STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized double-blind placebo-controlled parallel group study assessing the efficacy and safety of dupilumab in patients with Allergic Fungal Rhinosinusitis (AFRS)**
Protocol number:	**EFC16724**
Compound number (INN/Trademark):	**SAR231893** **dupilumab/Dupixent®**
Study phase:	**Phase 3**
Short Title:	**Dupilumab in AFRS** **LIBERTY-AFRS-AIMS**
Statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for Study EFC16724 is based on the protocol dated 01-Mar-2023. This section summarizes the modifications made in the SAP from the Statistical Section in the protocol.

The first participant was randomized on 21-May-2021.

Modifications in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	22-Jan-2025	Data collected regarding the impact of COVID-19 or other pandemics on the participants will no longer be summarized.	COVID-19 or other pandemics have limited impact on study conduct currently.
		Taking prohibited biologics will not be considered as an IE for all efficacy endpoints (see Section 1.2.1, Section 3.2.2, and Section 3.3.1.2).	Prohibited biologics use is highly unlikely under the study conditions, and up to time of SAP approval there is no confirmed case of prohibited biologics use for the treatment of AFRS.
		Population-level summary of binary endpoints is changed from odds ratio based CMH method to risk difference based MH method (details in Section 3.3.2.2)	MH estimate of risk difference is more appropriate to quantify the treatment effect, compared to odds ratio from CMH method.

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 3, multicenter, 52-week treatment, parallel-group, double-blind, randomized, placebo-controlled study to investigate the efficacy of dupilumab in adults and pediatrics aged 6 years and older with signs and symptoms of AFRS.

After a screening phase of 2 to 4 weeks, approximately 62 participants with AFRS who satisfy the inclusion and exclusion criteria will be centrally randomized (using permuted block randomization schedule) via Interactive Response Technology (IRT) in a 1:1 ratio to receive either dupilumab or matching placebo. Randomization will be stratified first by age (adults versus adolescents/children [≥6 years old]). In adults, randomization will be stratified further by time from last surgery (≤2 years [including surgery naive participants], >2 years), disease pattern (unilateral/bilateral in the endoscopy at screening), and country. In adolescents/children, randomization will not be stratified further.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS)	• Change from baseline in sinus opacifications assessed by computerized tomography (CT) scans using the Lund Mackay (LMK) score at Week 52
Secondary	
• To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS) at Week 24	• Change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 24
• To assess the efficacy of dupilumab to reduce the need for rescue treatments	• Proportion of participants who receive SCS for any reason and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period
• To evaluate the efficacy of treatment with dupilumab in improving symptoms in AFRS	• Change from baseline in monthly average nasal congestion/obstruction score from the Nasal Symptom Diary at Week 24 and Week 52
	• Change from baseline in the monthly average anterior/posterior rhinorrhea score from the Nasal Symptom Diary at Week 24 and Week 52
• To evaluate the efficacy of dupilumab to reduce nasal polyp formation in participants with AFRS	• Change from baseline in endoscopic nasal polyp score (NPS) compared with placebo at Week 24 and Week 52
• To evaluate the efficacy of dupilumab in improving overall symptom severity and quality of life in AFRS	• Change from baseline in 22-item sino-nasal outcome test (SNOT-22) total score at Week 24 and Week 52

Objectives	Endpoints
• To evaluate the efficacy of dupilumab in improving sense of smell in participants with AFRS	• Change from baseline in monthly average total symptom score (TSS) derived from the Nasal Symptom Diary at Week 24 and Week 52 • Change from baseline in visual analog scale (VAS) rhinosinusitis at Week 24 and Week 52 • Change from baseline in University of Pennsylvania smell identification test (UPSIT) at Week 24 and Week 52 • Change from baseline in the score of decreased/loss of smell using the Nasal Symptom Diary at Week 24 and Week 52
• To explore the effect of dupilumab as assessed by three-Dimensional CT volumetric measurement of the paranasal sinuses	• Change from baseline to Week 52 in three-Dimensional CT volumetric measurement of the paranasal sinuses
• To evaluate the safety and tolerability of dupilumab when administered to participants with AFRS	• Incidence of treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) through Week 52
• To evaluate the PK of dupilumab in participants with AFRS	• Dupilumab concentration in serum over time
• To characterize the effect of dupilumab on total IgE and fungal-specific IgE	• Percent change from baseline in total IgE in serum compared with placebo over the 52-week treatment period • Percent change from baseline in fungal-specific IgE in serum compared with placebo over the 52-week treatment period
• To assess immunogenicity to dupilumab in participants with AFRS	• Assessment of incidence of treatment-emergent anti-drug antibodies (ADA) to dupilumab over time

[redacted]

Objectives	Endpoints
[redacted]	

1.2.1 Estimands

Primary estimand defined for main endpoints are summarized below in Table 2. More details are provided in Section 3.

For all these estimands, the comparison of interest will be the comparison of dupilumab versus placebo.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category	Estimands			
	Endpoint	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Primary objective: To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS)				
Primary endpoint	Change from baseline in LMK score at Week 52	ITT	The following intercurrent events will be handled with a composite strategy; data after the IE will be excluded and the worst post-baseline value on or before the start of the IE will be assigned to the Week 52 value (WOCF); for participants with no post-baseline values, the baseline value will be used. • Undergo/plan to undergo surgery for AFRS prior to Week 52	Mean difference between interventions in change from baseline in LMK score at Week 52 will be analyzed using ANCOVA model with the baseline LMK score, intervention group, time from last surgery (≤2 years, >2 years), and region[a] (Americas, Asia) as covariates. In addition, the missing data imputation rules are as follows:

Endpoint Category	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
			• Taking SCS for any reason/indication prior to Week 52 The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite strategy). All assessments after starting such IE will be included. • Discontinuing the study intervention • Taking antifungals or other prohibited/rescue medications	• After applying the strategies for intercurrent events, if there is still missing data multiple imputation (MI) approach will be used to impute missing endpoint value, and this MI will use all participants excluding participants who have taken SCS for any indication or underwent/plan to undergo surgery for AFRS before Week 52. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule.
Secondary objective: • **To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS) at Week 24** • **To assess the efficacy of dupilumab to reduce the need for rescue treatments** • **To evaluate the efficacy of treatment with dupilumab in improving symptoms in AFRS** • **To evaluate the efficacy of dupilumab to reduce nasal polyp formation in participants with AFRS** • **To evaluate the efficacy of dupilumab in improving overall symptom severity and quality of life in AFRS** • **To evaluate the efficacy of dupilumab in improving sense of smell in participants with AFRS** • **To explore the effect of dupilumab as assessed by three-Dimensional CT volumetric measurement of the paranasal sinuses** • **To characterize the effect of dupilumab on total IgE and specific IgE**				
Secondary endpoint	Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period	ITT	The following IEs will be handled with a treatment policy strategy: • Discontinuation of study intervention • Taking antifungals or other prohibited/rescue medications	Risk difference between interventions will be estimated using Mantel-Haenszel estimate and confidence limits, with Mantel-Haenszel stratum weights for time from last surgery (≤2 years, >2 years) and region[a] (Americas, Asia) and the Sato variance estimator. The P-value associated with Mantel-Haenszel method will be provided if appropriate. In addition, the missing data imputation rules are as follows: • Discontinuing the study follow-up without an event prior to discontinuation: Participant will be considered as no event.

Endpoint Category	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary endpoint	Continuous secondary efficacy endpoints	ITT	The following intercurrent events will be handled with a composite strategy; data after the IE will be excluded and the worst post-baseline value on or before the start of the IE will be assigned to the endpoint value (WOCF); for participants with no post-baseline values, the baseline value will be used. • Undergo/plan to undergo surgery for AFRS prior to endpoint visit • Taking SCS for any reason prior to endpoint visit The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite strategy). All assessments after starting such IE will be included. • Discontinuing the study intervention • Taking antifungals or other prohibited/rescue medications	Mean difference between interventions will be analyzed with the same ANCOVA method as the primary endpoint. Same multiple imputation approach will also be used to impute missing data.
Secondary endpoint	Percent change from baseline in total IgE in serum at Week 52	Safety	The following intercurrent events will be handled with a composite strategy; data after the IE will be excluded and the worst post-baseline value on or before the start of the IE will be assigned to the Week 52 value (WOCF); for participants with no post-baseline values, the baseline value will be used. • Undergo/plan to undergo surgery for AFRS prior to Week 52 • Taking SCS for any reason prior to Week 52 The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite strategy). All assessments after starting such IE will be included. • Discontinuing the study intervention • Taking antifungals or other prohibited/rescue medications	Mean difference between interventions will be analyzed with the same ANCOVA method as the primary endpoint. Same multiple imputation approach will also be used to impute missing data.

a Americas: Argentina, USA, Canada; Asia: China, Japan, India, Turkey, Saudi Arabia

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received or not.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who have taken at least 1 dose of study intervention, regardless of the amount of treatment administered. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All participants from the safety population with at least one post-baseline PK result. Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they actually received.
ADA	All participants from the safety population with at least one post-baseline ADA result (positive, negative or inconclusive). Participants will be analyzed according to the intervention they actually received.

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

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

All comparisons will be of dupilumab (300 mg q2w for adults and adolescents/children ≥60 kg at screening, or 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening, or 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening) versus placebo.

A multiplicity-controlled hierarchical approach is proposed to control the overall type-I error rate for testing the primary and selected secondary efficacy endpoints at an alpha of 0.05. The study is considered positive when the primary endpoint achieves statistical significance with 2-sided significance level 0.05.

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical data will be summarized using the count and percentage of participants.

The baseline value is generally defined as the last available value before the first dose of double-blind investigational medicinal product (IMP). For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

For endpoints collected on the daily Nasal Symptom Diary, if there are 4 or more measurements collected within 7 days prior to the first dose of double-blind IMP (or prior to randomization for participants randomized but not treated), baseline is defined as the average of the scores in the 7 days prior to the first dose of double-blind IMP (or prior to randomization for participants randomized but not treated); if less than 4 measurements are collected, the baseline will be the average of the most recent 4 measurements prior to the first dose of double-blind IMP (or prior to randomization for participants randomized but not treated).

Stratification factors used in analyses will be derived based on eCRF data (for age, time from last surgery and country) and central-reading nasal endoscopy data (for disease pattern).

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 first investigational medicinal product (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 for adults and adolescents/children ≥30 kg at screening or 28 days for adolescents/children ≥15 kg and <30 kg at screening.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoint detailed in this section is the change from baseline in sinus opacifications assessed by computerized tomography (CT) scans using the Lund Mackay (LMK) score at Week 52.

3.2.1 Definition of endpoint(s)

The primary endpoint is the change from baseline in LMK score at Week 52.

Lund Mackay total 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 with the estimand defined according to the following attributes:

- Endpoint: Change from baseline in LMK score at Week 52
- Treatment condition: dupilumab will be compared to placebo
- Analysis population: ITT population
- Intercurrent events (IE):
  - The following intercurrent events will be handled with a composite strategy; data after the IE will be excluded and the worst post-baseline value on or before the start of the IE will be assigned to the Week 52 value (WOCF); for participants with no post-baseline values, the baseline value will be used.
    - Undergo/plan to undergo surgery for AFRS prior to Week 52
    - Taking SCS for any reason prior to Week 52

  - The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite strategy). All assessments after starting such IE will be included.
    - Discontinuing the study intervention
    - Taking antifungals or other prohibited/rescue medications

- Population-level summary:

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with the baseline LMK score, intervention group, time from last surgery (≤2 years, >2 years), and region (Americas: Argentina, USA, Canada; Asia: China, Japan, India, Turkey, Saudi Arabia) as covariates, with intercurrent event strategies and missing data handling as defined in Table 3.

Data of participants who undergo/plan to undergo surgery for AFRS or take SCS for any reason on or before Week 52 will be excluded from analysis after the IE, and the worst postbaseline value on or before the start of IE will be used to assign missing endpoint value (for participants whose postbaseline values are all missing, the baseline will be used to impute). Participants who discontinue the intervention prematurely are encouraged to follow the planned clinical visits and in those participants who did not have any of the above IE, all data collected after intervention 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. A multiple imputation (MI) approach will be used to impute missing endpoint value, and this MI method will use all participants excluding participants with the above IE. The imputation number will be 40.

Each of the imputed complete data will be analyzed by fitting an ANCOVA model as described above. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) will be provided. In addition, difference of the dupilumab group against placebo in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-value.

A separate summary of primary endpoint will be provided for pediatric patients.

The multiple imputation and analysis model for the primary analysis of change from baseline in LMK values will be built with the following sample SAS code.

1. 40 datasets with a monotone missing pattern will be obtained, induced by Markov Chain Monte Carlo (MCMC) method on all participants excluding participants who undergo/plan to undergo surgery for AFRS or take SCS for any reason on or before Week 52.

```
proc mi data=ads out=monotone nimpute=40 seed=16724;
    where wocffl='N';
    var time region trt01p value0 value24 value52;
    mcmc chain=multiple impute=monotone;
run;
```

2. For each of the imputed datasets with monotone missing pattern in step 1, the remaining missing data at baseline and post-baseline visits will be imputed using regression method for the monotone missing pattern with adjustment for covariates including time from last surgery (≤2 years, >2 years), region (Americas, Asia) and intervention group.

```
proc mi data=monotone out=dat_mi nimpute=1 seed=16724 minimum=. . . 0 0 0
maximum=. . . 24 24 24; /*LMK score range is 0-24*/
      by _imputation_;
      class time region trt01p;
      var time region trt01p value0 value24 value52;
      monotone reg ( /details);
run;
```

3. Each of the 40 imputed datasets will be merged with one dataset imputed by WOCF approach, and then be analyzed using the main statistical model. These 40 imputed datasets will be saved.

```
%macro w1;
        %do i=1%to 40;
        data wocf&i.;
        set ads;
        where wocffl='Y';
        _imputation_=&i.;
        run;
        %end;
        data wocf_all;
         set %do j=1 %to 40; wocf&j. %end;;
         run;
      %mend w1;

      %w1;

      data mi;
          set dat_mi wocf_all;
      run;

proc sort data=mi; by _imputation_; run;

proc glm data=mi;
      by _imputation_;
      class time region trt01p;
      model change=time region trt01p value0;
      lsmeans trt01p / stderr;
      estimate 'Diff dupilumab vs placebo' trt01p -1 1;
      ods output LSMeans=lsmeans Estimates=estimates;
run;
```

4. Applying Rubin's rules to combine analysis results (point estimates and standard errors) from 40 imputations using PROC MIANALYZE for the LS means and difference in LS means between dupilumab and placebo.

```
proc sort data=lsmeans; by trt01p _imputation_; run;

proc mianalyze data=lsmeans;
      by trt01p;
      modeleffects lsmean;
      stderr stderr;
      ods output ParameterEstimates=lsmean;
run;

proc mianalyze data=estimates;
      modeleffects estimate;
      stderr stderr;
      ods output ParameterEstimates=lsmeandiff;
run;
```

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are secondary efficacy endpoints and selected secondary biomarker endpoint. Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.7.1.1 (PK), Section 3.7.1.2 (immunogenicity) and Section 3.7.1.4 (biomarker).

3.3.1 Secondary endpoint(s)

The Secondary efficacy endpoints include:

- Change from baseline in sinus opacification assessed by CT scans using the LMK score at Week 24
- Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period
- Change from baseline in monthly average nasal congestion/obstruction score from the Nasal Symptom Diary at Week 24 and Week 52
- Change from baseline in the monthly average anterior/posterior rhinorrhea score from the Nasal Symptom Diary at Week 24 and Week 52
- Change from baseline in endoscopy nasal polyp score (NPS) at Week 24 and Week 52
- Change from baseline in 22-item sino-nasal outcome test (SNOT-22) total score at Week 24 and Week 52
- Change from baseline in monthly average total symptom score (TSS) derived from the Nasal Symptom Diary at Week 24 and Week 52
- Change from baseline in visual analog scale (VAS) rhinosinusitis at Week 24 and Week 52
- Change from baseline in University of Pennsylvania smell identification test (UPSIT) at Week 24 and Week 52
- Change from baseline in the score of decreased/loss of smell using the Nasal Symptom Diary at Week 24 and Week 52
- Change from baseline to Week 52 in three-Dimensional CT volumetric measurement of the paranasal sinuses

The selected secondary biomarker endpoint include:

- Percent change from baseline in total IgE in serum at Week 52

3.3.1.1 Definition of endpoint(s)

Sinus opacification assessed by CT scans using the LMK score

Please see the relevant definition of LMK score in Section 3.2.1.

Systemic corticosteroids use

Systemic corticosteroids use is defined as the use of SCS for rescue treatment of AFRS or for another reason, and will be captured by the Investigator (or designee) on the appropriate page(s) of the eCRF page and the date and dosing information (daily dose, duration, INN). The reason for SCS use will be also captured.

Surgery (actual or planned) for AFRS

For participants who undergo or plan to have surgery for AFRS, the reason (worsening signs and/or symptoms during the study), the expected and real surgery date, the type and outcome of surgery will be recorded in a specific eCRF page.

Nasal congestion/obstruction score from the Nasal Symptom Diary

Anterior/posterior rhinorrhea score from the Nasal Symptom Diary

Score of decreased/loss of smell using the Nasal Symptom Diary

Total symptom score (TSS) derived from the Nasal Symptom Diary

The Nasal Symptom Diary is designed to assess the severity of CRS nasal symptoms on a daily basis. These symptoms include nasal congestion/obstruction, loss of smell, anterior rhinorrhea and posterior rhinorrhea. Each of the individual items of the diary are scored with 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’), or 3 (‘Severe symptoms - symptoms that are hard to tolerate, cause interference with activities, or daily living’). Higher scores on the items of the individual symptoms denote greater symptom severity.

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

Endoscopy nasal polyp score (NPS)

The endoscopy NPS allows the assessment of nasal polyp formation. Polyps on each side of the nose will be graded based on polyp size scores: 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. The total score is the sum of the right and left nostrils, ranging from 0 to 8.

22-item sino-nasal outcome test (SNOT-22) total score

The SNOT-22 is a PRO questionnaire designed to assess the impact of CRS on participants HRQoL. SNOT-22 has 22 items covering symptoms, social/emotional impact, productivity, and

sleep consequences of CRS. The recall period is past 2 weeks. Each item is rated on a 6-point Likert scale response option, ranging from 0 ('No problem') to 5 ('Problem as bad as it can be'). A global score ranging from 0 to 110 is calculated by summing the responses to all items; higher score indicates greater rhinosinusitis-related health burden.

Visual analog scale (VAS) rhinosinusitis

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

- Mild = VAS 0 to 3
- Moderate = VAS >3 to 7
- Severe = VAS >7 to 10

University of Pennsylvania smell identification test (UPSIT)

The University of Pennsylvania smell identification test (UPSIT) (UPSIT 40 odorant test) is a rapid and easy-to-administer method to quantitatively assess human olfactory function. The test consists of 4 booklets, each containing 10 odorants with 1 odorant per page. Above each odorant strip is a multiple-choice question with 4 alternative words to describe the odor and the participant is asked to indicate which word best describes the odor. The score ranges from 0 to 40, with one point being awarded for each correctly identified odor, and 40 being the best possible score.

Three-Dimensional CT volumetric measurement of the paranasal sinuses

Three-dimensional volumetric measurement of the sinuses method is used to calculate:

- The volume of the air (mL)
- The volume of mucosa (mL)
- % occupied by disease
- Thickness of lateral wall

Each above test (the volume of the air, the volume of mucosa, % occupied by disease, and thickness of lateral wall), 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 analyzed.

3.3.1.2 Main analytical approach

Continuous secondary efficacy endpoints

Continuous secondary efficacy endpoints will be analyzed similarly as primary estimand of primary endpoint.

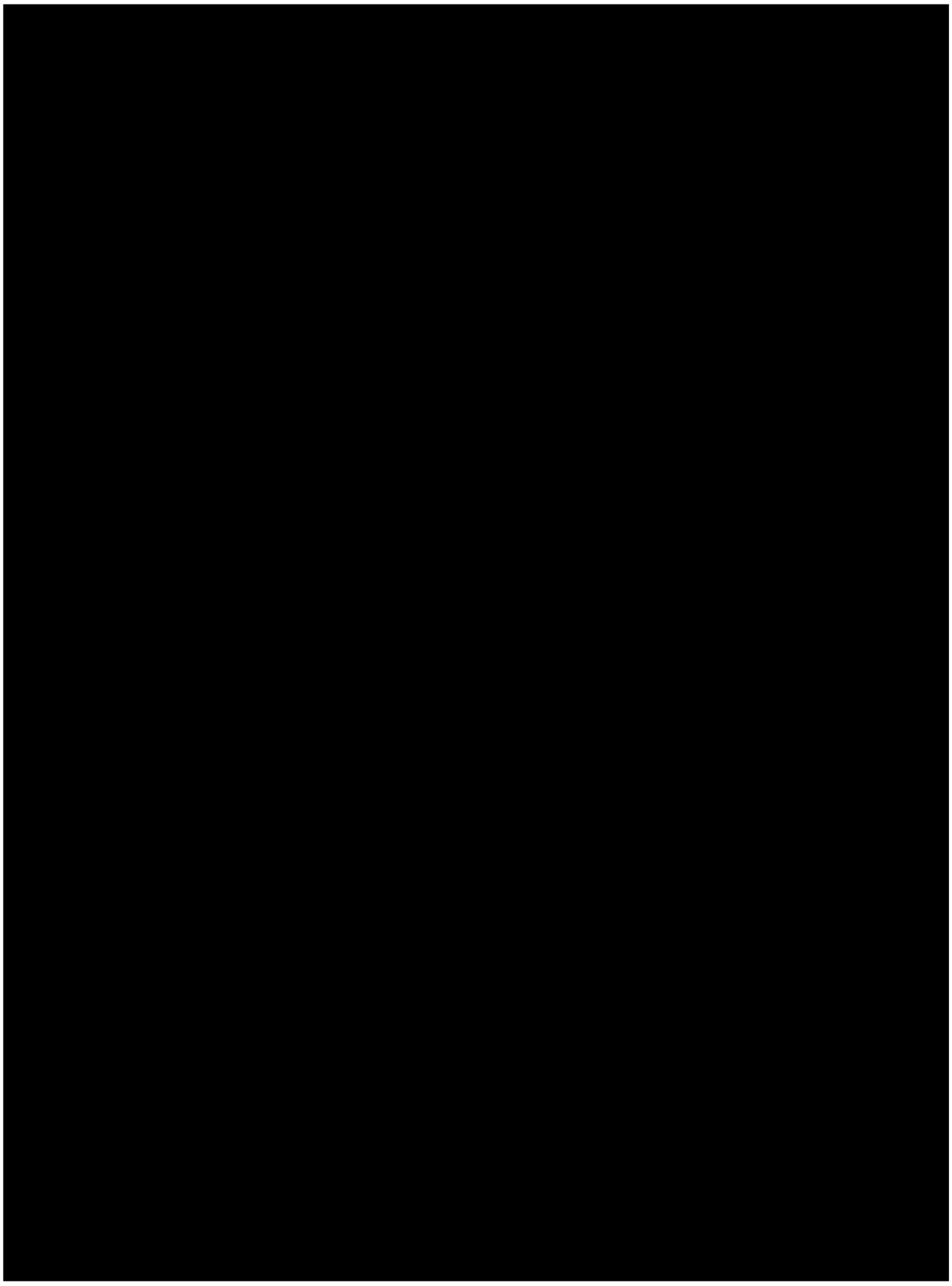
Percent change from baseline in total IgE in serum at Week 52

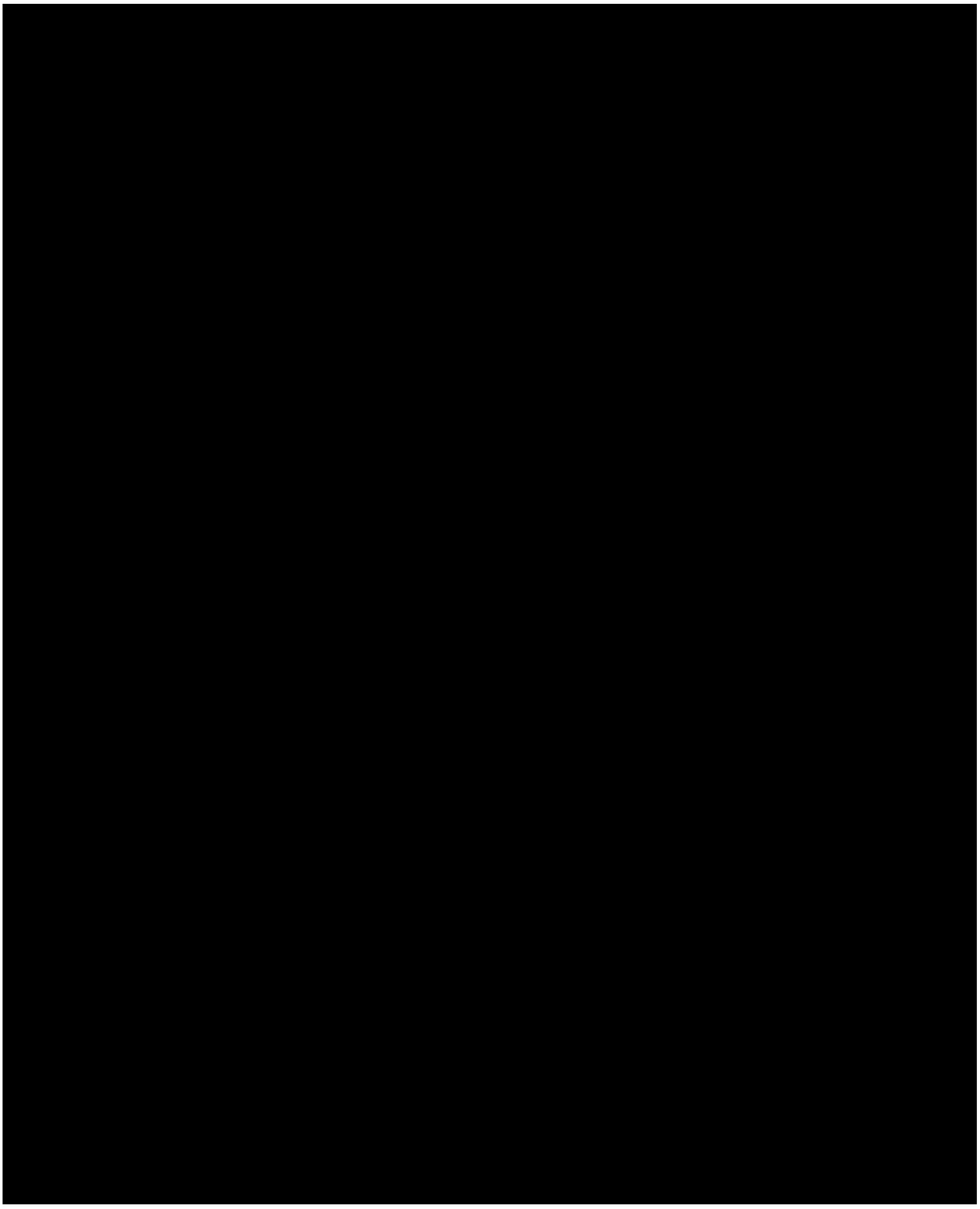
This secondary endpoint will be analyzed similarly as primary estimand of primary endpoint, and will be performed on safety population.

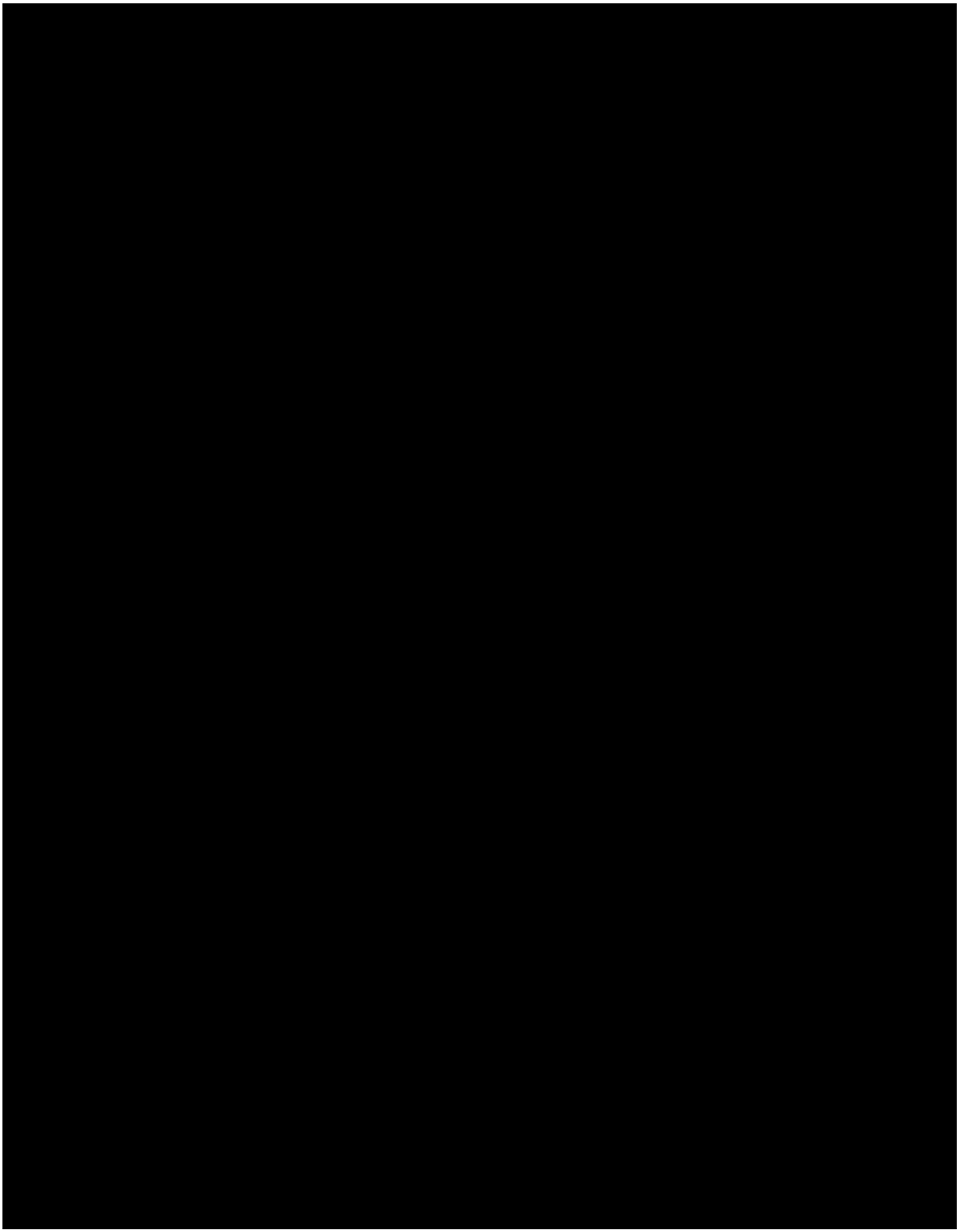
Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period

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

- Endpoint: Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period
- Treatment condition: dupilumab will be compared to placebo
- Analysis population: ITT population
- Intercurrent events (IE):
  - The following IEs will be handled with a treatment policy strategy:
    - Discontinuation of study intervention
    - Taking antifungals or other prohibited/rescue medications
- Population-level summary
  - After the implementation of IE handling strategy,
    - Missing data handling: Participant who discontinue the study prior to Week 52 without an event will be considered as no event.
    - Risk difference between interventions as well as the corresponding 95% confidence interval (CI) will be estimated using Mantel-Haenszel estimate and confidence limits, with Mantel-Haenszel stratum weights for time from last surgery (≤2 years, >2 years) and region (Americas, Asia) and the Sato variance estimator. The P-value associated with Mantel-Haenszel method will be provided.
    - Descriptive statistics including number and proportion of participants with events will be provided for each intervention group.







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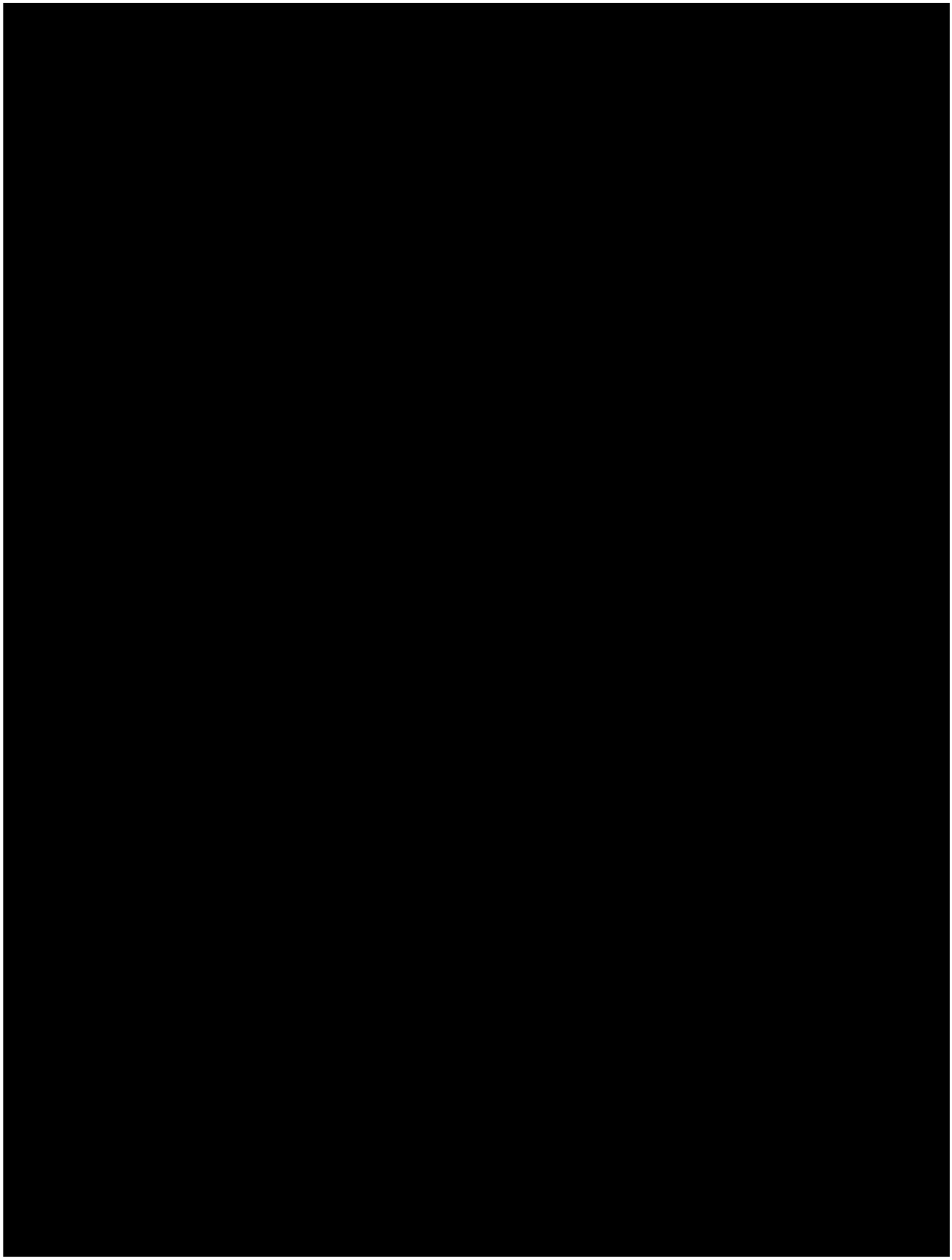

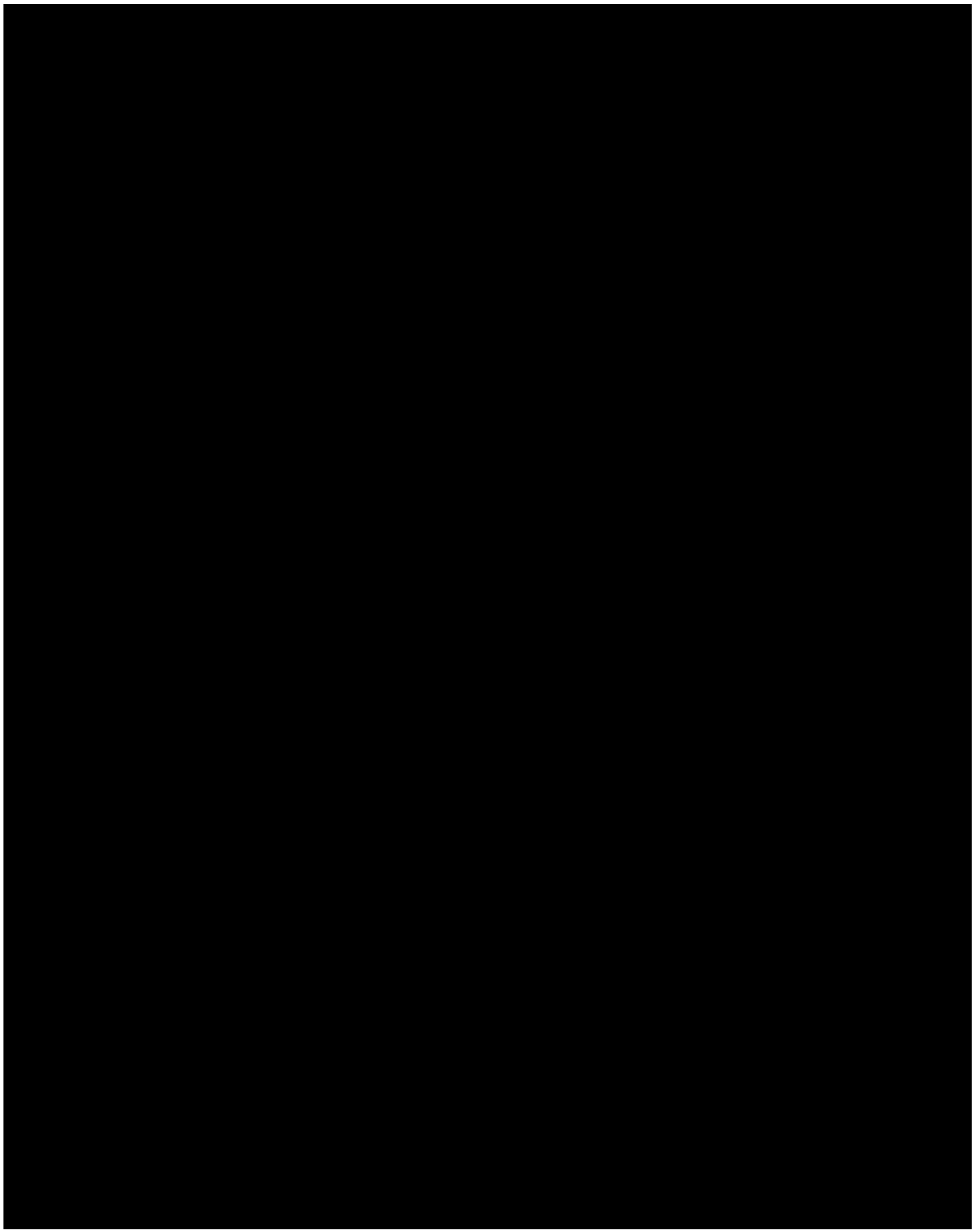

3.5 MULTIPLICITY ISSUES

The multiplicity procedure is proposed to control the overall type-I error rate for testing the primary and selected secondary endpoints. The overall alpha is 0.05. The comparisons with placebo will be tested based on the hierarchical order below at 2-sided $\alpha = 0.05$:

- Change from baseline in sinus opacifications assessed by CT scans using LMK score at Week 52
- Change from baseline in monthly average nasal congestion/obstruction score from the Nasal Symptom Diary at Week 24
- Change from baseline in endoscopy NPS at Week 24
- Change from baseline in sinus opacifications assessed by CT scans using LMK score at Week 24
- Change from baseline in monthly average TSS derived from the Nasal Symptom Diary at Week 24
- Change from baseline in UPSIT at Week 24
- Change from baseline in the score of decreased/loss of smell using the Nasal Symptom Diary at Week 24
- Change from baseline in endoscopy NPS at Week 52
- Change from baseline in monthly average nasal congestion/obstruction score from the Nasal Symptom Diary at Week 52
- Change from baseline in SNOT-22 total score at Week 52
- Change from baseline to Week 52 in three-dimensional CT total volume occupied by disease in all sinuses (%)
- Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study treatment period
- Change from baseline in SNOT-22 total score at Week 24
- Percent change from baseline in total IgE in serum at Week 52

The study is considered positive when the primary endpoint achieves statistical significance with 2-sided significance level 0.05.

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 separately.

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 for adults and adolescents/children ≥30 kg or 28 days for adolescents/children ≥15 kg and <30 kg at screening, 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 to 2 weeks, >2 to 4 weeks, >4 to 8 weeks, >8 to 12 weeks, >12 to 16 weeks, >16 to 20 weeks, >20 to 24 weeks, >24 to 28 weeks, >28 to 32 weeks, >32 to 36 weeks, >36 to 40 weeks, >40 to 44 weeks, >44 to 48 weeks, >48 to 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 scheduled 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%.

Cases of symptomatic overdose (defined as at least twice the intended dose during an interval of less than 11 days for adults and adolescents/children ≥30 kg at screening or less than 25 days for adolescents/children ≥15 kg and <30 kg at screening) are required to be reported as AESIs and will be listed as such.

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, the 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, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a,b]
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 intervention group.
b The table of all TEAEs presented by primary 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 treatment-emergent SAE
- TEAE leading to death
- Any TEAE leading to permanent 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. A separate analysis of TEAE by primary SOC and PT will be provided for pediatric patients.

Table 5 - Analyses of adverse events

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

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation
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 by main reason for death
- Deaths in non-randomized participants 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	Selection
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (Introductory Guide for Standardized 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 Appendix 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 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

AESIs and other AEs of interest	Selection
Significant ALT elevation	"ALT increase" and AESI answer "Yes" checked on AE eCRF as reported by the Investigator (ALT >5 × ULN in participants with baseline ALT ≤2 × ULN; OR ALT >8 × ULN if baseline ALT >2 × ULN)
Symptomatic overdose with IMP	Symptomatic Overdose is answered Yes, with Overdose of Study Treatment 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"
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 (FDA)[c]	CMQ10643 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye irritation, Eye inflammation, Giant papillary conjunctivitis][a]
Keratitis (FDA)[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 censored at time of the first event; for participants without an event, the number of participant-years corresponds 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 variables and vital signs 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, creatine phosphokinase
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Renal function: creatinine, blood urea nitrogen, uric acid
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin
- Urinalysis: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. If blood or protein is abnormal, microscopic examination will be performed by the central laboratory.
- Vital signs: pulse rate, systolic and diastolic blood pressure measured in a semi-supine or sitting position after 5 minutes rest, weight, respiratory rate, temperature and height (at each visit for pediatric participants, and at screening visit for adult participants)

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.

Quantitative analyses

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

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

- Time to onset of the initial alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (>3 × ULN) and total bilirubin elevation (>2 × 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.

Serum concentrations of dupilumab will be summarized in the PK population by actual intervention group 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.

These analyses will also be performed by age subgroup (<18, ≥18 years) and by dose regimens/age subgroup. Only listing will be provided for participants of <18 years receiving dupilumab, if the number of relevant participants is not sufficient (ie, ≤1) for descriptive analyses.

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 follow up at Week 64 will be provided. The neutralizing antibody results for ADA positive samples will be provided. ADA negative samples will be imputed as NAb negative.

On-treatment ADA incidence (measurements during the treatment epoch) 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

- 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
- Indeterminate response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
- Transient response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

Treatment-boosted response is defined as:

An ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Titer values (Titer value category)

- Low (Titer <1000)
- Moderate (1,000 ≤Titer ≤10,000)
- High (Titer >10,000)

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, including titer categories (low, moderate, and high titer) 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 serum concentration profile of dupilumab may be explored. Plot of serum concentration of functional dupilumab versus visit will be provided by ADA variables for the dupilumab dose group. Individual participant plots of dupilumab concentration according to ADA status will be provided to assess the impact of ADA on PK.

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)

[redacted]

3.7.1.4 Biomarker analyses

Total IgE in serum and fungal-specific IgE in serum will be summarized in 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 (mean +/- standard error of the mean) on values at each visit, changes from baseline and percent changes from baseline will be provided for the total IgE in serum and fungal-specific IgE in serum by intervention group and visit.

[redacted]

3.7.2 Subgroup analyses

Subgroup analyses of the primary efficacy endpoint will be performed to assess the homogeneity of the treatment effect across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

- Age group (<40, ≥40 years)
- Gender (Male, Female)
- Region (Americas: Argentina, USA, Canada; Asia: China, Japan, India, Turkey, Saudi Arabia)
- Race (White, Asian and Other)
- Ethnicity (Hispanic or Latino or unknown, Not Hispanic or Latino)
- Baseline weight (<70, ≥70- <90, ≥90 kg)

- Baseline BMI (<27, ≥27 kg/m^2)
- Time from last surgery (≤2 years [including surgery naive participants], >2 years)
- Asthma comorbidity (Yes, No), identified as investigator reported in the eCRF.

The subgroup analyses will be performed based on imputed datasets from the primary analysis. Treatment-by-subgroup interaction term and the subgroup factor term will be added in the primary model. In the case that the subgroup factor is identical or similar to a randomization strata factor adjusted in the main model already, the strata factor will not be kept in the model. Statistical inference obtained from all imputed data will be combined using Rubin's rule.

In each subgroup, the treatment effects (dupilumab versus placebo) for the primary endpoint will be provided, as well as the corresponding 95% CI, using the same method as applied to the primary analysis. Forest plots will be provided.

3.8 INTERIM ANALYSES

There is no interim analysis planned as part of this study.

A primary database lock will be performed when all randomized participants have completed or discontinued their treatment phase. Final analyses in the CSR will be based on all data collected up to this database lock.

The database will be updated at the end of the study for all participants to include the posttreatment follow-up information and updates for the events previously ongoing at the time of the primary lock. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

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

Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
3	01-Mar-2023	[redacted]	
		The sample size changed from 120 (60 per arm) to 62 (31 per arm). The updated study power is >99% for the primary endpoint and 80% for the secondary endpoint using an alpha=0.05. Updated text to reflect switching of primary to secondary endpoint and vice-versa.	A sample size of 62 participants would provide ample power for the new primary endpoint based on change from baseline in LMK at Week 52, which is a clinically relevant measure of efficacy. The new sample size would allow for sufficient power for the original primary endpoint of rescue therapy utilization as a secondary endpoint.
		In statistical considerations, 1) primary and secondary endpoint switched, 2) stratification factor of disease pattern removed from the statistical model, and 3) intercurrent event of taking SCS for any reason changed from treatment policy to composite strategy (WOCF).	The primary and secondary endpoints were switched, and the sample size was optimized based on this change. The stratification factor for disease pattern was removed from the statistical model due to only rare unilateral participants identified. The treatment policy was changed to composite strategy, an approach more appropriate for this clinical setting.
		Alpha level of 0.01 was changed to 0.05 and study is considered positive when the primary endpoint achieves statistical significant with 2-sided significance level 0.05.	The alpha level was adjusted to support an optimized sample size for this rare condition.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA: anti-drug antibody
AE: adverse event
AESI: adverse event of special interest
AESIs: adverse events of special interest
AFRS: allergic fungal rhinosinusitis
ALT: alanine aminotransferase
ANCOVA: analysis of covariance
AST: aspartate aminotransferase
CDG: company drug grouping
CI: confidence interval
CMH: Cochran-Mantel-Haenszel
CMQ: customized MedDRA query
CRS: chronic rhinosinusitis
CRSwNP: chronic rhinosinusitis with nasal polyposis
CSR: clinical study report
CT: computerized tomography
CV: coefficient of variation
eCRF: electronic case report form

[redacted]

HLGT: high level group term
HLT: high level term
HRQoL: health-related quality of life
ICF: informed consent form
IE: intercurrent event
IgE: immunoglobulin E
IMP: investigational medicinal product
INCS: intranasal corticosteroids
IRT: interactive response technology
ITT: intention-to-treat
LABA: long-acting β2-adrenergic receptor agonists
LAMA: long-acting muscarinic acetylcholine receptor antagonists
LLOQ: lower limit of quantification
LLT: lower level term
LMK: Lund Mackay
LS: least square
MCID: minimal clinically important difference
MCMC: Markov Chain Monte Carlo
MedDRA: medical dictionary for regulatory activities

MH:	Mantel-Haenszel
MI:	multiple imputation
NPS:	nasal polyp score
PCSA:	potentially clinically significant abnormality
[redacted]	
PRO:	patient report outcome
PT:	preferred term
SAE:	serious adverse event
SAP:	statistical analysis plan
SCS:	systemic corticosteroids
SD:	standard deviation
SEM:	standard error of the mean
SMQ:	standardised MedDRA query
SNOT-22:	22-item sino-nasal outcome test
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TSS:	total symptom score
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.

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.

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 and baseline characteristics

- age in years as quantitative variable and in categories (≥6-<12, ≥12- <18, ≥18- <65, ≥65 years)
- gender (Male, Female)
- Race (American Indian or Alaska Native, Asian, Japanese, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- Region (Americas: Argentina, USA, Canada; Asia: China, Japan, India, Turkey, Saudi Arabia)
- Baseline weight (<70, ≥70- <90, ≥90 kg)
- Baseline BMI (<27, ≥27 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. Allergic comorbidities will be summarized separately.

Disease characteristics at baseline

- Nasal polyp score
- Lund-Mackay score
- Nasal symptom diary scores for nasal congestion/obstruction, decreased/loss of sense of smell, rhinorrhea (anterior/posterior nasal discharge) and total symptom score (TSS) respectively
- UPSIT smell test score
- SNOT-22
- Time since first diagnosis of AFRS (years) to de derived as

  (Year of randomization – Year of first diagnosis of AFRS) + (month of randomization – month of first diagnosis of AFRS)/12
- Age at onset of AFRS (years)
- Number of prior sino-nasal surgeries (0, 1, 2, ≥3)
- Time from last sino-nasal surgery (≤2 years [including surgery naive participants], >2 years) to be derived as

  (Year of randomization – Year of last sino-nasal surgery) + (month of randomization – month of last sino-nasal surgery)/12
- Disease pattern (unilateral/bilateral in the endoscopy at baseline)
- Asthma comorbidity (Yes, No)

  For asthma patients, provide the following:

  - Age at onset of asthma (years), identified as investigator reported in the eCRF.
  - Time since first diagnosis of asthma (years) to de derived as

    (Year of randomization – Year of first diagnosis of asthma) + (month of randomization – month of first diagnosis of asthma)/12
- 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 systemic corticosteroid (SCS) use during the past 2 years (0, >0 - ≤7, >7 - ≤14, >14 - ≤21, >21 - ≤28, >28)

Prior or concomitant medications and procedures

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.

All procedures will be coded to a PT and associated primary SOC using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Prior medications/procedures are those the participant received prior to first IMP intake. Prior medications/procedures can be discontinued before first administration or can be ongoing during treatment period.

Concomitant medications/procedures are any medications/procedures received by the participant concomitantly to the IMP from the first administration of IMP to the last IMP intake +98 days.

Post-treatment medications/procedures are those the participant received in the period running from the end of the concomitant medications/procedures period up to the end of the study.

A given medication/procedure can be classified as a prior medication/procedure and/or as a concomitant medication/procedure and/or as post-treatment medication/procedure. If it cannot be determined whether a given medication/procedure 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, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

The prior and concomitant procedures will be summarized for the randomized population, by primary SOC and PT.

Background intervention

Participants that are using background INCS must have a stable dose regimen for at least 1 month at the time of V1. From the time of screening throughout the study treatment period, they should not change their background medications.

Intranasal corticosteroids (other than nasal spray) such as drops, stents, or devices are not allowed as background treatment.

The compliance of intranasal corticosteroids spray used from 1 month before the screening visit to Week 52, which is defined as the (number of days intranasal corticosteroids spray used during the period)/(number of days within the period) × 100%, will be summarized by intervention group for participants with stable use of intranasal corticosteroids spray at the screening visit.

Prohibited medications

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

- Intravenous immunoglobulin (IVIG) therapy.
- Any systemic immunosuppressive treatment, such as methotrexate, cyclosporine, mycophenolate, tacrolimus, etc.
- Initiation of allergen immunotherapy.
- Intranasal corticosteroid drops; intranasal steroid emitting devices/stents; nasal spray using Exhalation Delivery System such as Xhance.
- All forms of systemic steroids are prohibited during screening and study treatment period except that a short term (<2 weeks) oral corticosteroids are allowed only in study treatment period as rescue medication.
- Live, attenuated vaccines.
- Other monoclonal antibodies (biological immunomodulators), including but not limited to anti-IgE, anti-IL-5 and anti-TNF, etc.
- Systemic antifungals and antibiotics are prohibited during screening and study treatment period except for rescue use.

The concomitant prohibited medications will be summarized for the randomized population, by category (specified as above) and standardized medication name (sorted by decreasing frequency in the dupilumab group within each category).

Rescue medications/procedures

During the study treatment and follow-up periods, based on clinical evaluation, in case of worsening of signs and/or symptoms requiring medical intervention, the Investigator may consider rescue treatment with:

- Systemic antibiotics (up to 2 weeks) in case of acute infection.
- Short term courses (prednisone or prednisolone up to 2 weeks) of oral corticosteroids for AFRS or short courses of oral corticosteroids to treat other serious coexisting diseases (such as asthma exacerbation).
- Short term (≤4 weeks) systemic antifungal treatment based on participant's tolerability.
- Intranasal corticosteroids spray (initiation of INCS spray or change in dosing of a background INCS spray during the study period).
- Sino-nasal surgery for AFRS (8 weeks of IMP treatment is recommended prior to surgery to allow onset of treatment effect). For participants who undergo or are planned for surgery for AFRS, the Investigator may decide to continue IMP up to the time of surgery or end of treatment whichever date comes first. At the time of surgery, the participants will be permanently discontinued from study treatment.

The rescue medications will be summarized for the randomized population, by category (specified as above) and standardized medication name (sorted by decreasing frequency in the dupilumab group within each category).

The rescue procedures will be summarized for the randomized population, by primary SOC (sorted by internationally agreed order) and PT (sorted by decreasing frequency in the dupilumab group within each SOC).

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, PK and ADA variables.

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.

Efficacy assessment

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the day of first administration of intervention. If a participant was randomized but not treated, the reference date of efficacy assessment will be the randomization day for that participant.

For efficacy variables other than daily eDiary data (Nasal symptom diary), all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 7.

Table 7 - Analyses window definition for efficacy variables

Scheduled visit post baseline	Targeted study day	Analysis window in study days				[redacted]
		Nasal Endoscopy, SNOT-22	CT scan	UPSIT	VAS for rhinosinusitis	
Week 2 (Visit 3)	15			1+ to 49	1+ to 49	
Week 12 (Visit 4)	85	1+ to 126		50 to 126	50 to 126	
Week 24 (Visit 5)	169	127 to 210	1+ to 266	127 to 266	127 to 210	
Week 36 (Visit 6)	252	211 to 307			211 to 307	

Scheduled visit post baseline	Targeted study day	Analysis window in study days				
		Nasal Endoscopy, SNOT-22	CT scan	UPSIT	VAS for rhinosinusitis	[redacted]
Week 52 (Visit 7)	364	308 to 405	>266	267 to 405	308 to 405	
Week 64 (Visit 8)	448	>405		>405	>405	

Study days are calculated considering Day 1 as the day of first administration of intervention. For participants randomized but not treated, the randomization day is considered as Day 1.
1⁻: up to 1st dose date/time; 1⁺: after 1st dose date/time;

For daily eDiary data (Nasal symptom diary), the time period used to calculate the monthly average score is summarized in Table 8 below.

Table 8 - Monthly average of daily nasal symptom diary variables

Analysis visit	Targeted study day	Day range for calculating monthly 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
Week 52	365	338-365
Week 56	393	366-393
Week 60	421	394-421
Week 64	449	422-449

Study days are calculated considering Day 1 as the day of first administration of intervention. For participants randomized but not treated, the randomization day is considered as Day 1.

Safety assessment

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first administration of intervention. Selected safety variables will be summarized by the analysis window defined in Table 9 for the by visit descriptive analysis.

Table 9 - Analyses window definition for safety variables

Scheduled visit post baseline	Targeted study day	Analysis window in study days	
		Vital signs	Laboratory (hematology, biochemistry, urinalysis)
Week 12 (Visit 4)	85	1+ to 126	1+ to 126
Week 24 (Visit 5)	169	127 to 210	127 to 266
Week 36 (Visit 6)	252	211 to 307	
Week 52 (Visit 7)	364	308 to 405	267 to 405
Week 64 (Visit 8)	448	>405	>405

Study days are calculated considering Day 1 as the day of first administration of intervention.
1-: up to 1st dose date/time; 1+: after 1st dose date/time;

Pharmacokinetics/immunogenicity/biomarker assessment

For the pharmacokinetics/immunogenicity/biomarker variables summary, the reference date for the derivation of relative days of measurements will be the date of first administration of intervention. Pharmacokinetics/immunogenicity/biomarker variables will be summarized by the analysis window defined in Table 10 for the by visit descriptive analyses.

Table 10 - Analyses window definition for PK/ADA/biomarker variables

Scheduled visit post baseline	Targeted study day	Analysis window in study days		
		PK, ADA	Serum total IgE and fungal specific IgE,	[redacted]
Week 12 (Visit 4)	85	1+ to 126	1+ to 126	
Week 24 (Visit 5)	169	127 to 266	127 to 266	
Week 36 (Visit 6)	252			
Week 52 (Visit 7)	364	267 to 405	>266	
Week 64 (Visit 8)	448	>405		

Study days are calculated considering Day 1 as the day of first administration of intervention.
1-: up to 1st dose date/time; 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 SAMPLE SAS CODE

Part 1: Mantel-Haenszel method

```
proc freq data=ads;
    tables strata1*strata2*treat*bin_end / commonriskdiff (test=mh cl=mh) alpha=0.05;
    ods output CommonPdiff=mhdiff CommonPdiffTests=mhdifftest;
run;
```

5.6 APPENDIX 6 SELECTION CRITERIA FOR AE/MEDICATION GROUPINGS

Table 11 - 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

Grouping	Preferred Term/Medication Code	Preferred Term/Medication
Conjunctivitis	10075264	Oculoglandular syndrome
Conjunctivitis	10080825	Conjunctivitis fungal
Conjunctivitis	10084034	Conjunctival suffusion
Conjunctivitis	10084038	Giant fornix syndrome

Abbreviations: CAS : Chemical Abstract Service Registry Number RECNO : Drug Record Number

6 REFERENCES

Not applicable.

Signature Page for VV-CLIN-0690434 v1.0
efc16724-16-1-9-sap

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]