STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with uncontrolled, chronic rhinosinusitis without nasal polyposis (CRSsNP)**
Protocol number:	**EFC16723**
Compound number (INN/Trademark):	**SAR231893 dupilumab/Dupixent®**
Study phase:	**Phase 2**
Short Title:	**Dupilumab in CRSsNP Acronym: Liberty CRSsNP ORION**
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This Statistical Analysis Plan (SAP) for study EFC16723 is based on the protocol dated 23-Feb-2023 (amended protocol 02).

The first participant was randomized on 24-Feb-2021.

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in adult participants with uncontrolled chronic rhinosinusitis without nasal polyposis (CRSsNP).

After a screening period of 2 to 4 weeks, approximately 70 participants will be centrally randomized (using permuted block randomization schedule) via Interactive Response Technology (IRT) in a 1:1 ratio to dupilumab 300 mg q2w or placebo. Randomization will be stratified by screening blood eosinophil count ($\geq$300 cells/mm^3 or <300 cells/mm^3), background intranasal corticosteroids (INCS) use (yes or no) and region. To ensure enrollment according to the intended distribution of screening blood eosinophil count, the number of participants in each stratification group will be controlled as follows:

- $\geq$300 cells/mm^3: approximately 15 participants per arm,
- <300 cells/mm^3: approximately 20 participants per arm.

In addition, in order to have an adequate number of participants with comorbid asthma, the number of participants without comorbid asthma will be limited to no more than 70% of the randomized population.

The study has a 24 to 52-week treatment period. Study treatment will stop for all participants when the last participant has completed 24 weeks of treatment. Therefore, all participants following protocol amendment 02 will be treated for at least 24 weeks and the other participants (enrolled before amendment 02) will have a variable treatment period which may be up to 52 weeks.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on computerized tomography (CT) scan in the dupilumab group only	• Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the Lund-Mackay (LMK) score in the dupilumab group
Secondary	
To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on CT scan and sinus total symptom score (sTSS) compared to placebo	• Change from baseline to Week 24 in opacification of sinuses assessed by CT scan using the LMK score • Change from baseline to Week 24 in sTSS* **Composite severity score consisting of nasal congestion, anterior/posterior rhinorrhea, facial*

Objectives	Endpoints
	pain/pressure items of the CRSsNP sinonasal symptom e-diary
• To evaluate the safety and tolerability of dupilumab in CRSsNP patients compared to placebo	• Incidence of treatment-emergent adverse events (TEAEs), of treatment-emergent serious AEs (TESAEs), and TEAEs leading to treatment discontinuation, abnormal laboratory values, and vital signs
• To evaluate the pharmacokinetics (PK) of dupilumab in CRSsNP patients	• Dupilumab concentration in serum
• Assessment of immunogenicity to dupilumab over time	• Assessment of immunogenicity to dupilumab as determined by the incidence, titer, and neutralizing antibody (NAb) status of treatment-emergent anti-drug antibody (ADA) response over time
Exploratory	
• [redacted]	[redacted]

Objectives	Endpoints
• [redacted]	[redacted]

1.2.1 Estimands

Primary estimand defined for the primary endpoint is summarized in Table 2. More details are provided in Section 3.2.2.

Table 2 - Summary of primary estimand for the primary endpoint

Endpoint Category	Estimand			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary objective: To evaluate the efficacy of dupilumab as assessed by the reduction at Week 24 in sinus opacification on computerized tomography (CT) scan in the dupilumab group only				
Primary endpoint	Change from baseline in LMK score at Week 24	ITT with screening blood eosinophil count ≥ 300 cells/mm^3	The intercurrent events (IEs) will be handled as follows: • Undergoing sinonasal surgery for CRSsNP or taking systemic corticosteroids (SCS) for any reason prior to Week 24: data after the IE will be excluded from the analysis and the worst post-	Descriptive statistics and 95% confidence interval (CI) in the dupilumab group will be provided.

Endpoint Category	Estimand			
	Endpoint	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
			baseline value on or before the time of the IE will be used to assign the Week 24 value (WOCF). For participants with no post-baseline values, the baseline value will be used (composite strategy). • Taking other prohibited/rescue medications: all data collected after use will be used in the analysis (treatment policy strategy). • Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy). Missing data will not be imputed.	

2 ANALYSIS POPULATIONS

The following populations for analyses are defined. The primary population of the efficacy endpoints is the ITT population with screening blood eosinophil count ≥ 300 cells/mm^3.

Table 3 - Populations for analyses

Population	Description
Screened	All participants who sign the informed consent form.
Randomized	The randomized population includes all participants with a treatment kit number allocated and recorded in the IRT database, and regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.
Intent-to-treat (ITT)	All randomized participants analyzed according to the treatment group allocated by randomization regardless if treatment kit is used or not.
ITT with screening blood eosinophil count ≥300 cells/mm^3	All randomized participants with screening blood eosinophil count ≥300 cells/mm^3 analyzed according to the treatment group allocated by randomization regardless if treatment kit is used or not.
ITT with screening blood eosinophil count <300 cells/mm^3	All randomized participants with screening blood eosinophil count <300 cells/mm^3 analyzed according to the treatment group allocated by randomization regardless if treatment kit is used or not.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who accidentally receive different study intervention from the planned, the actual intervention allocation for as-treated analysis will be the dupilumab group.
Pharmacokinetic (PK)	The PK population includes all participants in the safety population with at least 1 non-missing result for functional dupilumab concentration in serum after the first dose of the study intervention. Participants will be analyzed according to the intervention actually received.
Anti-drug antibody (ADA)	ADA population includes all participants in the safety population who have at least 1 non-missing result in the ADA assay after the first dose of the study intervention. Participants will be analyzed according to the intervention actually received.
Population without trial impact (disruption) due to COVID-19	All randomized participants: • without any critical or major deviation related to COVID-19 • and who did not permanently discontinue treatment due to COVID-19 • and who did not permanently discontinue study due to COVID-19.

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

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

For any participant randomized more than once, only the data associated with the first randomization (except if the first randomization is done by error) will be used in any analysis

population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the dupilumab group.

If >10% participants are impacted by the COVID-19 pandemic, additional summaries by COVID-19 subgroups will be provided. 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.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants. The summary statistics will be provided at each visit, including data collected beyond Week 24.

The baseline value of efficacy parameters is defined as the last available value up to randomization date and prior to the first dose of study medication unless otherwise specified. The baseline value of the other parameters is defined as the last available value prior to the first dose of investigational medicinal product (IMP) if the participant is treated, or the last available value up to randomization date if the participant is not exposed to IMP.

For endpoints collected on the daily CRSsNP sinonasal symptom diary, baseline is defined as the average of the scores in the 7 days prior to randomization. If there are less than 7 but at least 4 non-missing scores available, the baseline score is the average of the available scores in the 7 days. If there are less than 4 non-missing scores, then baseline will be the average of the most recent 4 days with non-missing scores prior to randomization.

Stratification factors used in analyses will be derived based on eCRF data (for background INCS and region) or central laboratory data (for screening blood eosinophil count).

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

Observation period

The observation period will be divided into 4 segments:

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

The on-study observation period is defined as the time from the first IMP until the end of the study defined as the last scheduled visit for those who completed the study and the end-of-study date

collected on electronic case report form (e-CRF) page "Completion of End of Study/Follow-up" for those who did not complete the study. If death is the end-of-study reason, date of death will be used.

3.2 PRIMARY ENDPOINT ANALYSIS

3.2.1 Definition of endpoint

The primary endpoint is the change from baseline to Week 24 in LMK score in the dupilumab group. The LMK score is based on assessment of the CT scan findings for each sinus area (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side). The extent of mucosal opacification is rated on a 3-point scale ranging from 0 = normal to 2 = total opacification. In addition, the ostiomeatal complex is graded as 0 = not occluded or 2 = occluded. The maximum score is therefore 12 per side for a maximum total score of 24, corresponding to the sum of all sinuses and the ostiomeatal unit.

3.2.2 Main analytical approach

The primary endpoint will be analyzed on the ITT with screening blood eosinophil count ≥ 300 cells/mm^3 population in the dupilumab group. Intercurrent events (IE) handling strategies are described below:

- The following IE will be handled with the composite strategy:
  - Undergoing sinonasal surgery for CRSsNP or taking SCS for any reason prior to Week 24: data after surgery (actual date) or SCS use will be excluded from the analysis and the worst post-baseline value on or before the time of surgery or SCS use will be used to assign the Week 24 value (ie, WOCF approach). For participants with no post-baseline values, the baseline value will be used.
- The following IEs will be handled with the treatment policy strategy (without IE that need to be handled with composite strategy). Data collected after starting such IEs will be included.
  - Taking other prohibited/rescue medications.
  - Discontinuing the study intervention.

No missing data will be imputed. Descriptive statistics (number of participants, mean, SD, median, minimum and maximum) and 95% CI of the mean (based on the t distribution) in the dupilumab group will be provided.

3.3 SECONDARY ENDPOINTS ANALYSIS

Efficacy secondary endpoints are described in this section. Non-efficacy secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3.1 (laboratory abnormalities and vital signs), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity).

3.3.1 Definition of endpoints

The sTSS is the sum of nasal congestion/obstruction, anterior/posterior rhinorrhea, and facial pain/pressure. The total score ranges from 0 to 9 with higher scores indicating greater overall symptom severity. The sTSS will be analyzed as 28-day averages (Table 8).

3.3.2 Main analytical approach

Change from baseline to Week 24 in LMK score and in sTSS comparing dupilumab to placebo will be analyzed on the ITT with screening blood eosinophil count ≥ 300 cells/mm^3 population. Handling of IEs will follow that of the primary endpoint. Otherwise, no missing data will be imputed. Descriptive statistics will be provided by intervention group. Mean treatment difference (dupilumab vs placebo) and the corresponding 95% CI (based on the t distribution) will be provided.

3.4 EXPLORATORY ENDPOINTS ANALYSIS

The exploratory endpoints described in this section are the change from baseline to Week 24 efficacy endpoints and PGIC at Week 24. Other exploratory endpoints analyses are defined in Section 3.7.1.3 (biomarkers) and Section 3.7.1.4 (health care resource utilization and productivity). Analyses of [redacted] in the type-2 inflammation transcriptome signature, as well as endpoints related to [redacted] will be addressed in separate documents.

3.4.1 Definition of endpoints

EQ-5D-5L health status will be converted into a single index value by using value sets based on UK population. The anterior/posterior rhinorrhea score is the average of the anterior and posterior scores. The ACQ-6 global score is the mean of the 6 questions. UPSIT score and the SNOT-22 total score are the sum of all items.

For endpoints related to sinonasal symptom diary (NC, anterior/posterior rhinorrhea, facial pain/pressure, loss of smell and headache), the 28-day average scores will be used for analysis (Table 8).

For the three-dimensional CT volumetric measurement of the paranasal sinuses, each test (air volume, lateral wall thickness, volume occupied by disease, and mucosal volume), including location (ethmoid sinus, frontal sinus, maxillary sinus, and sphenoid sinus), laterality (right and left) and direction (anterior and posterior for ethmoid sinus) will be analyzed separately and as the mean of the left and right measurements. The total volume occupied by disease in all sinuses will also be summarized.

3.4.2 Main analytical approach

Change from baseline to Week 24 endpoints and PGIC at Week 24 will be analyzed on the ITT with screening blood eosinophil count ≥ 300 cells/mm^3 population comparing dupilumab to placebo except for the following:

- Change from baseline to Week 24 in FEV_1 and in ACQ-6 will be analyzed on the ITT with screening blood eosinophil count ≥ 300 cells/mm^3 and with comorbid asthma subgroup in the dupilumab group.
- Change from baseline to Week 24 in LMK and in sTSS will be analyzed on the ITT population (regardless of blood eosinophil count) in the dupilumab group.

Handling of IEs will follow that of the primary endpoint. Otherwise, no missing data will be imputed. Descriptive statistics will be provided by intervention group. For endpoints comparing dupilumab to placebo, treatment difference (dupilumab vs placebo) and the corresponding 95% CI will be provided. For endpoints analyzed in the dupilumab group, 95% CI in the dupilumab group will be provided. The 95% CI will be constructed based on the t distribution.

3.4.3 Exploratory analyses on the [redacted]

Change from baseline to Week 24 in [redacted] comparing dupilumab to placebo will be analyzed using the same approach as the secondary endpoints on the [redacted] populations.

3.5 MULTIPLICITY ISSUES

No adjustments for multiplicity are planned for this Phase 2 study.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided.

3.6.1 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.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 14 days, 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: >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 and ≤28 weeks, >28 and ≤32 weeks, >32 and ≤36 weeks, >36 and ≤40 weeks, >40 and ≤44 weeks, >44 and ≤48 weeks, >48 and ≤52 weeks, >52 weeks and ≤52 weeks + 3 days, >52 weeks + 3 days.

Additionally, the cumulative duration of treatment exposure (expressed in participant-years) will be provided.

Treatment compliance

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

Percentage of treatment compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.

3.6.2 Adverse events

General common rules for adverse events

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 Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

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

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

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. Missing 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 4.

Table 4 - 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[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the dupilumab 300mg q2w group

Analysis of all adverse events

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

- Any TEAE
- Any severe TEAE
- Any treatment-emergent SAE
- TEAE leading to death
- Any TEAE leading to permanent study intervention discontinuation
- Any treatment-emergent AESI
- Any treatment-emergent other AE of interest grouping
- Any TEAE related to IMP

The AE summaries of Table 5 will be generated with number (%) of participants experiencing at least one event.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
	PT
	Primary and secondary SOC, HLGT, HLT and PT
Common TEAE (≥5% in any group)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment-emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent intervention discontinuation	Primary SOC and PT
TEAE leading to death[b]	Primary SOC and PT
COVID-19 related TEAE	Primary SOC and PT
Pre-treatment AE	Overview[a]
Post-treatment AE	Overview[a]

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation (pre-treatment AEs only)
b Death as an outcome of the AE as reported by the Investigator in the AE page

Analysis of deaths

In addition to the analyses of deaths included in Table 5 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods
- Deaths in non-randomized or randomized but not treated participants

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 6. Number (%) of participants experiencing at least one event will be provided for each event of interest, by PT if applicable. Tables will be sorted as indicated in Table 4.

Table 6 - Selections for AESIs and other AEs of interest

AESIs and other AEs of interest	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1): 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 5.5)[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 followed by blinded medical review
Pregnancy of female participants entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP	"Pregnancy" or "Partner Pregnancy" checked on the Pregnancy eCRF page as reported by the investigator
Significant ALT elevation	"ALT increase" and AESI answer "Yes" checked on AE eCRF as reported by the Investigator (ALT >5 x ULN in participants with baseline ALT ≤2 x ULN; OR ALT >8 x ULN if baseline ALT >2 x ULN)
Symptomatic overdose with IMP	Symptomatic Overdose is answered Yes, with Overdose of Study Treatment answered Yes on AE eCRF.
Symptomatic overdose with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP 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 reactions' 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	Infection type "Parasitic" checked on eCRF "Infection Event Form"
Opportunistic infection	Has the AE been assessed as opportunistic infection? is answered Yes on eCRF "Infection Event Form"

AESIs and other AEs of interest	Criteria
Drug-related hepatic disorder	SMQ [20000006] Drug-related hepatic disorders- narrow
Injection site reactions	HLT = 'Injection site reactions'
Malignancy	SMQ [20000091]- Malignant or unspecified tumors narrow
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 [redacted])[c]	CMQ10643 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye irritation, Eye inflammation, Giant papillary conjunctivitis] [a]
Keratitis [redacted])[c]	CMQ30102 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, ophthalmic herpes simplex] [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
c Labeling subgroup of preferred terms included in the USPI for Dupixent.

The following summaries will be provided:

- All TEAEs, by selected standardized MedDRA query (SMQ)/Customized MedDRA query (CMQ) and PT, showing the number (%) of participants with at least 1 PT.
- For each AESI and other selected AE groupings,
  - Number (%) of participants with any TEAE
  - Number (%) of participants with any serious AE (regardless of treatment-emergent status)
  - Number (%) of participants with any treatment-emergent serious AE
  - Number (%) of participants with any AE leading to death
  - Number (%) of participants with any TEAE leading to permanent study intervention discontinuation
  - Number (%) of participants with any TEAE related to IMP reported by investigator
  - Number (%) of participants with any TEAE by maximum intensity, corrective treatment, and final outcome
  - Number (%) of participants with any TEAE adjusted by the exposure duration
- Number (%) of participants with injection site reactions by the related injection.
- Number (%) of participants with different number of injection site reactions.

In addition, AESIs reported by the investigator in eCRF will be summarized separately.

Analysis of exposure-adjusted incidence rate

If the cumulative duration of treatment exposure is imbalanced between dupilumab and placebo, then the number of participants with at least one TEAE per 100 participant-years will be provided for the below summaries:

- Overview of adverse events profile
- TEAE by primary SOC and PT
- Common TEAE (≥5% in any group) by primary SOC and PT
- Treatment-emergent SAE by primary SOC and PT
- TEAE leading to permanent intervention discontinuation by primary SOC and PT
- Treatment-emergent AESI and other selected AE grouping events by category and PT

For participants with an event, the number of participant-years will be calculated up to the first event; for participants without an event, the number of participant-years will correspond to the length of the treatment-emergent period.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables and vital signs

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

- 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
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Renal function: creatinine, creatinine clearance, blood urea nitrogen, uric acid
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin
  - Pregnancy test: Urine pregnancy test
- Vital signs: heart rate, systolic and diastolic blood pressure, weight, respiratory rate, temperature, BMI

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

Quantitative analyses

For laboratory and vital signs variables above, descriptive statistics for results and changes from baseline will be provided for each analysis window, the last value and the worst value during the on-treatment period. These analyses will be performed using central measurements only for laboratory variables.

For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time.

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. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

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

For laboratory and vital signs variables 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

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

- Time to onset of the initial alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) during the treatment-emergent period will be analyzed using Kaplan-Meier method.
- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ ULN in case of missing baseline) before last IMP dose, Returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

Predose serum dupilumab concentrations at Visit 2 (Day 1), dupilumab trough levels at Week 12, Week 24, Week 52 and posttreatment serum dupilumab at the End of Study (EOS) visit will be provided. Given the variable treatment period, the EOS visit may be between 36 to 64 weeks.

Serum concentrations of SAR231893 (REGN668) will be summarized in the PK population using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time. If date and/or time of the drug injection and/or sampling is missing, then the concentration will not be taken into account. For drug-treated participants, where concentration values are below the LLOQ, one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three significant figures. For participants in the placebo group, concentration values below the LLOQ will be taken into account with a plasma concentration considered equal to 0.

3.7.1.2 Immunogenicity analyses

Dupilumab anti-drug antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 12, Week 24, Week 52 and EOS visit will be provided. Given the variable treatment period, the EOS visit may be between 36 to 64 weeks. The neutralizing antibody results for ADA positive samples will be provided.

Incidence will be provided for the following ADA response categories. Treatment-emergent and treatment-boosted response will be defined based on samples collected in the on-treatment period.

Pre-existing immunoreactivity is defined as:

An ADA positive response in the assay at baseline with all post first dose ADA results negative, OR an ADA positive response at baseline with all post first dose ADA responses less than 4-fold over baseline titer levels.

Treatment-emergent ADA responses are defined as:

A positive response in the ADA assay post first dose, when baseline results are negative or missing.

Treatment-emergent ADA responses are further classified as persistent, indeterminate or transient

a) Persistent response - defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days), with no ADA negative samples in between.

b) Indeterminate response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay

c) [redacted]

Treatment-boosted response is defined as:

[redacted]

The following summary will be provided based on ADA population:

- Number (%) of participants with pre-existing immunoreactivity
- Number (%) of participants with treatment-emergent ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for participants with treatment-emergent ADA, and participants with persistent, indeterminate and transient ADA response
- Number (%) of participant with transient treatment-emergent ADA
- Number (%) of participants with persistent treatment-emergent ADA
- Number (%) of participants with indeterminate treatment-emergent ADA
- Number (%) of participants with treatment-boosted ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for participants with treatment-boosted ADA
- The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) of the ratio of peak post-baseline titer to baseline titer for participants with treatment-boosted ADA
- Listing of ADA peak titer levels and neutralizing antibody status
- Number (%) of participants with neutralizing antibody status

Kinetics of treatment-emergent ADA response

Number (%) of participants with treatment-emergent ADA positive response at each visit will be summarized by each intervention group.

Plot of percentage of participants with treatment-emergent ADA positive response at each visit will be provided by each intervention group.

3.7.1.2.1 Association of Immunogenicity with Exposure, Safety and Efficacy

The safety and efficacy analysis mentioned below will be conducted using the following categories:

ADA positive participants: Participants with treatment-emergent or treatment-boosted response.

ADA negative participants: Participants with pre-existing immunoreactivity or negative in the ADA assay at all time points.

Impact of ADA on PK profile

Potential associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and impact on serum concentration profile of dupilumab may be explored. Plot of serum concentration of functional dupilumab versus visit will be provided by ADA variables for each dupilumab dose group. Individual participant plots of dupilumab concentration according to ADA status will be provided.

Impact of ADA on clinical efficacy endpoints

Associations between the ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, treatment-boosted) and the primary efficacy endpoint may be explored for the dupilumab dosed group.

Association of ADA with clinical safety endpoints

Association of safety versus ADA status may be analyzed in the ADA population. The safety assessment may focus on the following events:

- Severe injection site reactions last longer than 24 hours or serious injection site reactions
- Hypersensitivity reactions (SMQ (20000214) hypersensitivity narrow search confirmed by medical review)
- Anaphylactic reactions (SMQ (20000021) anaphylactic reaction narrow search)

3.7.1.3 Biomarker analyses

Blood, urine, nasal secretions and nasal brushing biomarkers will be summarized on the safety population. Baseline values will be the last value collected prior to the first IMP. Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) of biomarkers at baseline and each post-baseline visit will be summarized.

Summary plots at each visit (mean, mean change from baseline and median percent change from baseline) will be provided for each biomarker by intervention group.

3.7.1.4 Health care resource utilization and productivity

The cumulative number of health care resource utilization and cumulative number of missed days of school/work will be summarized over the treatment period. Descriptive statistics (number of participants, mean, SD, median, minimum and maximum) will be provided.

3.8 INTERIM ANALYSES

No interim analysis is planned.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Table 7 - Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
1	08-Jul-2021	Addition of a secondary objective and related endpoints in Part A (at Weeks 24 and 52) as follows: Objective: To evaluate the effect of dupilumab in the subgroup of participants with screening blood eosinophil count ≥300 cells/mm^3 compared to placebo Endpoints: -Change from baseline to Weeks 24 and 52 (Part A) in opacification of sinuses assessed by CT scan using LMK score in the screening blood eosinophil count ≥300 cells/mm^3 population. -Change from baseline to Weeks 24 and 52 (Part A) in sinus total symptom score (sTSS) using the screening blood eosinophil count ≥300 cells/mm^3 population. -Evaluation of other secondary endpoints listed above in the screening blood eosinophil count ≥300 cells/mm^3 population.	To evaluate the effect of dupilumab in a subgroup of interest as the primary analysis population was changed to the ITT population regardless of eosinophil levels in Part A, per Health Authority request.
		The primary efficacy analysis population was changed from ITT population with screening blood eosinophil count ≥300 cells/mm3 to ITT population for Part A. Intercurrent event handling strategy for prohibited medications added in Table 7.	Per Health Authority request for Part A
		Power calculations updated for Part A. Screening blood eosinophil count added as covariate in model-based analyses for Part A. Multiplicity considerations updated	To reflect change in the primary efficacy analysis population
		Intercurrent event handling strategy for undergoing sinonasal surgery for CRSsNP prior to Week 24 was changed from “data after surgery will be assigned to the worst possible score (composite strategy)” to “Data	To change handling of sinonasal surgery in the primary estimand to an approach more appropriate for

Amendment Number	Approval Date	Changes	Rationale
		collected after surgery will be set to missing and the worst post-baseline value on or before the time of surgery will be used to impute missing Week 24 value (WOCF). For participants with no post-baseline values, the baseline value will be used (hypothetical strategy)." Sensitivity/supplementary analyses updated	this clinical setting and to update supplementary analyses accordingly
2	23-Feb-2023	Sample size determination updated. Primary population changed from ITT population to ITT population with screening blood eosinophil count ≥ 300 cells/mm3.	To reflect changes in the study primary objective and endpoint.
		Statistical hypotheses removed. Multiplicity consideration removed. Multiple imputation removed. Model-based analyses removed. Sensitivity and subgroup analyses removed. Use of descriptive statistics for all endpoints.	To apply more appropriate analysis methods based on the reduced sample size.
		The intercurrent events handling strategy for taking SCS for any reason prior to Week 24 was changed from 'all data collected after SCS use will be used in the analysis' to 'data after the IE will be set to missing and the worst post-baseline value on or before the time of the IE will be used to impute missing Week 24 value (WOCF)'.	To change handling of taking SCS for any reason in the primary estimand to an approach more appropriate for this clinical setting.
		Description of secondary analyses for proportion and time-to-event endpoints removed.	To reflect changes in the secondary objectives and endpoints.
		Updated the timing of analyses to only one database lock after all participants have completed the study.	To reflect the removal of Part B and shortened treatment duration of Part A.

4 SAMPLE SIZE DETERMINATION

Sample size calculation was performed to ensure reasonable accuracy for the estimation of the primary endpoint in participants treated with dupilumab with screening blood eosinophil count ≥300 cells/mm^3. With a 1:1 randomization ratio, a standard deviation (SD) of 5 and a dropout rate of 10%, a sample size of approximately 30 participants (15 per arm) with screening blood eosinophil count ≥300 cells/mm^3 will provide a half-width of approximately less than 3 for the 2-sided 95% CI in the dupilumab group which is deemed reasonable.

In addition, it is planned to include approximately 40 participants (20 per arm) with screening blood eosinophil count <300 cells/mm^3. Thus, the planned total sample size is approximately 35 participants per arm.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ACQ-6: asthma control questionnaire-6 items
ADA: anti-drug antibody
AE: adverse event
AESIs: adverse events of special interest
ALT: alanine aminotransferase
ATC: anatomic category
CI: confidence interval
CLcr: Creatinine clearance
CRSsNP: chronic rhinosinusitis without nasal polyposis
CT: computerized tomography
CV: coefficient of variation
e-CRF: electronic case report form
EOS: End of Study
FEV_1: forced expiratory volume
HLT: high level term
HRQoL: health-related quality of life
IEs: intercurrent events
IMP: investigational medicinal product
INCS: intranasal corticosteroids
IRT: Interactive Response Technology
ITT: intent-to-treat
LLOQ: lower limit of quantification
LLT: lower-level term
LMK: Lund-Mackay
MedDRA: medical dictionary for regulatory activities
NAb: neutralizing antibody
NC: nasal congestion
NES: Normalized Enrichment Score
PCSA: potentially clinically significant abnormality
PGIC: Patient Global Impression of Change
PGIS: Patient Global Impression of Severity
PK: pharmacokinetics
PT: preferred term
SCS: systemic corticosteroids
SD: standard deviation
SEM: standard error of the mean
SMQ: standardized MedDRA query
SNOT-22: Sino-Nasal Outcomes Test-22 item
SOC: system organ class
sTSS: sinus total symptom score

TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TESAEs:	treatment-emergent serious adverse events
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
UPSIT:	University of Pennsylvania smell identification test
VAS:	visual analog scale
WHO-DD:	World Health Organization-drug dictionary
WOCF:	worst observation carried forward

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. 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:

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation.
- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to the COVID-19 pandemic, if applicable.

The number (%) of exposed and not randomized participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, randomized, with permanent intervention discontinuation and with early study discontinuation will be provided by country and site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population as well as displayed separately as related versus not related to the COVID-19 pandemic if applicable. In addition, deviations potentially impacting the primary endpoint analysis may be summarized.

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

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population.

Demographic variables are:

- Age in years as quantitative variable and in categories (18-<65, 65 - <75, 75 - <85 and ≥85 years)
- Gender (Male, Female)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Island, Multiple, Not reported, Unknown)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- Region (**Asia:** China, South Korea; **Latin America:** Argentina, Chile; **East Europe:** Hungary, Russia, Ukraine; **Western Countries:** Belgium, Canada, Portugal, Spain, Sweden, USA)
- Territory (**North America:** Canada, USA; **European Union:** Belgium, Hungary, Spain, Portugal, Sweden**; Rest of World:** Argentina, Chile, China, South Korea, Russia, Ukraine)
- Weight in kg as quantitative variable
- BMI in kg/m^2 as quantitative variable and in categories (<25, ≥25-<30, ≥30 kg/m^2)

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

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 a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

CRSsNP and allergic comorbidities will be summarized separately. The following comorbid disease will be summarized from eCRF pages which were filled in by investigators based on participant reporting.

- Chronic rhinosinusitis without nasal polyps (Yes, Ongoing condition)
- Posterior nasal drip (Yes, Ongoing condition)
- Diminished sense of smell (Yes, Ongoing condition)
- Nasal congestion (Yes, Ongoing condition)
- Nasal discharge (Yes, Ongoing condition)
- Nasal polyps (Yes, Ongoing condition)
- Facial pain/pressure (Yes, Ongoing condition)
- Seasonal allergic rhinitis (Yes, Ongoing condition)
- Perennial allergic rhinitis (Yes, Ongoing condition)
- Allergic rhinitis (Yes, Ongoing condition)
- Allergic conjunctivitis (Yes, Ongoing condition)
- Atopic dermatitis (Yes, Ongoing condition)
- Epistaxis (Yes, Ongoing condition)
- Aspirin-exacerbated respiratory disease (Yes, Ongoing condition)
- Hives (Yes, Ongoing condition)
- Eosinophilic esophagitis (Yes, Ongoing condition)
- Egg allergy (Yes, Ongoing condition)
- Fish allergy (Yes, Ongoing condition)
- Milk allergy (Yes, Ongoing condition)
- Peanut allergy (Yes, Ongoing condition)
- Allery to nuts (Yes, Ongoing condition)
- Shellfish allergy (Yes, Ongoing condition)
- Soy allergy (Yes, Ongoing condition)
- Flour sensitivity (Yes, Ongoing condition)
- Gluten sensitivity (Yes, Ongoing condition)

Prior sinonasal surgery and systemic corticosteroid history will be summarized as below.

- Number of participants with prior sinonasal surgery and/or SCS use in the past 2 years before screening visit
- Number of participants with prior sinonasal surgery

- Number of prior sinonasal surgeries (quantitative and in categories of 1 or ≥ 2)
- Number of participants with prior sinonasal surgery by type
- Time since most recent sinonasal surgery (years)
- Number of participants with SCS use in the past 2 years before screening visit
- Number of SCS courses in the past 2 years before screening visit (quantitative and in categories of 1, 2, 3, 4, ≥ 5)
- Number of days with SCS use in the past 2 years before screening visit (quantitative and in categories of >0 - ≤7, >7 - ≤ 14, >14 - ≤ 21, >21 - ≤28, >28 - ≤56, >56 - ≤84, >84 - ≤112, >112)

In addition, asthma history will be summarized for participants with comorbid asthma:

- Age at asthma onset (years)
- Time since first diagnosis of asthma (years)

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by intervention group:

- Age at onset of CRSsNP (years)
- Time since first diagnosis of CRSsNP (years)
- Baseline LMK score
- Baseline sTSS
- Baseline 3-dimensional CT volumetric measurement of the paranasal sinuses
- Baseline nasal congestion/obstruction score
- Baseline anterior/posterior rhinorrhea score
- Baseline facial pain/pressure severity score
- Baseline loss of smell symptom severity score
- Baseline headache severity score
- Baseline UPSIT score
- Baseline SNOT-22 score
- Baseline rhinosinusitis VAS score
- Baseline EQ-VAS score
- Baseline EQ-5D-5L single index score
- Baseline PGIS score
- Comorbid asthma (Yes, No)

- Baseline FEV1 (L)
- Baseline FEV1 percent predicted (%)
- Baseline ACQ-6 score in participants with comorbid asthma
- Background INCS use
- Smoking history (Never, Former, Current)
- Frequency of alcohol drinking in the past 12 months (never, occasional, at least monthly, at least weekly, at least daily) and number of drinks on a typical day (1 or 2, >2)
- Screening blood eosinophil count (10^9/L)
- Screening blood eosinophil count category (<0.3, ≥0.3×10^9/L)

Prior or concomitant medications

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

- Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any interventions received by the participant concomitantly to the IMP, from first administration of IMP to last IMP intake + 98 days.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the randomized population.

Medications will be summarized by intervention 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 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 tables for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across intervention groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medication received between the first IMP to last IMP +14 days and concomitant medication received between the first IMP to last IMP + 98 days will be summarized separately. The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the dupilumab group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Demographic formulas

Age at onset of CRSsNP (years):

Year of first diagnosis of CRSsNP – Year of birth

Time since first diagnosis of CRSsNP (years):

(Year of randomization − Year of first diagnosis of CRSsNP) +

(Month of randomization − Month of first diagnosis of CRSsNP)/12

Time since most recent sinonasal surgery (years):

(Date of randomization – Date of most recent sinonasal surgery)/365.25 if a complete date of most recent sinonasal is available;

(Year of randomization – Year of most recent sinonasal surgery) + (Month of randomization – Month of most recent sinonasal surgery)/12 if year and month are available;

(Year of randomization – Year of most recent sinonasal surgery) if only year is available

Age at onset of asthma (years):

Year of first diagnosis of asthma – Year of birth

Time since first diagnosis of asthma (years):

(Year of randomization − Year of first diagnosis of asthma) +

(Month of randomization − Month of first diagnosis of asthma)/12

BMI is calculated as:

Weight in kg / (height^2 in meters)

Renal function formulas

For adults, creatinine clearance (CLcr) value will be derived using the equation of Cockroft and Gault:

$$\text{CLcr (ml/min)} = (140 - \text{age}) \times \text{weight (kg)} \times (1 - 0.15 \times \text{sex (0-M, 1-F)}) / (0.814 \times \text{creatinine (μmol/L)})$$

For participants <18 years old, CLcr value will be derived using the equation of GFR Bedside Schwartz

$$\text{GFR (mL/min/1.73 m}^2) = k \times \text{height (cm)} / \text{sCr (mg/dL)},$$

where the coefficient k = 0.65 for male adolescent participants or k = 0.55 for female adolescent participants

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

$$\text{Age} = \text{age collected at screening} + \text{integer part of (lab sampling analysis day / 365.25)}$$

Normalization of nasal secretion and urine biomarkers

Nasal secretion biomarkers will be normalized with total protein as the reference. Urine biomarkers will be normalized with creatinine as the reference. For example,

$$\text{normalized Tryptase (ug/mg)} = \text{Tryptase (ug/L)} / \text{Total protein (ug/mL)}$$

$$\text{normalized Leukotriene E4 (ng/mg)} = \text{Leukotriene E4 (ng/mg)} / \text{Creatinine (mg /mL)}$$

Daily e-diary weekly scores

For the daily efficacy endpoints (sTSS, NC, rhinorrhea, facial pain/pressure, loss of smell and headache), the time period used to calculate the periodical average score at each designated study day is summarized in Table 8. Randomization day is used as the reference day (Day 1).

Table 8 - Periodical average of daily efficacy assessment from e-diary

Analysis visit	Target day	Day range for calculating periodical average score
Week 4	29	2-29
Week 8	57	30-57
Week 12	85	58-85
Week 16	113	86-113
Week 20	141	114-141
Week 24	169	142-169
Week 28	197	170-197
Week 32	225	198-225
Week 36	253	226-253
Week 40	281	254-281
Week 44	309	282-309
Week 48	337	310-337

Analysis visit	Target day	Day range for calculating periodical average score
Week 52	365	338-d
EOT + 4 weeks	29*	2-29*
EOT + 8 weeks	57*	30-57*
EOT + 12 weeks	85*	58-85*

d: planned EOT date, EOT: End of Treatment, EOS: End of Study

* Relative to d

Analysis windows for time points

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP administration. Selected safety variables will be summarized by the analysis window defined in Table 9 for the by visit descriptive analysis. All available values from central lab will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same number of days away from the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to the Visit 2 window.

Table 9 - Time window for safety endpoints

Analysis visit	Target day	Time windows for		
		Vital signs	Laboratory (hematology, chemistry, urinalysis)	Urine pregnancy
Screening	-28 to -14	<-14	<-14	
Baseline	1	-14-1^{-}	-14-1^{-}	14-1^{-}
Week 2	15	1^{+}-49		
Week 4	29			1^{+}-42
Week 8	57			43-70
Week 12	85	50-126	1^{+}-126	71-98
Week 16	113			99-126
Week 20	141			127-154
Week 24	169	127-224	127-224	155-182
Week 28	197			183-210
Week 32	225			211-238
Week 36	253			239-266
Week 40	281	225-322	225-322	267-294
Week 44	309			295-322
Week 48	337			323-350
Week 52	365	>322	>322	>350

1^{-}: up to 1st dose date/time; 1^{+}: after 1st dose date/time;

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the randomization day. If a participant receives IMP prior to the randomization by mistake, the reference date of efficacy assessment will be the date of the first IMP administration for that participant. For the primary analyses, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 10. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same number of days away from the target day, the latest one will be used.

Table 10 - Time window for efficacy variables

		Time windows for							
Analysis visit	**Target day**	**LMK /3-D CT**	**UPSIT, VAS**	**SNOT-22**	**Spirometry**	**ACQ-6**	**EQ-5D-5L**	**PGIS, HCRU/P**	**PGIC**
Screening	-28 to -14				<-14				
Baseline	1	<1^{-}	<1^{-}	<1^{-}	-14-1^{-}	1^{-}	1^{-}	<1^{-}	
Week 2	15		1^{+}-91						
Week 12	85				1^{+}-126	1^{+}-126		1^{+}-126	1^{+}-126
Week 24	169	1^{+}-266	92-224	1^{+}-224	127-266	127-224	1^{+}-224	127-224	127-224
Week 40	281		225-322	225-322		225-322	225-322	225-322	225-322
Week 52	365	267-d	323-d	323-d	267-d	323-d	323-d	323-d	323-d
EOS*	NA		NA	NA	NA	NA			

d: planned EOT date, EOT: End of Treatment, EOS: End of Study

1^{-}: up to randomization and before 1st dose date/time; 1^{+}: after randomization or 1st dose date/time

* Data collected at the EOS visit will not be remapped

For the pharmacokinetics/pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP administration if the participant is treated with study intervention, or the randomization date if the participant is not treated. Pharmacokinetics /pharmacodynamics variables will be summarized by the analysis window defined in Table 11 for the by visit descriptive analyses. All available values of measurements will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same number of days away from the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to the Visit 2 window.

Table 11 - Time window for pharmacokinetics/pharmacodynamics variables

		Time windows for				
Analysis visit	**Target day**	**Serum dupilumab, ADA**	**Blood biomarkers**	**Urine biomarkers**	**Nasal secretions for protein biomarkers**	**Nasal brushing for RNA and cytology**
Screening	-28 to -14					
Baseline	1	<1^{-}	<1^{-}	<1^{-}	<1^{-}	<1^{-}
Week 2	15					
Week 12	85	1^{+}-126	1^{+}-126	1^{+}-126	1^{+}-126	
Week 24	169	127-266	127-266	127-266	127-266	1^{+}-266
Week 40	281					
Week 52	365	>266	>266	>266	>266	>266
EOS*	NA	NA				

1^{-}: up to randomization and before 1st dose date/time; 1^{+}: after randomization or 1st dose date/time
*PK and ADA data collected at the EOS visit will not be remapped

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. Unscheduled visit measurements for efficacy data will be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.5 APPENDIX 5 SELECTION CRITERIA FOR AE GROUPINGS

Table 12 - List of PTs for CMQs

Grouping	Preferred Term Code	Preferred Term
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

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