputation · rescue treatment define as undergone surgery or received SCS

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

5.3.1 Protocol deviations

Critical and major protocol deviations (automatic or manual), including drug dispensing irregularities, will be summarized in the Enrolled analysis population. Protocol deviations due to the COVID-19 pandemic will be categorized as such.

5.3.2 Demographics and baseline characteristics

Demographic variables are

- Gender (Male, Female)
- Race
- Ethnicity
- Age in years (quantitative and qualitative variable: 18-64, 65-74, ≥75)
- Region
- Weight in kg (quantitative and qualitative variable: <50, 50-<100, ≥100 kg)

- BMI in kg/m^2 (quantitative and qualitative variable: <30, ≥30 kg/m2)

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for all enrolled participants. Categorical and ordinal data will be summarized using the number and percentage of participants enrolled.

Baseline safety and efficacy parameters will be presented along with the safety and efficacy summaries.

5.3.3 Medical or surgical history

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

This information will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at the time of database lock.

Comorbidity will be summarized separately. The following comorbid disease will be summarized from eCRF pages completed by investigators based on participant reporting. Asthma will be captured under disease characteristics at baseline.

Medical and surgical history will be summarized for enrolled participants and by SOC and PT, sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC.

5.3.4 Disease characteristics at baseline

The following baseline disease characteristics will be summarized (see Section 5.4.1 for calculation details):

- Time since first diagnosis of nasal polyposis (years)
- Age of onset at nasal polyposis (years)
- 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 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 (anterior)
  - Excision, nasal polyp(s), extensive
  - Excision, nasal polyp(s), simple
  - Excision or destruction (eg,laser), intranasal lesion; internal approach
- Time since most recent nasal polyposis surgery (years)
- Smoking history (former, current, never)
- Cessation prior to screening (months) for former smokers
- Smoking quantity (cigarettes per day)
- Frequency of alcohol drinking in the past 12 months (never, occasional, at least monthly, as least weekly, at least daily)
- For daily drinkers, Number of standard alcohol drinks on a typical day (1 or 2, >2)
- Asthma comorbidity status (Yes, No)
  For asthma participants, the following will be provided:
  - Age at onset of asthma (Years)
  - Time since first diagnosis of asthma (years)
  - Time since last asthma exacerbation (days)
  - Number of asthma exacerbations experienced 1 year before visit 1 (comorbid asthma patients only, quantitative variable and qualitative variable: 0, 1, 2, 3, ≥4)
- Number of courses of systemic corticosteroid (SCS) use during the past 2 years (0, 1, 2, 3, 4, ≥5). A course of SCS is considered continuous if treatment is separated by less than 7 days.
- Number of days of SCS use during the past 2 years (0, >0 - ≤7, >7 - ≤14, >14 - ≤21, 21 - ≤28, >28)

Any technical details related to computation, dates, and imputations for missing dates are described in Section 5.4.2.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for enrolled participants. Categorical and ordinal data will be summarized using the number and percentage of enrolled participants.

5.3.5 Prior and concomitant medications

All medications taken within 30 days prior to screening and until end of the study, including nasal polyposis medications, chronic rhinosinusitis medications, asthma medications, and all other medications are to be reported in the case report form (CRF) pages.

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

Prior medications are those the participant used prior to first IMP injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.

Concomitant medications are any treatments received by the participant concomitantly to the IMP, anytime from the first administration of IMP to the end of study. A given medication can be classified as a prior medication and a concomitant medication at the same time.

Any technical details related to computation, dates, imputation for missing dates are described in Section 5.4.4.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, patients may be counted several times for the same medication.

Medication tables will be sorted by decreasing frequency of ATC followed by all other therapeutic classes. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used. Concomitant medication received during first IMP to last IMP +14 days and concomitant medication received during first IMP to end of study will be summarized separately.

Medications will also be summarized by generic name sorted by decreasing frequency.

COVID-19 vaccines

The participants who received COVID-19 vaccines are summarized.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 Demographic formulas

Age (years) = Year of informed consent - Year of birth

Age at onset of nasal polyposis (years) =
Year of nasal polyposis diagnosis date - Year of birth

BMI (kg/m^2) = Weight (kg) / $height^2$ (meters)

They all will be 18 and above per the inclusion, creatinine clearance (CLcr) value will be derived using the equation of Cockroft and Gault:

CLcr (ml/min) =
(140-age) × weight (kg) × (1 - 0.15 × sex(0-M, 1-F)) / (0.814 × creatinine (µmol/l))

CLcr will be calculated using the last weight measurement on or before the visit of the creatinine measurement and age at the lab sampling date.
Here age is calculated as following:

Age = Year of lab sampling date - Year of birth

5.4.2 Disease characteristics formulas

- Time since first diagnosis of nasal polyposis (years):
(Year of enrollment – Year of first diagnosis of nasal polyposis) + (month of enrollment-month of first diagnosis of nasal polyposis)/12
- Time since most recent nasal polyposis surgery (years):
(Year of enrollment – Year of most recent nasal surgery) + (month of enrollment-month of most recent nasal surgery)/12
- Cessation prior to screening (months) for former smokers:
(Year of enrollment - Year of cessation)×12 + (month of enrollment – month of cessation)
- For asthma participants, the following will be provided:
  - Time since first diagnosis of asthma (years):
(Year of enrollment - Year of first diagnosis of asthma) + (month of enrollment - month first diagnosis asthma)/12Times since last asthma exacerbation (days):
Date of enrollment - date of last asthma exacerbation

5.4.3 Reference dates

The baseline value of efficacy parameters is defined as the last available value up to enrollment but prior to the first dose of study medication unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of investigational medicinal product (IMP).

5.4.4 Missing Data

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

Treatment Duration when IMP end date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

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

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 and a concomitant medication.

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 treatment, the adverse event will be classified as treatment emergent. 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.

Missing date and time of first IMP administration

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 treatment-emergent adverse events.

The **exposure duration** should be kept as missing.

Missing assessment of relationship of AEs to IMP

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 possibly related adverse events, but no imputation should be done at the data level.

Missing severity of adverse events

If the severity 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.

Missing data while evaluating PCSAs

Participants missing baseline will be grouped in the category “normal/missing at baseline.”

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.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

5.4.5 Timepoint assessment

Analysis windows for time points

For VAS for rhinosinusitis, Vital signs, and Laboratory assessments. The analysis windows post baseline of Table 10 will be generated.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

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

Table 10 - Analysis window definition

Scheduled visit post baseline	Target day	Nasal endoscopy	CT scan	VAS for rhinosinusitis	Vital signs	Laboratory assessments
V3 (W2)	15	-	-	1+ to 21	-	-
V4 (W4)	29	1+ to 42	-	22 to 42	-	-
V5 (W8)	57	43 to 84	-	43 to 84	1+ to 84	1+ to 112
V6 (W16)	113	85 to 140	-	85 to 140	85 to 140	-
V7 (W24)	169	141 to 224	1+ to 265	141 to 224	141 to 224	113 to 265
V8 (W40)	281	225 to 321	-	225 to 321	225 to 321	-
V9 (W52)	364	322 =<	266 =<	322 =<	322 =<	266 =<

1+: after 1st dose date/time

Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.5 APPENDIX 5 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA

Table 11 - Criteria for Potentially Significant Abnormalities – for Phase 2/3 studies

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI >1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT >3 ULN and TBILI >2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

Parameter	PCSA	Comments
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		

Parameter	PCSA	Comments
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN ≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
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.

Parameter	PCSA	Comments
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline	FDA Feb 2007.
	≥5% decrease from baseline	

5.6 APPENDIX 6 SELECTION CRITERIA FOR AE/MEDICATION GROUPINGS

Table 12 - List of PTs or Medications for CMQs/CDGs

Grouping	Preferred Term/Medication Code	Preferred Term/Medication
Conjunctivitis	10001257	Adenoviral conjunctivitis
Conjunctivitis	10010725	Conjunctival irritation
Conjunctivitis	10010726	Conjunctival oedema
Conjunctivitis	10010736	Conjunctival ulcer
Conjunctivitis	10010741	Conjunctivitis
Conjunctivitis	10010744	Conjunctivitis allergic
Conjunctivitis	10010745	Conjunctivitis chlamydial
Conjunctivitis	10010749	Conjunctivitis gonococcal neonatal
Conjunctivitis	10010754	Conjunctivitis tuberculous
Conjunctivitis	10010755	Conjunctivitis viral
Conjunctivitis	10018258	Giant papillary conjunctivitis
Conjunctivitis	10021629	Inclusion conjunctivitis
Conjunctivitis	10030861	Ophthalmia neonatorum
Conjunctivitis	10048908	Seasonal allergy
Conjunctivitis	10049458	Herpes simplex virus conjunctivitis neonatal
Conjunctivitis	10051625	Conjunctival hyperaemia
Conjunctivitis	10053991	Inclusion conjunctivitis neonatal
Conjunctivitis	10061784	Conjunctivitis bacterial
Conjunctivitis	10062889	Pingueculitis
Conjunctivitis	10063669	Photoelectric conjunctivitis
Conjunctivitis	10067317	Oculorespiratory syndrome
Conjunctivitis	10067817	Acute haemorrhagic conjunctivitis
Conjunctivitis	10069166	Blebitis
Conjunctivitis	10071570	Ligneous conjunctivitis
Conjunctivitis	10074701	Noninfective conjunctivitis
Conjunctivitis	10075264	Oculoglandular syndrome
Conjunctivitis	10080825	Conjunctivitis fungal
Conjunctivitis	10084034	Conjunctival suffusion

Grouping	Preferred Term/Medication Code	Preferred Term/Medication
Intravenous immunoglobulin therapy	CAS 8000012671	IMMUNOGLOBULIN HUMAN NORMAL
Intravenous immunoglobulin therapy	CAS 8000050682	IMMUNOGLOBULIN, PORCINE
Intravenous immunoglobulin therapy	CAS 8000056919	IMMUNOGLOBULIN G HUMAN
Intravenous immunoglobulin therapy	CAS 8600000563	IMMUNOGLOBULINS NOS
Intravenous immunoglobulin therapy	CAS 8600001670	IMMUNOGLOBULIN HUMAN NORMAL SLRA
Intravenous immunoglobulin therapy	CAS 8600001671	IMMUNOGLOBULIN HUMAN NORMAL IFAS
Intravenous immunoglobulin therapy	RECNO 900708	OTHER IMMUNOGLOBULINS
Intravenous immunoglobulin therapy	RECNO 900722	IMMUNE SERA AND IMMUNOGLOBULINS
Intravenous immunoglobulin therapy	RECNO 900728	IMMUNOGLOBULINS
Intravenous immunoglobulin therapy	RECNO 900914	SPECIFIC IMMUNOGLOBULINS
Intravenous immunoglobulin therapy	RECNO 901112	IMMUNOGLOBULINS, NORMAL HUMAN

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