STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double-blind, placebo-controlled efficacy and safety study of dupilumab, in Chinese adult participants with chronic rhinosinusitis with nasal polyposis (CRSwNP) on a background therapy with intranasal corticosteroids**
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VERSION HISTORY

This statistical analysis plan (SAP) for study EFC17026 is based on the protocol dated 14-Sep-2022.

The first participant was randomized on 13-Jun-2023. This SAP is approved before the database lock.

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of dupilumab 300 mg every 2 weeks (Q2W) compared to placebo, in Chinese adult participants with moderate-to-severe signs and symptoms of bilateral nasal polyposis (NP) on a background treatment with intranasal corticosteroids (INCS).

The clinical study consists of 3 periods, a run-in period to determine a participant's eligibility and for run−in/standardization of background INCS (budesonide nasal spray) prior to randomization, a treatment period during which participants will be randomized to and treated with either dupilumab or placebo, and a follow-up period to continue to collect data for safety after the participant has completed the study drug treatment period.

The study duration consists of the following periods:

- Run-in period (4weeks +/- 3 days)
- Randomized dupilumab/placebo treatment period (24 weeks +/-3 days)
- Follow-up period (12 weeks +/-3 days)

Randomization will be stratified by screening blood eosinophil count (≥300 cells/mm^3 or <300 cells/mm^3). Approximately 62 participants (randomization ratio [1:1], 31 per arm) will be randomized to 1 of 2 treatment arms of either dupilumab 300 mg SC Q2W or placebo matching dupilumab SC Q2W.

Study primary analysis will be conducted after study completion. No interim analysis will be performed before the final database lock for this study.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab compared to placebo on a background of budesonide nasal spray in reducing endoscopic nasal polyps score (NPS) in Chinese participants with bilateral nasal polyposis (NP).	• Change from baseline in NPS at Week 24.
Secondary	
• To evaluate the efficacy of dupilumab in reducing nasal congestion/obstruction (NC) severity.	• Change from baseline in NC score (NCS) based on the participant daily morning assessment at Week 24.
• To evaluate the efficacy of dupilumab in improving total symptoms score (TSS).	• Change from baseline in TSS at Week 24: composite severity score consisting of the participant daily morning assessed NC, decreased/loss of sense of smell, anterior/posterior rhinorrhea.
• To evaluate the efficacy of dupilumab in improving sense of smell.	• Change from baseline in the severity of decreased/loss of smell assessed daily by participants at Week 24.
• To evaluate the effect of dupilumab on patient quality of life.	• Change from baseline in total score of 22-item sino-nasal outcome test (SNOT-22) at Week 24.
• To evaluate the ability of dupilumab to reduce proportion of participants who require treatment with systemic corticosteroid (SCS) or surgery for NP.	• Proportion of participants receiving SCS for any reason or undergo surgery for nasal polyps during the study treatment.
• To evaluate the safety of dupilumab in Chinese participants with bilateral NP.	• Safety (incidence of treatment-emergent adverse events [TEAEs], of treatment-emergent serious adverse events [TESAEs], and TEAEs leading to treatment discontinuation), laboratory values, vital signs.
Tertiary/Exploratory	
• To demonstrate tertiary outcome measures	• Change from baseline in NPS, NCS, TSS, severity of decreased/loss of smell, and SNOT-22 up to Week 24.

1.2.1 Estimands

Primary estimands defined for primary efficacy endpoints are summarized in Table 2 below. More details are provided in Section 3.2.

For all these estimands, the comparison of interest will be the comparison of dupilumab 300 mg Q2W vs. placebo.

Table 2 - Summary of primary estimands for primary endpoint

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 dupilumab compared to placebo on a background of budesonide nasal spray in reducing endoscopic nasal polyps score (NPS) in Chinese participants with bilateral nasal polyposis (NP).				
Primary endpoint	Change from baseline in NPS at Week 24.	ITT	The intercurrent events will be handled as follows: • Undergoing surgery for CRSwNP or taking SCS for any reason prior to Week 24: data after surgery/SCS will be excluded from analysis values, and the worst post-baseline value on or before the time of surgery/SCS will be used to assign missing 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 (but not undergoing surgery for CRSwNP or taking SCS for any reason prior to Week 24): all data collected after discontinuation will be used in the analysis (treatment policy strategy).	Mean change difference between interventions from ANCOVA model with study intervention and screening blood eosinophil count strata, and baseline measurement as covariates is used. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule. For missing data, a multiple imputation approach will be used to impute missing Week 24 values, and this multiple imputation will use all participants excluding those who have undergone surgery or received SCS for any reason on or before Week 24.

ITT: intent-to treat; CRSwNP: chronic rhinosinusitis phenotype with nasal polyps; SCS: systemic corticosteroids; ANCOVA: analysis of covariance; WOCF: worst observation carried forward.

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	The randomized population includes all participants with a treatment kit number allocated and recorded in the IRT database, 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 of whether the treatment kit was 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 receive. 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 receive a different treatment from the planned one, the participants who take at least one dose of dupilumab will be allocated to dupilumab group, otherwise will be allocated to placebo group.
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 study intervention due to COVID-19 • and who did not permanently discontinue study due to COVID-19

ICF: informed consent form; IRT: interactive response technology, ITT: intent-to-treat.

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.

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 (placebo and dupilumab) during the study, the intervention group for as-treated analysis 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, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized.

The baseline value of efficacy parameters is defined as the last available value before randomization unless otherwise specified (see below for daily Diary of NCS, TSS and severity of decreased/loss of sense of smell).

The calculation of the baseline for endpoints collected on a daily basis, baseline is defined as the average of the scores in the 7 days prior to randomization. If there are 4 or more measurements collected within 7 days prior to randomization, the baseline will be the average of these measurements; if less than 4 measurements are collected, the baseline will be the average of the most recent 4 prior to randomization.

The baseline value of the other parameters is defined as the last available value prior to the first dose of IMP if the participant is treated, or the last available value up to randomization if the participant is not exposed to IMP.

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 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 start of treatment until the end of the study (defined as last protocol planned visit or lost to follow-up or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

3.2 PRIMARY ENDPOINT(S) ANALYSIS

3.2.1 Definition of endpoint(s)

The primary endpoint is the change from baseline in NPS at Week 24. All the efficacy assessments collected during the study will be used, including those obtained after IMP discontinuation or introduction of rescue therapy, unless the participant undergoes surgery for CRSwNP or takes SCS for any reason prior to Week 24.

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

Table 4 - Endoscopic nasal polyp score

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

Nasal endoscopy should be performed at the end of the scheduled visits before the administration of IMP and preceded by local administration of anesthetic drugs in combination with a decongestant.

Standard video sequences will be downloaded or sent to centralized reader. Centralized imaging data assessments and scoring by independent physician reviewer(s) for the imaging data will be performed for all endoscopies. Specifically, a double central reading with adjudication process will be performed to improve scoring quality.

To confirm eligibility at V2, only the V1 central reading will be made available to the site. In addition, at V2 the investigator will perform the nasal endoscopy to confirm eligibility score and enter the result in the e-CRF. Thus the participant is considered eligible based on a V1 central reading followed by a V2 local reading NPS score of 5 or more and at least 2 on each side. The final results of central reading from V2 onward will be made available after the study.

The adjudication for V1 will not be required if both readers score ineligible (total NPS score less than 5 or at least one side less than 2, in which case the participant will be considered as ineligible) or both readers score eligible (total NPS score of 5 or more and at least 2 in each side, in which case the participant will be considered as eligible). Unreadable scores (bad quality

videos) at V1 even from one reader should have endoscopy redone as soon as possible (requiring participant to come back at site). In the case the two readers differ on eligibility for the study, an adjudicator will read the endoscopy again independently. The total NPS score and each side score to determine eligibility will be based on the average of the adjudicator and one of the two readers whose total NPS score is closer to the adjudicator's reading (in the case that the two readers' scores are different but equidistant from the adjudicator's score, the reader with the higher score will be used in the calculation). In the special case that the two readers give different eligibility opinions but the total NPS scores are the same (the only possibility of the total NPS score for such a case is 5), eligibility will follow the adjudicator's opinion.

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

More details regarding the study eligibility determination based on the double central reading with are listed in Section 5.6

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

3.2.2 Main analytical approach

The primary endpoint will be analyzed with the primary estimand defined in Table 2 according to the following attributes:

- Endpoint: Change from baseline in NPS at Week 24. The statistical hypotheses for comparing dupilumab against placebo on the primary endpoint are as follows:
  - Null hypothesis H0: No treatment difference between dupilumab and placebo.
  - Alternative hypothesis H1: There is a treatment difference between dupilumab and placebo.
- Treatment condition: dupilumab 300 mg Q2W will be compared to placebo, on top of background therapy.
- Analysis population: ITT population

- Intercurrent events (IE):
  - Undergoing surgery for CRSwNP or taking SCS for any reason prior to Week 24 will be handled with the composite strategy; Data after surgery/SCS will be excluded from analysis values, and the worst post-baseline value on or before the time of surgery/SCS will be used to assign missing Week 24 value (WOCF). For participants with no post-baseline values, the baseline value will be used.
  - Taking other prohibited/rescue medications will be handled with the treatment policy strategy; All data collected after use will be used in the analysis.
  - Discontinuing the study intervention (but not undergoing surgery for CRSwNP or taking SCS for any reason prior to Week 24) will be handled with treatment policy strategy; All data collected after discontinuation will be used in the analysis.
- Population-level summary: mean change difference between dupilumab 300 mg Q2W and placebo from ANCOVA. Model with study intervention and screening blood eosinophil count strata, and baseline measurement as covariates will be used. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule. Missing data at Week 24 will be imputed using the multiple imputation and this multiple imputation will use all participants excluding those who have undergone surgery or received SCS on or before Week 24.

In the primary analysis approach for the primary endpoint, for participants who undergo surgery for NP or are taking SCS for any reason, data collected after surgery or SCS will be excluded from analysis values, and the worst post-baseline value on or before the time of surgery or taking SCS will be used to assign missing Week 24 value (ie, WOCF approach). For participants with no post-baseline values, the baseline value will be used. For participants taking other prohibited/ rescue medications, all data collected after use will be used in the analysis. Participants who discontinue the study intervention prematurely are encouraged to follow the planned clinical visits and, in these participants, who did not undergo surgery or take SCS for any reason, all data collected after study intervention discontinuation will be used in the analysis. In case there is missing data, a multiple imputation will be used to impute missing Week 24 values, and this multiple imputation will use all participants excluding those who have undergone surgery or taking SCS for any reason on or before Week 24. Each of the imputed completed data will be analyzed by fitting an ANCOVA model with the baseline covariate and factor for study intervention and screening blood eosinophil count strata. Statistical inference obtained from all imputed data will be combined using Rubin's rule.

Descriptive statistics including number of participants, mean, standard error, and LS means will be provided. In addition, difference in LS means and the corresponding 95% CI will be provided along with the p-values.

See Section 5.5 for the sample SAS code for the imputation and how the analysis model will be built.

3.2.3 Sensitivity analyses

Additional analyses including the following will be performed to confirm robustness of the results with respect to missing data handling strategy:

Tipping point analysis

The primary efficacy endpoint will be analyzed with imputed missing value at Week 24 as follows.

Step 1. Monotone missing pattern was induced by Markov Chain Monte Carlo (MCMC) method using PROC MI: for participants who have intermediate missing values, the intermediate missing values will be imputed assuming a multivariate normal distribution over observations from all visits. 40 datasets with a monotone missing pattern will be obtained using this method.

Step 2. For each of the imputed dataset with monotone missing pattern obtained in Step 1, the remaining missing data will be imputed using the regression method for the monotone pattern with adjustment for covariates including factor for screening blood eosinophil count strata, treatment groups, and baseline value of the primary endpoint. All available data in the monotone missing pattern data will be used. One imputed dataset will be obtained for each of the imputed dataset at Step 1. So, 40 fully imputed datasets will be obtained altogether.

Step 3. The imputed values in Dupilumab group are added by a positive amount *d* for each imputed data sets.

Step 4. The imputed values in placebo group are subtracted by a positive amount *p* for each imputed data sets.

Step 5. Change from baseline in endpoint will be analyzed using ANCOVA model same as the one in primary analysis. Then the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 3 to Step 5 will be repeated iteratively until the p-value for combined treatment effect of dupilumab compared to placebo estimated in Step 5 is >0.05 or the maximum applicable treatment effect has been reached.

LS mean difference between dupilumab and placebo in change from baseline in NPS at Week 24 and the corresponding p-values will be provided for each combination of shift parameters.

3.2.4 Supplementary analyses

Additional analysis including the following will be performed to confirm robustness of the results with respect to intercurrent event handling strategy.

Data collected after initiation SCS for any reason will be included in the analysis

All data including data collected after SCS for any reason and treatment discontinuation but excludes post NP surgery data will be included in the analysis. For participants who undergo

surgery for NP, data collected post-surgery will be excluded from analysis values (as a comparison, data collected post-surgery and post SCS for any reason are both excluded from analysis values in the primary approach), and the worst post-baseline value on or before the time of surgery will be used to assign missing Week 24 value (for participants whose post-baseline values are all missing, the baseline will be used to assign). For participants who discontinue the treatment without being rescued by surgery, all data collected after treatment discontinuation or after SCS for any reason will be included in the analysis and a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants who have not been rescued by NP surgery at Week 24. The data will be analyzed in the same ANCOVA model for the primary approach. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

3.2.5 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 (<65, ≥65 years)
- Gender (Male, Female)
- Baseline weight (<70, ≥70 - <90, ≥90 kg)
- Baseline body mass index (BMI) level (<25, ≥25 - <30, ≥30 kg/m^2)
- Prior NP surgery history (Yes, No)
- Asthma comorbidity (Yes, No)
- Allergic rhinitis at baseline (Yes, No)
- SCS use during the past 2 years prior to V1 (Yes, No)

To assess the consistency of the treatment effects across the subgroup levels, subgroup analyses will be conducted for primary endpoints at Week 24. The analysis 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, the strata factor will not be kept in the model.

To test the interaction between treatment and subgroup factor, an ANCOVA model incorporating subgroup-by-treatment interaction will be built for each subgroup factor. The model will include all the covariates in the main statistical model plus the subgroup variable (if not one of the covariates adjusted in the main model already) and the subgroup-by-treatment interaction. Statistical inference obtained from all imputed data will be combined using Rubin's rule. A p-value for the test of interaction will be provided based on the combined inference.

In each subgroup, the primary endpoint will be analyzed using the primary approach, but on the specific subgroup of the imputed primary analysis population. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) means for each subgroup will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided for each subgroup. Forest plots will be provided.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are secondary efficacy endpoints. Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3.1 (laboratory abnormalities and vital signs).

3.3.1 Secondary endpoint(s)

The secondary endpoints detailed in this section are indicated in Table 1 and presented below:

- Change from baseline in NCS at Week 24
- Change from baseline in TSS at Week 24
- Change from baseline in the severity of decreased/loss of smell daily assessed by the participant at Week 24
- Change from baseline in SNOT-22 at Week 24
- Proportion of participants receiving SCS for any reason or undergo surgery for nasal polyp during the study treatment

3.3.1.1 Definition of endpoint(s)

3.3.1.1.1 Nasal congestion/obstruction scores (NCS)

Nasal congestion/obstruction score is a reflective score of the worst symptom severity over the past 24 hours by the participant (see Table 5).

Table 5 - Symptom severity score

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

The e-diary is used for daily recording of participant's answers to the questionnaires. This device will be dispensed at the Screening Visit (V1). Recorded information will be downloaded from this device daily.

A severity ≥2 on the day of V1 and a weekly average severity greater than 1 at time of randomization (V2) is required and will be provided to the site to determine participant eligibility.

If there are 4 or more measurements collected within 7 days prior to randomization available, the baseline will be the average of these measurements; if less than 4 measurements are collected within 7 days prior to randomization, the baseline will be the average of the most recent 4 measurements prior to randomization (between V1 and V2).

For the baseline to EOT analysis, the average of all scores from the preceding 4 weeks to the corresponding visit will be used as the analysis score for that visit.

3.3.1.1.2 Disease specific daily symptom assessment and total symptom score (TSS)

On a daily basis from V1 and throughout the study, the participant will use an e-diary to respond to the morning individual rhinosinusitis symptom questions using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms) (1):

- Congestion and/or obstruction.
- Loss of sense of smell.
- Anterior rhinorrhea (runny nose).
- Posterior rhinorrhea (postnasal drip).

The total symptom score is a composite score (ranging between 0 and 9) consisting of the sum of the following symptoms assessed daily in the morning: NC, decreased/loss of sense of smell, rhinorrhea (average of anterior/posterior nasal discharge). Higher scores on TSS indicate greater overall symptom severity. TSS is a reflective score of the worst symptom severity over the past 24 hours by the participant.

The symptom scores at baseline and from baseline to EOT analysis will be calculated using the same approach as for NCS as described in Section 3.1 and Section 3.3.1.1.1. If there are 4 or more measurements collected within 7 days prior to randomization, the baseline will be the average of these measurements; if less than 4 measurements are collected, the baseline will be the average of the most recent 4 prior to randomization. For the baseline to EOT analysis, 4 weeks average of the symptom scores prior to the corresponding visit will be used as the analysis score for that visit.

3.3.1.1.3 Decreased/loss of sense of smell

The decreased/loss of sense of smell severity is assessed by the participant on a daily basis from V1 and throughout the study, using an e-diary and using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). This is a reflective score of the worst symptom severity over the past 24 hours by the participant. The symptom scores at baseline and from baseline to EOT analysis will be calculated using the same approach as for NCS.

3.3.1.1.4 22-Item sino-nasal outcome test (SNOT-22)

The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on HRQoL (Section 5.7). The SNOT-22 has 22 items on a 5-category scale applicable to sino-nasal conditions and surgical treatments. The range of the global score is 0 to 110 with a minimal important difference (MID) of 8.9 (2). Lower scores indicate less impact and the recall period is the past 2 weeks. There are 5 domains that can be described within SNOT-22, including nasal, ear, sleep, general and practical, and emotional.

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

3.3.1.1.5 Proportion of participants during the treatment period who receive SCS rescue or are planned to undergo surgery for NP

SCS rescue

Systemic steroids for rescue treatment of nasal polyps or for another reason will be prescribed to the participant by the site. PROs and a nasal endoscopy should be performed before starting treatment with SCS. The Investigator records the date and dosing information (daily dose, duration, INN) on the appropriate page(s) of the e-CRF. Indication for SCS use will also be captured by selecting one or more of the following categories:

1. Nasal polyposis
2. Asthma
3. Other respiratory disease (specify)
4. Other ear nose or throat disease (specify)
5. Other reason (specify).

Surgery (actual or planned) for NP

For participants who undergo or are planned for sino-nasal surgery for NP, the reason (worsening signs and/or symptoms during the study), the planned date and the effective surgery date, the type and outcome of surgery will be recorded in a specific e-CRF page.

Participants scheduled for surgery may continue IMP up to the time of surgery or EOT whichever date comes first. At time of surgery participants will be permanently discontinued from study treatment and perform as soon as possible the efficacy and safety assessments planned at the EOT visit and will be instructed to return to the study site as described in the protocol. An AE or SAE page will be completed.

If the surgery is performed during the post-treatment follow-up period, at the time of surgery the participants will be assessed according to the procedures normally planned for the EOS Visit and will be instructed to return to the study site for additional visits as described in protocol. An AE or SAE page will be completed.

If surgery is scheduled after the planned end of study, EOS visit will not be delayed. A follow up contact(s) should be performed around the time of planned surgery to document the surgery date and outcome. Surgery data will be collected until e-CRF closure of the trial.

3.3.1.2 Main analytical approach

The change from baseline in NCS, TSS, severity of decreased/daily loss of smell, and SNOT-22 at Week 24 will be analyzed using the same primary analysis approach as for the primary endpoint.

To assess treatment differences in time to events defined in Section 3.3.1.1.5, proportion of participants with first SCS rescue for any reason or surgery (actual or planned) for NP during the 24-week treatment period will be summarized and time-to-event will be analyzed using the Cox proportional hazards model and log rank test stratified by screening blood eosinophil count, by considering the first SCS rescue use for any reason or surgery (actual or planned) for NP as the event, which is earlier if both occur. The decision date of surgery for nasal polyps or the first SCS intake date will be used as the event date, whichever is earlier if both occur. In case the decision date of NP surgery is missing, the planned surgery date will be used in place. In case the planned surgery date is also missing, the actual surgery date will be used in place.

Descriptive statistics including number of participants with rescue SCS or surgery and number of participants without rescue SCS or surgery (censored) and the corresponding rates will be provided by study intervention group. The Cox model will include the event as the dependent variable, and treatment group, screening blood eosinophil count strata as covariates. The estimates of the hazard ratio and corresponding 95% CI will be provided for the dupilumab group versus the placebo group. The Kaplan-Meier method will be used to derive the probabilities that a participant would experience events up to Week 24 for 300 mg Q2W and placebo. Kaplan-Meier curves will be generated; quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% point wise confidence intervals.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

3.4.1 Definition of endpoint(s)

- Change from baseline in NPS, NCS, TSS, severity of decreased/loss of smell, and SNOT-22 up to Week 24.

3.4.2 Main analytical approach

Analyses of efficacy endpoints for dupilumab versus placebo up to Week 24

For the continuous efficacy endpoints, descriptive statistics including number of participants, mean, standard error, and least squares (LS) means will be provided and plotted separately by treatment group for dupilumab 300mg Q2W versus placebo at each specified timepoint up to Week 24. In addition, using the hybrid method of the worst-observation carried forward (WOCF) and the multiple imputation separately at each specified timepoint, difference in LS means and the

corresponding 95% confidence intervals (CI) will be provided along with the p-values. Such analyses will be conducted on the following variables:

- Change from baseline in NPS and SNOT-22 at Week 16 and Week 24
- Change from baseline in NCS, TSS and severity of decreased/loss of smell at Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24

3.5 MULTIPLICITY ISSUES

A hierarchical procedure is proposed to strongly control the family wise type-I error rate at the 2-sided α=0.05. The primary endpoint will be tested first, followed by selected secondary endpoints:

- Change from baseline in NPS at Week 24.
- Change from baseline in NCS at Week 24.
- Change from baseline in TSS at Week 24.
- Change from baseline in the severity of decreased/loss of smell daily assessed by the participant at Week 24.
- Change from baseline in SNOT-22 at Week 24.

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, 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 descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- >0 and ≤2 weeks
- >2 and ≤4 weeks
- >4 and ≤8 weeks
- >8 and ≤12 weeks
- >12 and ≤16 weeks
- >16 and ≤20 weeks
- >20 and ≤24 weeks
- >24 weeks and ≤24 weeks + 3 days
- >24 weeks + 3 days

Additionally, the cumulative duration of treatment exposure (expressed in patient-years) will be provided, defined as the sum of the duration of treatment exposure for all participants.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the planned dose and number of administrations 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%.

Cases of symptomatic overdose (defined as at least twice the intended dose during an interval of less than 11 days) will be considered an AESI per dupilumab clinical programs 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 (TEAEs): 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 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. If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the 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 6.

Table 6 - 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 SAR231893 dupilumab 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 7 will be generated with number (%) of participants experiencing at least one event. The all TEAE summary by Primary SOC and PT (and other safety summaries (eg, SAEs, deaths), if deemed needed after TEAE evaluation) will be performed by trial impact (disruption) due to COVID-19.

Table 7 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
	PT
	Primary and secondary SOC and PT
Common TEAE (≥2% and 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 (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Pre-treatment AE	Overview[a]
	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 full intervention discontinuation

In addition, the exposure adjusted incidence rate of TEAEs by primary SOC and PT will be generated, showing the number of participants with at least one TEAE per 100 patient-years. For participants with an event, patient-years will be calculated up to the first event, and for participants without an event, patient-years will correspond to the length of the TE period.

A listing of all treatment-emergent and post-treatment adverse events will be presented.

Analysis of deaths

In addition to the analyses of deaths included in Table 7 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods.

- Deaths in non-randomized participants or randomized but not exposed 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 8. 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 6.

Table 8 - Selections for AESIs and other AEs of interest

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries (SMQs) Version 27.0): 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 5.8)[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 and AESI answer 'Yes'
Pregnancy of a female participant entered in a study with IMP/NIMP	"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 IMP answered Yes on AE eCRF.
Symptomatic overdose with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP answered Yes on AE eCRF.

AE Grouping	Criteria
Other selected AE Grouping	
Injection site reaction	HLT = 'Injection site reaction'
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥24 hours or ongoing
Severe or serious infection	Primary SOC = 'Infections and infestations' and with severe or serious status
Opportunistic infection	Has the AE been assessed as opportunistic infection? is answered Yes on eCRF page "Infection Event Form"
Drug-related hepatic disorder	SMQ [20000006] Drug-related hepatic disorders- narrow
Malignancy	SMQ [20000091]– Malignant or unspecified tumors narrow
Epistaxis/nose bleeding	PT in (Epistaxis, Nasal septum haematoma)
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]

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

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,
- The exposure adjusted incidence rate by selected SMQ/CMQ and PT showing the number of participants with at least one TEAE per 100 patient-years.
- For each AESI and other selected AE groupings,
  - Number (%) of participants with any specific TEAE
  - Number (%) of participants with any specific serious AE (regardless of treatment emergent status)
  - Number (%) of participants with any specific treatment emergent serious AE
  - Number (%) of participants with any specific AE leading to death
  - Number (%) of participants with any specific TEAE leading to permanent study drug discontinuation
  - Number (%) of participants with any specific TEAE related to IMP reported by investigator
  - Number (%) of participants with any specific TEAE by maximum intensity, corrective treatment, and final outcome

- Number of any specific TEAE adjusted by the exposure duration
- Number of participants with any specific TEAE adjusted by the exposure duration at risk. For each specific TEAE, Kaplan-Meier estimates of cumulative incidence at Week 12, and 24 and K-M plot may be provided to depict the course of onset over time if the number of events is large enough
- 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.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) 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, 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, albumin
  - Pregnancy test: Serum β-human chorionic gonadotropin (all female participants) will be performed at screening (V1) in women of childbearing potential, and a urine pregnancy test will be performed at V2 and every 4 weeks thereafter.
- Vital signs: pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg) in a sitting position after 5 minutes, weight (kg), respiratory rate (breaths per minute), temperature (degrees Celsius), and height (screening only)

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

Quantitative analyses

When relevant, for all laboratory variables and vital signs, descriptive statistics (number, mean, median, Q1, Q3, standard deviation, minimum and maximum) for results and changes from baseline will be provided for each planned visit, 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 (when available) for laboratory variables.

For all laboratory variables and vital signs variables above, 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, 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 PK analyses

PK parameters are not evaluated in this study.

3.7.2 Immunogenicity analyses

Immunogenicity assessments are not performed in this study.

3.7.3 Biomarker analyses

Biomarkers are not evaluated in this study.

3.8 INTERIM ANALYSES

No interim analysis will be performed before the final database lock for this study.

3.9 TIMING OF DATABASE LOCKS

A primary database lock will be performed when all randomized participants in this study have completed their 24-week treatment period, including early dropouts. The database will be updated at the end of the study for all participants to include the post-treatment follow-up information and updates for the events previously ongoing at the time of the primary lock. Analysis will be based on all data collected up to final database lock and will be considered in the CSR.

3.10 CHANGES TO PROTOCOL-PLANNED ANALYSES

The modifications to the protocol statistical section in the SAP are listed below.

Table 9 - Modifications to the statistical section of the protocol in the SAP

	Text in the protocol	Text in the SAP	Rationale
1	The following description on the planned database lock date in the protocol Section 9.2.1 General considerations Additional data collected between the primary database lock and last participant completing last visit will be summarized in a separate CSR addendum, as needed.	Is changed in the SAP Version 1 to: Analysis will be based on all data collected up to final database lock and will be considered in the CSR.	Analyses in the CSR will be based on the data collected up to end of study.
2	Tertiary/exploratory endpoint(s) analyses were not planned in the protocol.	Tertiary/exploratory endpoint(s) analysis was added in the SAP Version 1.	To evaluate the efficacy of dupilumab in continuous endpoints at selected visits/weeks.

4 SAMPLE SIZE DETERMINATION

Approximately 62 participants will be randomized to study intervention.

A total sample size of about 62 participants (randomization ratio [1:1], ie, [31 per intervention group]) was determined to demonstrate superiority of dupilumab 300mg Q2W versus placebo with 90% power and 2-sided test with 5% significance level based on the following assumptions on the primary endpoint:

- True mean difference of -1.8 between dupilumab 300 mg Q2W and placebo
- Common SD of 1.83
- A 25% dropout rate

Calculations were made based on two sample t-test using nQuery Advisor 7.0.

Assumptions are based on the following:

- Mean treatment difference= -1.8 (lowest observed effect size of NPS at Week24 in the EFC14146 [SINUS-24] and EFC14280 [SINUS-52])
- SD=1.83 (highest SD of NPS reduction at Week24 in the EFC14146 [SINUS-24] and EFC14280 [SINUS-52])
- Dropout rate 25% (higher than 10% due to COVID-19 uncertainties)

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomic category
BID:	twice a day
BMI:	body mass index
CI:	confidence interval
CLcr:	creatinine clearance
COVID-19:	coronavirus disease 2019
CSR:	clinical study report
ECG:	electrocardiogram
EOS:	end of study
EOT:	end of treatment
HLGT:	high level group term
HLT:	high level term
IE:	intercurrent event
IMP:	investigational medicinal product
INCS:	intranasal corticosteroid
ITT:	intent-to-treat
K-M:	Kaplan-Meier
LLOQ:	lower limit of quantitation
LLT:	lower-level term
LS:	least squares
MCMC:	Markov Chain Monte Carlo
MedDRA:	medical dictionary for regulatory activities
NCS:	nasal congestion/obstruction score
NIMP:	noninvestigational medicinal product
NP:	nasal polyposis
NPS:	nasal polyp score
PCSA:	potentially clinically significant abnormality
PT:	preferred term
Q2W:	every 2 weeks
QM:	every morning
SAE:	serious adverse event
SAP:	statistical analysis plan
SCS:	systemic corticosteroid
SD:	standard deviation
SMQ:	standardized MedDRA query

SNOT-22: sino-nasal outcome test
SOC: system organ class
TEAEs: treatment-emergent adverse events
TSS: total symptom score
ULN: upper limit of normal
ULOQ: upper limit of quantification
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. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 may 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 including due to COVID-19 pandemic.
- 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 including due to COVID-19 pandemic.
- Vital status at last study contact

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19, 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 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 COVID-19 if applicable. In addition, deviations potentially impacting the primary endpoint analysis will 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 and baseline characteristics

- Age in years as quantitative variable and in categories (18-64, 65-74, 75-84, and ≥85)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, unknown),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown),
- Weight in kg as quantitative variable and in categories (<70, 70 - <90, ≥90 kg),
- BMI in kg/m^2 as quantitative variable and in categories (<25, ≥25 - <30, ≥30 kg/m^2),
- Screening blood eosinophil count in $cells/mm^3$ as quantitative variable and in categories (<300, ≥300 $cells/mm^3$)
- Baseline blood eosinophil count in $cells/mm^3$ as quantitative variable and in categories (<300, ≥300 $cells/mm^3$)

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.

Comorbidity will be summarized separately. The following comorbid diseases will be summarized from eCRF pages which were filled in by investigators based on participant reporting.

- Nasal polyps history (Yes, Ongoing condition)
- Nasal congestion (Yes, Ongoing condition)

- Nasal blockage/obstruction history (Yes, Ongoing condition)
- Decreased of sense of smell history (Yes, Ongoing condition)
- Loss of sense of smell history (Yes, Ongoing condition)
- Anterior rhinorrhea (runny nose) history (Yes, Ongoing condition)
- Posterior rhinorrhea (postnasal drip) history (Yes, Ongoing condition)
- Seasonal allergic rhinitis history (Yes, Ongoing condition)
- Perennial allergic rhinitis history (Yes, Ongoing condition)
- Allergic rhinitis history (Yes, Ongoing condition)
- Allergic conjunctivitis history (Yes, Ongoing condition)
- Asthma history (Yes, Ongoing condition)
- Atopic dermatitis history (Yes, Ongoing condition)
- Epistaxis history (Yes, Ongoing condition)
- Aspirin-exacerbated respiratory disease history (Yes, Ongoing condition)
- Hives history (Yes, Ongoing condition)
- Eosinophilic esophagitis history (Yes, Ongoing condition)
- Egg allergy history (Yes, Ongoing condition)
- Fish allergy history (Yes, Ongoing condition)
- Milk allergy history (Yes, Ongoing condition)
- Peanut allergy history (Yes, Ongoing condition)
- Allergy to nuts history (Yes, Ongoing condition)
- Shellfish allergy history (Yes, Ongoing condition)
- Soy allergy history (Yes, Ongoing condition)
- Flour sensitivity history (Yes, Ongoing condition)
- Gluten sensitivity history (Yes, Ongoing condition)

Disease characteristics at baseline

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

- NPS
- Symptom scores for nasal congestion/obstruction (NCS), decreased/loss of sense of smell, rhinorrhea (anterior/posterior nasal discharge) and total symptom score (TSS) respectively
- SNOT-22

- Time since first diagnosis of nasal polyposis (years) to be derived as
  - (Year of randomization – Year of first diagnosis of nasal polyposis) + (month of randomization – month of first diagnosis of nasal polyposis)/12
- Age of onset of nasal polyposis (years)
- Number of previous surgeries for nasal polyposis (0, 1, 2, ≥3)
- Number of previous surgery for nasal polyposis by type:
  - Nasal/sinus endoscopy surgical; with ethmoidectomy, total (anterior and posterior)
  - Nasal/sinus endoscopy, surgical, with maxillary and antrostomy with removal of tissue from maxillary sinus
  - Nasal/sinus endoscopy, surgical with frontal sinus exploration, with or without removal of tissue from frontal sinus
  - Nasal/sinus endoscopy, surgical, with maxillary antrostomy
  - Nasal/sinus endoscopy, surgical, with sphenoidotomy with removal of tissue from the sphenoid sinus
  - Nasal/sinus endoscopy, surgical, with sphenoidotomy
  - Nasal/sinus endoscopy, surgical with ethmoidectomy, partial
  - Excision, nasal polyp(s), extensive
  - Excision, nasal polyp(s), simple
  - Excision or destruction (eg, laser), intranasal lesion; internal approach
  - Other
- Time since most recent nasal polyposis surgery (years) to be derived as
  - (Year of randomization – Year of most recent nasal surgery) + (month of randomization – month of most recent nasal surgery)/12
- Smoking history (former, current, never), smoking duration (years) and smoking quantities in pack-year.
- Cessation prior to screening (months) for former smokers to be derived as
  - (Year of randomization – Year of cessation)×12 + (month of randomization – month of cessation)
- Frequency of alcohol drinking in the past 12 months (never, occasional, at least daily, at least weekly, at least monthly)
  - For daily drinkers, provide the following
    - Number of standard alcohol drinks on a typical day (1 or 2, >2)

- 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)

Any technical details related to computation, dates, and imputations for missing dates are described in Section 5.4.

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.

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 injection. 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 period up to the end of the study.
- A given medication/procedures can be classified as a prior medication/procedure and/or as a concomitant medication/procedures and/or as post-treatment medication/procedures. If it cannot be determined whether a given medication/procedures was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication/procedures.

The prior and concomitant medications/procedures will be summarized for the randomized population. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

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 time for the same medication.

The table 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 during first IMP to last IMP +14 days and concomitant medication received during 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.

Medications will also be summarized by generic name sorted by decreasing frequency based on the incidence in the dupilumab group.

Procedures will be summarized by intervention group by primary SOC (sorted by internationally agreed order) and PT (sorted in alphabetical order), sorting is based on the overall incidence across intervention groups.

Background intervention

Participants will be prescribed INCS (daily use of budesonide nasal spray) during the run-in period and throughout the whole study as described in protocol.

On a daily basis throughout the study, budesonide nasal spray will be self-administered (and recorded using an e-diary) by the participant. During the randomized treatment period, two actuations (64 µg/actuation) in each nostril QM, or 1 actuation in each nostril BID (total daily dose of 256 µg). One actuation in each nostril once daily (total daily dose of 128 µg) if the participants are unable to tolerate total daily dose of 256 µg, in which case they can stay on a lower dose regimen (128 µg) of budesonide nasal spray.

The prescription of INCS background therapy at randomization will be summarized regarding dose regimen (128 µg or 256 µg) by treatment group if applicable.

During the study, the daily intake of the INCS background therapy will be recorded on the electronic diary every morning by participants as number of actuations. Compliance for INCS will be calculated for each participant. For each day, a participant is considered as compliant to the prescribed background medication if the actual dose is the same as or greater than the prescribed dose (ie, two actuations) for each nostril during each administration throughout the day: a participant following a QM (or BID) regimen is considered as compliant to the prescribed INCS therapy if the actual dose for each nostril administered in the morning (or both in the morning and evening) is the same as or greater than the prescribed dose.

The compliance of INCS used from baseline visit to Week 24 (or end of treatment) visit, which is defined as the (number of days when the participant is compliant to the prescribed background therapy)/(the number of days the participant stays in the treatment period, which is from first IMP to last IMP + 14 days) × 100% will be summarized by intervention group.

Rescue medications/procedures

The following rescue medications/procedures may be received by participants:

- Nasal lavage with saline (only considered rescue if initiated after Visit 2) and/or systemic antibiotics (up to 2 weeks in case of acute infection).
- Short course SCS (oral prednisone, prednisolone or equivalent up to 2 weeks).
- Surgery for nasal polyps. Based on the observations from previous studies, 8 weeks of IMP treatment is recommended prior to surgery to allow onset of treatment effect.

Participants receiving rescue treatment other than surgery during the study should continue on study drug unless the Investigator decides to withdraw the study treatment. Handling conventions of surgery for NP is detailed in section Section 3.3.1.1.5.

The number and percentage of participants who take the rescue medications/procedures will be provided.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 General conventions

Demographic formulas

Parameter	Unit	Calculation
Age at onset of nasal polyposis	Year	Year of nasal polyposis diagnosis – Year of birth
Time since first diagnosis of nasal polyposis	Year	(Year of randomization - Year of first diagnosis of nasal polyposis) + (month of randomization month of first diagnosis of nasal polyposis)/12
BMI	kg/m^2	Weight in kg/(height^2 in meters)
Smoking quantity	pack-year	Number of pack-year = (packs smoked per day) × (years as a smoker)

Renal function formulas

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

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

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:

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

5.4.2 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 and safety 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 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 efficacy variable of NPS and SNOT-22, 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

Scheduled visit	Targeted study day	Analysis window in study days
Run-in (Visit 1)	-28	<-14
Week 0 (Visit 2)	1	-14 to 1^-
Week 16 (Visit 5)	113	1^+ to 140
Week 24 (Visit 6)	169	≥141

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

For daily eDiary data (NCS, disease specific daily symptom assessment and TSS, decreased/loss of sense of smell), all available values of daily measurements will be assigned to each week window according to Table 11, and then 28-day average score will be calculated. Randomization day is used as the reference day (Day 1).

Table 11 - Time window for eDiary efficacy variables

Time	Targeted day	Day range for calculating 28-day score
Week 4	29	2 to 29
Week 8	57	30 to 57
Week 12	85	58 to 85
Week 16	113	86 to 113
Week 20	141	114 to 141
Week 24	169	142 to 169
Week 28	197	170 to 197
Week 32	225	198 to 225
Week 36	253	226 to 253

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 12 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 Visit 2 time window.

Table 12 - Time window for safety endpoints

Visit	Targeted day	Time windows for		
		Vital signs	Hematology, biochemistry	Serum pregnancy test
Run-in (Visit 1)	-28	<-14	<-14	<-14
Week 0 (Visit 2)	1	-14 to 1^{-}	-14 to 1^{-}	-14 to 1^{-}
Week 2 (Visit 3)	15	1^{+} to 35	-	-
Week 4	29	-	-	1^{+} to 42
Week 8 (Visit 4)	57	36 to 84	1^{+} to 84	43 to 70
Week 12	85	-	-	71 to 98
Week 16 (Visit 5)	113	85 to 140	85 to 140	99 to 126
Week 20	141	-	-	127 to 154
Week 24 (Visit 6)	169	≥141	≥141	155 to 210
Week 36 (Visit 7)	253	-	-	≥211

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).
1^{-}: up to 1st dose date/time; 1^{+}: after 1st dose date/time;

5.4.3 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 SAMPLE SAS CODE

The multiple imputation and analysis model for the primary analysis of change from baseline in NPS at Week 24 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 participants who have not been rescued by surgery or receiving SCS at Week 24.

```
proc mi data=dat_etd seed=17026 nimpute=40 out=dat_mc;
     mcmc impute=monotone;
     var stratarn trt01p basenps chg16nps chg24nps;
run;
```

2. For each of the imputed dataset with monotone missing pattern in step 1, the remaining missing data will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, screening blood eosinophil count strata and baseline value of the response variable.

```
proc mi data=dat_mc nimpute=1 seed=17026 out=dat_mi;
     by _imputation_;
     class stratarn trt01p;
     monotone method=reg;
     var stratarn trt01p basenps chg16nps chg24nps;
run;
```

3. Each of the 40 imputed datasets will be merged with the 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 wocf;
     _imputation_=&i.;
     run;
     %end;
     data wocf_all;
     set %do j=1 %to 40; wocf&j. %end;;
     run;
%mend w1;
```

```
%w1

data dat_imp;
     set dat_mi wocf_all;
Run;

proc sort data=dat_imp;
     by _imputation_;
run;

proc glm data= dat_imp;
     by _imputation_;
     class stratarn trt01p;
     model chg24nps = basenps stratarn trt01p;
     lsmeans treatment / stderr;
     estimate 'Diff Dupilumab vs Placebo' trt01p -1 1;
     ods output LSMeans=implsmeans Estimates=implsmeandiff;
run;
```

4. Applying Rubin's rule 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. Sample code:

```
proc sort data=implsMeans; by trt01pn _imputation_;run;

proc mianalyze data=implsmeans;
     by trt01pn;
     modeleffects lsmean;
     stderr stderr;
     ods output ParameterEstimates=lsmeans;
run;

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

5.6 APPENDIX 6 DOUBLE CENTRAL READING WITH ADJUDICATION PROCEDURE

Standard video sequences of the nasal endoscopy will be scored by two readers independently. Further independent adjudication may be needed following the rules below. Here, the phrase independent adjudication refers to the procedure that another reader who is different with the initial two readers (so-called the adjudicator) reads the same video independently without knowing the scores by the initial two readers.

V1 central readings

Adjudication rule

For V1, independent adjudication is only required if the two readers differ on eligibility for the study: one reading is eligible (a total NPS score of 5 or more and at least 2 each side) while the other reading is ineligible (a total NPS score less than 5, or either side less than 2).

In the case of unreadable scores (bad quality videos) even from one reader (including the adjudicator when adjudication is needed based on the rule above), the endoscopy should be redone as soon as possible (require participant to come back at site).

Eligibility determination

When both readers score eligible, there will be no adjudication and the decision will be eligible.

When both readers score ineligible, there will be no adjudication and the decision will be ineligible.

When adjudication is performed, the total NPS score and each side score to determine eligibility will be based on the average of the adjudicator and one of the two readers whose total NPS score is closer to the adjudicator's reading (in the case that the two readers' scores are different but equidistant from the adjudicator's score, the reader with the higher score will be used in the calculation). In the special case that the two readers give different eligibility opinions but the total NPS scores are the same (the only possibility of the total NPS score for such a case is 5), eligibility will follow the adjudicator's opinion.

V2 and onward central readings

Adjudication rule

For V2 and onward, independent adjudication is required if the two readers differ more than 1 in their total NPS scores or if one and only one of the two readers scores unreadable.

Calculations of the total NPS score for analysis

When the two readers' total NPS scores are the same or differ 1, there will be no adjudication and the total NPS score for analysis will be the average of the two total NPS scores.

When the two readers' total NPS scores differ more than 1, adjudication will be performed and the total NPS score for analysis will be the average of the total NPS score read by the adjudicator and one of the two readers' total NPS scores whichever is closer to the adjudicator reading. In the case that the two readers' scores are equidistant from the adjudicator's score, the higher score will be used in the calculation. If the adjudicator gives unreadable scores, the total NPS scores will be missing values.

When the endoscopy is scored unreadable by both readers, the analysis score will be set to missing.

When one and only one of the two readers scores unreadable, adjudication will be performed and the total NPS score for analysis will be the average of the two available readings (if the adjudicator gives a readable score) or missing value (if the adjudicator scores it also unreadable).

Calculations of the NPS score for analysis in each nostril

In any case, the NPS score for analysis in each nostril will be calculated using the same readers as in the calculation of the total NPS score for analysis.

Adjudication for V1 when V2 is unreadable

Adjudication rule

For the analysis, central reading of V2 will be used as the baseline. In the scenario that V2 total NPS score for analysis is missing, V1 will be used instead and adjudication will be required if the total NPS scores by two readers at V1 differ more than 1 and adjudication has not been performed.

Calculations of the NPS scores for analysis

Calculations of the total NPS score for analysis and the NPS score for analysis in each nostril for such V1 readings will follow the aforementioned approach for V2 and onward.

5.7 [redacted]

[redacted]

5.8 APPENDIX 8 SELECTION CRITERIA FOR AE/MEDICATION GROUPINGS

Table 13 - List of PTs or medications for CMQs/CDGs

Grouping	Preferred Term/Medication Code	Preferred Term/Medication
Conjunctivitis	10001257	Adenoviral conjunctivitis
Conjunctivitis	10010725	Conjunctival irritation
Conjunctivitis	10010726	Conjunctival oedema
Conjunctivitis	10010736	Conjunctival ulcer
Conjunctivitis	10010741	Conjunctivitis
Conjunctivitis	10010744	Conjunctivitis allergic
Conjunctivitis	10010745	Conjunctivitis chlamydial
Conjunctivitis	10010749	Conjunctivitis gonococcal neonatal
Conjunctivitis	10010754	Conjunctivitis tuberculous
Conjunctivitis	10010755	Conjunctivitis viral
Conjunctivitis	10018258	Giant papillary conjunctivitis
Conjunctivitis	10021629	Inclusion conjunctivitis
Conjunctivitis	10030861	Ophthalmia neonatorum
Conjunctivitis	10048908	Seasonal allergy
Conjunctivitis	10049458	Herpes simplex virus conjunctivitis neonatal
Conjunctivitis	10051625	Conjunctival hyperaemia
Conjunctivitis	10053991	Inclusion conjunctivitis neonatal
Conjunctivitis	10061784	Conjunctivitis bacterial
Conjunctivitis	10062889	Pingueculitis
Conjunctivitis	10063669	Photoelectric conjunctivitis
Conjunctivitis	10067317	Oculorespiratory syndrome
Conjunctivitis	10067817	Acute haemorrhagic conjunctivitis
Conjunctivitis	10069166	Blebitis
Conjunctivitis	10071570	Ligneous conjunctivitis
Conjunctivitis	10074701	Noninfective conjunctivitis
Conjunctivitis	10075264	Oculoglandular syndrome
Conjunctivitis	10080825	Conjunctivitis fungal
Conjunctivitis	10084034	Conjunctival suffusion
Conjunctivitis	10084138	Giant fornix syndrome

5.9 APPENDIX 9 DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death." (3)

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

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

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

5.10 APPENDIX 10 LIST OF OPPORTUNISTIC INFECTIONS

- Aspergillosis.
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers).
- Candidiasis – only systemic or extensive mucosal or cutaneous cases.
- Coccidioides immitis (endemic south-western US and Central and South America).
- Cryptococcus.
- Cytomegalovirus.
- Herpes Simplex (disseminated).
- Herpes Zoster (disseminated; ophthalmic; involvement of 2 or more dermatomes).
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins).
- Listeriosis.
- Mycobacterium TB
- Mycobacterium avium.
- Nontuberculosis mycobacteria.
- Pneumocystis pneumonia (PCP).

This list is indicative and not exhaustive.

6 REFERENCES

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