# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Protocol title:** | **A randomized, double-blind, placebo-controlled, multi-center, parallel-group study of dupilumab in patients with chronic inducible cold urticaria who remain symptomatic despite the use of H1-antihistamine treatment** |
| **Protocol number:** | **EFC16720** |
| **Compound number (INN/Trademark):** | **SAR231893/REGN668 dupilumab/Dupixent** |
| **Study phase:** | **Phase 3** |
| **Short title:** | **Dupilumab for the treatment of chronic inducible cold urticaria in patients who remain symptomatic despite the use of H1-antihistamine**<br>**LIBERTY-CINDU CUrIADS** |
| **Statistician:** | [redacted] |
| **Statistical project leader:** | [redacted] |
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## TABLE OF CONTENTS

## LIST OF TABLES

# VERSION HISTORY

This Statistical Analysis Plan (SAP) is based on the protocol amendment 01 dated 27 September 2022.

The first participant was randomized on 04 January 2021.

# 1 INTRODUCTION

## 1.1 STUDY DESIGN

The EFC16720 study is a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the use of dupilumab in adults and adolescents (≥12 to <18 years old) with primary acquired chronic inducible cold urticaria (ColdU) who remain symptomatic despite the use of H1-antihistamine treatment. The study is designed to test the hypothesis that dupilumab will increase the proportion of participants with a negative ice cube provocation test at Week 24 compared with placebo. A negative ice cube provocation test is defined as the absence of a confluent hive/wheal at the entire skin site of exposure after an ice cube provocation test.

The study consists of 3 periods:

- Screening period (2 to 4 weeks).
- Randomized IMP treatment period (24 weeks).
- Post IMP treatment period (12 weeks).

Chronic inducible ColdU signs and symptoms will be evaluated after the ice cube provocation test, by the Investigator (hives/wheals intensity) and participant (itch severity, skin pain, skin sensation). In addition, chronic inducible ColdU disease activity will be assessed daily by the participant using ColdUAS questionnaire in an e-diary where the participant will report his/her skin reactions (wheals and swelling), skin sensations (itching, burning, pain or feeling hot), if they have been in contact with cold temperatures that usually cause skin reactions, if they have avoided trigger exposure, and overall symptoms severity. The study will also assess the effect of dupilumab on urticaria control, participants' HRQoL and overall health status, proportion of patients with cold urticaria requiring emergency medical care visit or treatment with epinephrine and on reduction of rescue therapy.

The total anticipated number of participants randomized in the study is 78. This corresponds to approximately 39 participants who will be randomly assigned to each intervention arm:

- Dupilumab: 300 mg every q2w for adults; 200 mg q2w for adolescents ≥30 kg and <60 kg at baseline or 300 mg q2w for adolescents ≥60 kg at baseline.
- Matched placebo.

At least 4 participants randomized in the study will be adolescents (≥12 to <18 years old) who will be recruited in a few selected sites in selected countries. Randomization will be stratified by age (adolescent versus adult) and within adult group by country and background H1-antihistamine regular/daily use (Yes/No).

The number of participants using H1-antihistamine as needed prior to study entry should be at least [redacted]

During the study, participants should continue their established standard of care background therapy with a long acting non-sedating H1-antihistamine, at up to 4-fold (2-fold in Japan) the approved dose for Chronic Spontaneous Urticaria (CSU).

- Participants who used H1-antihistamine regularly/daily prior to study entry should continue to take it daily. Note: regular/daily use of H1-antihistamine prior to study entry is defined as H1-antihistamine intake for at least 4 days per week for at least 1 month prior to screening visit (Visit 1).
- Participants who took H1-antihistamine as needed prior to study entry should limit the use to short-term.

The H1-antihistamine dose used during the study should be the same dose the participants took to prevent ColdU symptoms prior to study entry ("prescreening dose"). However, if participants experience a flare rescue therapy may be initiated.

If participants are on a dose higher than 4-fold (2-fold in Japan) the approved CSU dose at the screening visit (Visit 1), the investigator can adjust the participant's dose within the stipulated range at the screening visit (Visit 1).

All participants will be allowed to take study-defined H1-antihistamine as rescue therapy as long as they do not exceed 4-fold (2-fold in Japan) the approved CSU dose during screening, treatment, and follow-up periods. If symptoms are still uncontrolled after increase of H1-antihistamine to the maximum allowed dose, or if the participant is already on the 4-fold (2-fold in Japan) approved dose of H1-antihistamine, participants can switch to another antihistamine up to 4-fold (2-fold in Japan) the approved dose for CSU or a short course of oral corticosteroids (OCS) is allowed during the treatment and follow-up periods. However, for the purpose of the primary analysis, data collected after OCS use will be set to missing and the worst post-baseline value before OCS will be used to impute the data.

## 1.2 OBJECTIVE AND ENDPOINTS

**Table 1 - Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To demonstrate the efficacy of dupilumab in adult and adolescent participants with primary acquired chronic inducible cold urticaria (ColdU) who remain symptomatic despite the use of an H1-antihistamine | • Proportion of participants with negative ice cube provocation test* at Week 24 compared with placebo<br>*Negative ice cube provocation test is defined as the absence of a confluent hives/wheal at the entire skin site of exposure after ice cube provocation test [a] |
| **Secondary** | |
| • To demonstrate the efficacy of dupilumab on primary acquired chronic inducible ColdU disease control | • Change from baseline in urticaria control test (UCT 4-item) at Week 24 compared with placebo<br>• Proportion of well-controlled participants (UCT ≥12) at Week 24 compared with placebo |

| Objectives | Endpoints |
|---|---|
| | • Proportion of participants with an improvement of ≥3 in UCT 4-item from baseline to Week 24 compared with placebo. |
| • To demonstrate the efficacy of dupilumab on primary acquired chronic inducible ColdU local signs and symptoms (hives/wheals, itch, burning sensation and pain) after provocation test | • Change from baseline in local wheal intensity at the provocation site at Week 12 and Week 24 using the wheal intensity Likert scale ranging from 0 to 5 (clinician evaluation) compared with placebo<br>• Change from baseline in local itch severity at the provocation site at Week 12 and Week 24 using the Peak Pruritus Numerical Rating Scale (NRS, score 0 to 10) (patient reported) compared with placebo<br>• Change from baseline in local skin burning sensation at the provocation site at Week 12 and Week 24 using the peak burning sensation NRS (patient reported) compared with placebo<br>• Change from baseline in local pain severity at the provocation site at Week 12 and Week 24 using the peak pain sensation NRS (patient reported) compared with placebo<br>• Proportion of participants with negative ice cube provocation test at Week 12 compared with placebo |
| • To demonstrate the efficacy of dupilumab on primary acquired chronic inducible ColdU disease activity | • Change from baseline in cold urticaria signs and symptoms severity at Week 24 on cold exposure days as measured by ColdUAS, compared with placebo<br>• Change from baseline in the proportion of cold urticaria sign and symptom free days at Week 24 on cold exposure days as measured by ColdUAS, compared with placebo |
| • To demonstrate improvement in health-related quality-of-life and overall disease status and severity | • Change from baseline in health-related quality-of-life (HRQoL) as measured by Dermatology Life Quality Index (DLQI) in participants ≥16 years old, and in Children's Dermatology Life Quality Index (CDLQI) in participants ≥12 to <16 years old at Week 24 compared with placebo<br>• Change from baseline in Cold Urticaria Quality of Life (ColdU-QoL) at Week 24 compared with placebo. |
| • To evaluate the ability of dupilumab in reducing the proportion of participants who require rescue therapy | • Proportion of participants receiving rescue therapy for primary acquired chronic inducible ColdU during the planned treatment period compared with placebo |
| • To evaluate the proportion of participants with cold exposure triggered urticaria | • Proportion of participants with cold exposure triggered urticaria requiring emergency medical care visit or treatment with epinephrine (at provocation test and/or at home) |
| • To evaluate safety outcome measures | • Percentages of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) |

| Objectives | Endpoints |
|---|---|
| • To evaluate immunogenicity of dupilumab | • Incidence of treatment-emergent antidrug antibodies (ADA) against dupilumab over time |
| **Tertiary/exploratory** | |
| [redacted] | |
| **Pharmacokinetic (PK)/Pharmacodynamic (PD)** | |
| • To evaluate PK of dupilumab | • Functional dupilumab concentrations in serum and PK profile |
| • To evaluate PD effect of dupilumab | • Total immunoglobulin E over time. |

*a* Provocation test reading time for all endpoints: 15 minutes after the ice cube application start = 5 minutes ice cube application plus 10 minutes after removal of ice cube

### 1.2.1 Estimands

Primary estimand defined for main endpoints are summarized in below Table 2. More details are provided in Section 4.

**Table 2 - Summary of primary estimand for main endpoints**

| Endpoint Category | Estimands | | | |
|---|---|---|---|---|
| | **Endpoint** [a] | **Population** | **Intercurrent event(s) strategy and missing data handling** | **Population-level summary** |
| Primary objective: To demonstrate the efficacy of dupilumab in adult and adolescent participants with primary acquired chronic inducible ColdU who remain symptomatic despite the use of an H1-antihistamine | | | | |
| Primary endpoint | Proportion of participants with negative ice cube provocation test at Week 24 | ITT | The intercurrent events will be handled as follows:<br>• Discontinuation of study intervention before Week 24 (but not taking highly influential prohibited medications and/or highly influential rescue medications [b] prior to Week 24): Off-study intervention data up to Week 24 will be included in the analysis (treatment policy strategy).<br>• Taking highly influential prohibited medications and/or highly influential rescue medications [b] prior to Week 24: Participants will be considered as having positive ice cube provocation tests at Week 24 (composite strategy).<br><br>In addition, the missing data imputation rules are as follows:<br>• Having missing data at Week 24: Participants will be considered as having positive ice cube provocation tests at Week 24. | CMH test stratified by region (combined countries) and background H1-antihistamine regular/daily use (Yes/No). The comparison of the proportions of treatment response between dupilumab and placebo will be derived, and the corresponding odd ratios and the 95% CI will be reported. |

| Endpoint Category | Estimands | | | |
|---|---|---|---|---|
| | Endpoint [a] | Population | Intercurrent event(s) strategy and missing data handling | Population-level summary |
| Secondary objective: To demonstrate the efficacy of dupilumab on primary acquired chronic inducible ColdU local signs and symptoms | | | | |
| Secondary endpoint | Change from baseline in local wheal intensity at the provocation site at Week 24 using the wheal intensity Likert scale ranging from 0 to 5 (clinician evaluation)<br><br>Change from baseline in the proportion of cold urticaria sign and symptom free days at Week 24 on cold exposure days as measured by ColdUAS | ITT | The intercurrent events will be handled as follows:<br>• Discontinuation of study intervention before Week 24 (but not taking highly influential prohibited medications and/or highly influential rescue medications [b] prior to Week 24): Off-study intervention data up to Week 24 will be included in the analysis (treatment policy strategy)<br>• Taking highly influential prohibited medications and/or highly influential rescue medications [b] prior to Week 24: data will be set to missing values after the medication usage, and WOCF approach (worst post-baseline observation for the participant will be carried forward) will be used to impute missing endpoint value (for participants whose post-baseline values are all missing, the participant's baseline value will be used to impute the missing endpoint value) ( composite strategy)<br><br>In addition, the missing data imputation rules are as follows:<br>• For participants who discontinue study intervention due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute missing Week 24 value if needed. For participants who discontinue study intervention not due to lack of efficacy, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants excluding participants who have taken the highly influential prohibited medications and/or highly influential rescue medications [b] on or before Week 24 and excluding patients who discontinue due to lack of efficacy on or before Week 24. | ANCOVA model with treatment group, baseline value, region (combined countries), and background H1-antihistamine regular/daily use (Yes/No) as covariates will be used. Statistical inference obtained from all imputed data by ANCOVA model 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) score will be provided. In addition, difference of the dupilumab group against placebo in LS means and the corresponding 95% CI will be provided along with the p-values. |

a Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (i.e., Continuous, proportion) at other weeks
b Highly influential prohibited medications and/or highly influential rescue medications are listed in Table 4.

# 2 SAMPLE SIZE DETERMINATION

Sample size is calculated based on the following assumptions:

1. The placebo group has [redacted] participants with negative ice cube provocation test at Week 24 and the dupilumab group has [redacted] participants with negative ice cube provocation test at Week 24.
2. There is a drop-out rate of 10% in both groups.
3. The statistical test is a Z test that is based on the difference of the 2 proportions with unpooled variance estimate and 2-sided 1% significance level.
4. Participants are equally randomized to the dupilumab group and the placebo group.

With these assumptions, 39 participants per group (78 participants in total) will provide 90% power to detect the difference of [redacted] response rate in the dupilumab group and [redacted] response rate in the placebo group. The sample size calculations were performed using nQuery+nTerim 4.0.

# 3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

**Table 3 - Populations for analyses**

| Population | Description |
|---|---|
| Screened | All participants who sign the ICF |
| Randomized | All participants from the screened population who have been allocated to a randomized intervention by IRT regardless of whether the treatment kit was used or not.<br>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 intervention group allocated by randomization. |
| Safety | All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.<br>Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized.<br>For participants who accidentally receive a different intervention from that which was planned, the actual intervention allocation for as-treated analysis will be the dupilumab group.<br>The pharmacodynamic (PD) analyses will be performed on the safety population. |
| Pharmacokinetic (PK) | The PK population includes all participants in the safety population with at least one non-missing result for functional dupilumab concentration in serum after first dose of the study intervention. Participants will be analyzed according to the intervention actually received. |
| Anti-drug antibody (ADA) | ADA population includes all participants in the safety population who have at least one non-missing ADA result after first dose of the study intervention. Participants will be analyzed according to the intervention actually received. |

Abbreviations: ITT = intent-to-treat, ADA = antidrug antibody; ICF = Informed consent form, IRT = Interactive response technology; PD = Pharmacodynamic, PK = Pharmacokinetic

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

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

For any participant randomized more than once, only the data associated with the first randomization 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.

# 4 STATISTICAL ANALYSES

## 4.1 GENERAL CONSIDERATIONS

This SAP provides a comprehensive and detailed description of strategy and statistical techniques for the summary and analysis of EFC16720.

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

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

***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 from the end of the treatment-emergent period.

The on-study period is defined as the time from start of intervention until the end of the study defined as the status date collected on e-CRF page “Completion of End of Study”.

## 4.2 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 intervention period as per protocol
- Participants who did not complete the study intervention 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

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

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population and according to COVID-19 impact (i.e., deviations related to COVID-19 pandemic and deviations not related to COVID-19 pandemic). In addition, deviations potentially impacting the primary endpoint analysis may be summarized.

## 4.3 PRIMARY ENDPOINT(S) ANALYSIS

### 4.3.1 Definition of endpoint(s)

The primary endpoint is the proportion of participants with negative ice cube provocation test (absence of a confluent hive/wheal at the entire skin site of exposure) at Week 24.

### 4.3.2 Main analytical approach

The primary analysis population for the efficacy endpoints will be the ITT population. The statistical hypotheses for comparing dupilumab against placebo on the primary endpoint of proportion of participants with negative ice cube provocation test at Week 24:

- Null hypothesis H0: No treatment difference between dupilumab and placebo.
- Alternative hypothesis H1: There is a treatment difference between dupilumab and placebo.

For efficacy analysis, Table 4 presents the highly influential prohibited medications and highly influential rescue medications which will be considered as intercurrent events if the last column indicates as “Yes” and confirmed through blinded medical review and therefore will be handled in the estimands for endpoints defined in Table 2. Blinded medical review of participants who received the medications listed in Table 4 will be implemented before database lock to ensure the medication use was due to treatment failure instead of an unrelated condition.

**Table 4 - Highly influential prohibited medications and/or highly influential rescue medications impact on efficacy**

| Medication | Comment | Highly influential (Yes/No) [a] / Selection criteria |
|---|---|---|
| Systemic immunosuppressants (immunosuppressive/immunomodulating drugs) e.g., systemic corticosteroids (oral or parenteral [intravenous, intramuscular, SC]), cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, hydroxychloroquine, dapsone, sulfasalazine, colchicine, etc. | IMP to be discontinued | Yes (Standardized drug groupings (SDGs) Other immunosuppressants, tumour necrosis factor (TNF) alpha inhibitors, Calcineurin inhibitors, Interleukin inhibitors, Selective immunosuppressants – all Narrow) |
| Any cell-depleting agents including but not limited to rituximab | | Yes (CDG10236 Cell depletion agents) |
| Other monoclonal antibodies (which are biological response modifiers) including anti-IgE therapy (omalizumab). | | Yes (SDG Monoclonal antibodies Narrow) |
| IVIG | | Yes (CDG00488 Intravenous immunoglobulin therapy - See Section 5.5) |
| Plasmapheresis | | Yes (CMQ00079 based on the following PTs: Plasmapheresis, Apheresis) |
| Other investigational drugs. | | No, except ones with mechanism of action that may impact efficacy |
| Topical corticosteroids. | No IMP discontinuation | No |
| Topical calcineurin inhibitors. | | No |
| Topical and oral antihistamines (other than those allowed as background therapy). | | No |
| Routine doses of doxepin (daily or every other day during 5 or more consecutive days). | | No |
| LTRAs and H2 receptor antagonists, unless stable and taken for diseases other than chronic inducible ColdU. | | Yes for LTRAs; No for H2 receptor antagonists (SDG Leukotriene receptor antagonists for obstructive airway diseases Narrow) |
| Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid | | No |
| Phototherapy, including tanning beds. | | No |
| Additional H1-AH up to 4-fold (2-fold in Japan) | No IMP discontinuation | No |
| Corticosteroids | | Yes (SDG Corticosteroids Narrow excluding where Route is Topical, Nasal, Respiratory (Inhalation) or Ophthalmic) |

*a* When yes, if confirmed through blinded medical review that the medication use was due to treatment failure instead of an unrelated condition, the estimand for the intercurrent event handling strategy will be as follows: composite for continuous and responder endpoints. Otherwise, a treatment policy strategy will be applied.

The intercurrent event handling strategy for the primary estimand is the treatment policy/composite approach.

The primary efficacy endpoint will be analyzed using the Cochran-Mantel-Haenszel test stratified by region (combined countries) and background H1-antihistamine regular/daily use (Yes/No). The comparison of the proportions of participants with negative ice cube provocation test at Week 24 between dupilumab and placebo will be derived, and the corresponding odd ratios and the 95% confidence interval (CI) will be reported. Participants who receive highly influential prohibited medications and/or highly influential rescue medications (see Table 4) will be considered as having positive ice cube provocation tests for time points after the medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the positive/negative ice cube provocation test outcome. Participants with missing ice cube provocation test data at Week 24 will be considered as having positive ice cube provocation tests.

The following is a sample code for the primary analysis.

```
proc freq data=dataice;

   tables region*background*trtgrp*response/relrisk cmh;

   weight Count;

run;
```

### 4.3.3 Sensitivity analysis

The following sensitivity analyses will be performed targeting the same estimand as in the primary analysis to assess the impact of other missing data handling strategies. In the primary analysis, participants with missing ice cube provocation test data at Week 24 will be considered as having positive ice cube provocation tests.

Tipping point analysis

A tipping point analysis will be performed for the primary endpoint with imputed missing Week 24 values as follows:

- **Step 1.** With the complete data, fit a logistic regression model with the ice cube provocation test result (1: negative, 0: positive) at Week 24 as outcome and treatment group, region (combined countries), and background H1-antihistamine regular/daily use (Yes/No) as covariates.
- **Step 2.** Compute the probability of having negative ice cube provocation test for the participant with missing Week 24 value in placebo group from the fitted model but with the coefficient of the treatment group being added by a constant *d*. At the same time, compute the probability of having negative ice cube provocation test for the participant with missing Week 24 value in dupilumab group from the fitted model but with the coefficient of the treatment group being subtracted by a constant *p*.
- **Step 3.** With the probabilities computed in **Step 2**, impute the missing ice cube provocation results at Week 24 by generating binary random variables with the corresponding probabilities. Repeat this process to generate 40 imputed datasets.

- **Step 4.** Apply the Cochran-Mantel-Haenszel test stratified by region and background H1-antihistamine regular/daily use (Yes/No) for each imputed dataset. The results obtained from multiple imputed datasets will be combined to generate statistical inference, i.e. p-value and treatment difference between 2 treatment groups. Then use the SAS MIANALYZE procedure to generate statistical inferences of the odds ratios by combining results from the 40 analyses using Rubin's formula.

**Step** 2 to **Step** 4 will be repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated is >0.01.

### 4.3.4 Supplementary analyses

The following supplementary analysis will be performed:

As-observed analysis (Including all data after taking highly influential prohibited medications and/or highly influential rescue medications)

The data collected after taking the highly influential prohibited medications and/or highly influential rescue medications will be included in the supplementary analysis to evaluate the robustness of the primary analysis results with respect to the intercurrent event handling strategy. Missing ice cube provocation test result at Week 24 will be considered as positive.

### 4.3.5 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary endpoint across the following subgroups:

- Age group (< median, ≥ median; adult, adolescent)
- Gender (Male, Female)
- Baseline weight (< median, ≥ median, <60, ≥60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/$m^2$)
- Region (see Section 5.3)
- Race (White, all the Others)
- Ethnicity (Hispanic, non-Hispanic)
- Baseline H1-AH use (regular vs per-need)
- Baseline serum Total IgE (<100 IU/mL, ≥100 IU/mL)
- Duration of cold urticaria before screening visit (<5, ≥ 5 years)
- History of allergy (Allergic, non-Allergic)
- History of angioedema

To assess the consistency of the treatment effects across the subgroup levels, subgroup analyses will be conducted for the primary endpoint at Week 24. The analysis will be performed based on imputed datasets from the primary analysis.

To test the interaction between intervention and subgroup factor, a logistic regression 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.

In each subgroup, the primary endpoint will be analyzed using the primary approach for the primary endpoint, but on the specific subgroup. Forest plots will be provided.

## 4.4 SECONDARY ENDPOINT(S) ANALYSIS

### 4.4.1 Key/Confirmatory secondary endpoint(s)

#### *4.4.1.1 Definition of endpoint(s)*

Key secondary endpoints are listed below.

- Change from baseline in local wheal intensity at the provocation site at Week 24 using the wheal intensity Likert scale ranging from 0 to 5 (clinician evaluation)
- Change from baseline in the proportion of cold urticaria sign and symptom free days at Week 24 on cold exposure days as measured by ColdUAS

*Wheal intensity Likert scale*

The Wheal intensity Likert scale (ranging from 0 to 5) is a clinician-reported outcome measure completed at the study visit, 10 minutes after removal of the ice cube from the participant's arm. This scale is comprised of a single item assessing the intensity of patients' cutaneous reaction rated as follows: 0=no wheals; 1=numerous small, non-coalescent wheals; 2=a large, regular, slightly edematous, coalescent wheal; 3=a large and moderately edematous wheal; 4=a large, regular, and significantly edematous wheal without pseudopodia; and 5=a large, very edematous wheal with pseudopodia

*Proportion of cold urticaria sign and symptom free days on cold exposure days as measured by ColdUAS*

The ColdUAS is a disease-specific PRO questionnaire designed to determine cold urticaria disease activity which is administered daily via e-diary (the details can be found in the protocol). The proportion of cold urticaria sign and symptom free days is defined in two steps: (1) take a window of 14 days before each visit date (i.e., Baseline, Week 12 and Week 24), count the number of days when the patient reports "exposed" to cold (i.e., ColdUAS Q3>0); (2) within the "exposed" days, count the number of days when the patient reports no ColdU related sign and symptom (i.e., ColdUAS Q1=0 and Q2=0). If the number of exposure days is zero, then the

proportion is set to missing, otherwise, it is the ratio of the sign and symptom free days over the exposure days in the 14-day window.

The e-diary completion days should be no less than 6 and exposure days should be no less than 1 in the 14-day window, otherwise the proportion of sign and symptom free days is considered as missing. Additionally, analyses based on exposure days no less than 3 will be conducted.

#### *4.4.1.2 Main analytical approach*

The intercurrent event handing strategy for the key secondary endpoints is the treatment policy/composite approach.

This key secondary endpoints will be analyzed using an analysis of covariance (ANCOVA) model with baseline value of the endpoint, treatment group, region (combined countries), and background H1-antihistamine regular/daily use (Yes/No) as covariates, with intercurrent events and missing data being handled by a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation. For participants who took highly influential prohibited medications and/or highly influential rescue medications (see Table 4), their data after the medication usage will be set to missing, and worst post-baseline value on or before the time of the medication usage will be used to impute missing Week 24 value (for participants whose post-baseline values are all missing, the baseline will be used to impute). Participants who discontinue the treatment prematurely are encouraged to follow the planned clinical visits. For participants who did not take the highly influential prohibited medications and/or highly influential rescue medications, all data collected after treatment discontinuation will be used in the analysis. For participants who discontinue study intervention due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute missing Week 24 value if needed (i.e., due to study discontinuation). For participants who discontinue study intervention not due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a multiple imputation approach will be used to impute missing Week 24 value if needed (i.e., due to study discontinuation). This multiple imputation will use all participants excluding participants who have taken the highly influential prohibited medications and/or highly influential rescue medications on or before Week 24 and excluding participants who discontinue due to lack of efficacy on or before Week 24. Each of the imputed complete data will be analyzed by fitting an analysis of covariance 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) score 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-values.

### 4.4.2 Supportive secondary endpoint(s)

The change from baseline endpoints:

- Change from baseline in urticaria control test (UCT 4-item) at Week 24
- Change from baseline in local wheal intensity at the provocation site at Week 12 using the wheal intensity Likert scale ranging from 0 to 5 (clinician evaluation)

- Change from baseline in local itch severity at the provocation site at Week 12 and Week 24 using the Peak Pruritus Numerical Rating Scale (NRS, score 0 to 10) (patient reported)
- Change from baseline in local skin burning sensation at the provocation site at Week 12 and Week 24 using the peak burning sensation NRS (patient reported)
- Change from baseline in local pain severity at the provocation site at Week 12 and Week 24 using the peak pain sensation NRS (patient reported)
- Change from baseline in cold urticaria signs and symptoms severity at Week 24 on cold exposure days as measured by ColdUAS
- Change from baseline in health-related quality of life (HRQoL) as measured by Dermatology Life Quality Index (DLQI) in participants ≥16 years old, and in Children's Dermatology Life Quality Index (CDLQI) in participants ≥12 to <16 years old at Week 24
- Change from baseline in Cold Urticaria Quality of Life (ColdU-QoL) at Week 24

The Week 12 and Week 24 values will be analyzed separately and use the same procedure as the key secondary endpoint. The endpoint change from baseline in DLQI will be summarized and analyzed in participants ≥ 16 years old who completed the DLQI at baseline. The endpoint change from baseline in CDLQI will be summarized separately in participants ≥12 to <16 years old using descriptive analysis only.

The proportion endpoints below will be analyzed like the primary endpoint.

- Proportion of well-controlled participants (UCT ≥12) at Week 24
- Proportion of participants with an improvement of ≥3 in UCT 4-item from baseline to Week 24
- Proportion of participants with negative ice cube provocation test at Week 12

The two endpoints below will be summarized using the count and percentage of participants.

- Proportion of participants receiving rescue therapy for primary acquired chronic induced ColdU during the planned treatment period
- Proportion of participants with cold exposure triggered urticaria requiring emergency medical care visit or treatment with epinephrine (at provocation test and/or at home)

## 4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

### 4.5.1 Definition of endpoint(s)

Additional details are provided below for specific exploratory efficacy endpoints.

- Patient Global Impression of Change (PGIC) of primary acquired chronic inducible ColdU at Week 12 and Week 24
- Change from baseline in Patient Global Impression of Severity (PGIS) of primary acquired chronic inducible ColdU at Week 12 and Week 24

[redacted]

### 4.5.2 Main analytical approach

Exploratory efficacy endpoints will be analyzed using the same methodology as above for similar data (continuous, proportion).

## 4.6 MULTIPLICITY ISSUES

To strongly control the family-wise type-I error rate for testing the primary and selected secondary endpoints, hierarchical testing procedure is used. The overall two-sided alpha is 0.01. The comparisons with placebo will be tested based on the hierarchical order below at 2-sided $\alpha = 0.01$.

**Order of the testing hierarchy:**

1. Proportion of participants with negative ice cube provocation test at Week 24.
2. Change from baseline in local wheal intensity at the provocation site at Week 24 using the wheal intensity Likert scale ranging from 0 to 5 (clinician evaluation).
3. Change from baseline in proportion of cold urticaria symptom free days at Week 24 (exposure-adjusted and measured by ColdUAS).
4. Change from baseline in local itch severity at the provocation site at Week 24 using the Peak Pruritus Numerical Rating Scale (NRS, score 0 to 10) (patient reported).
5. Change from baseline in health-related quality-of-life (HRQoL) as measured by Dermatology Life Quality Index (DLQI) in participants ≥16 years old.

## 4.7 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 3, 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 (e.g., exposed but not randomized) will be provided separately.

### 4.7.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population.

**Duration of IMP exposure**

Duration of IMP exposure is defined as last dose date – first dose date + 15 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 IMP 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 IMP exposure will be provided, defined as the sum of the duration of treatment exposure for all participants, and will be expressed in participant years.

**Treatment compliance**

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

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

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

Cases of overdose (defined as at least twice the intended dose during an interval of less than 11 days) are considered an AESI and will be listed as such.

### 4.7.2 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 focus of AE reporting 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. 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 5.

**Table 5 - 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 SOC and PT will define the presentation order for all other tables (e.g., 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 6 will be generated with number (%) of participants experiencing at least one event.

**Table 6 - Analyses of adverse events**

| Type of AE | MedDRA levels |
|---|---|
| All TEAE | Primary SOC, HLGT, HLT and PT |
| | Primary SOC and PT |
| | PT |
| | Primary and secondary SOC, HLGT, HLT and PT |
| Common TEAE ≥5% in any group) | Primary SOC and PT |
| TEAE related to IMP as per Investigator's judgment | Primary SOC, 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, HLGT, HLT and PT |
| TEAE leading to permanent intervention discontinuation | Primary SOC, HLGT, HLT and PT |
| | 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, HLGT, HLT and PT |
| Pretreatment 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 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.

Risk differences (constructed using the Miettinen and Nurminen method) and hazard ratios (Cox proportional hazards model) for dupilumab versus placebo with corresponding 95% CIs will be provided for the common TEAEs (PT ≥ 5% in any intervention group). Participants without an event will be censored at the end of the treatment-emergent period in the Cox model. Forest plots will also be presented.

## Analysis of deaths

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

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

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

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 7. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 5.

**Table 7 - 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 18.1): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not. |
| Systemic hypersensitivity reactions | SMQ [20000214] hypersensitivity narrow search and [AE corrective treatment/therapy = 'Y' or Action taken with IMP = 'Drug withdrawn' or Action taken with IMP = 'Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events |
| Helminthic infections | CMQ10544 based on HLGT as "Helminthic disorder" |
| Any severe type of conjunctivitis | CMQ10498 based on PTs (See Section 5.5) [a] and "Severe" ticked in Adverse Events eCRF page |
| Any severe type of blepharitis | CMQ10497 based on HLT as "Lid, lash and lacrimal infections, irritations and inflammations" and "Severe" ticked in Adverse Events eCRF page |
| Keratitis | CMQ10642 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, herpes ophthalmic, ophthalmic herpes simplex, corneal infection] [a] |

| AE Grouping | Criteria |
|---|---|
| Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms) [b] | CMQ10641 based on HLT = Eosinophilic disorders or PT = Eosinophil count increased |
| Pregnancy of a female patients entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP | "Pregnancy" or "Partner Pregnancy" checked on the Pregnancy eCRF page as reported by the investigator |
| Significant ALT elevation | ALT >5 x ULN in participants with baseline ALT ≤2 x ULN;<br>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. |
| **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 |
| Drug-related hepatic disorder | SMQ [20000006] Drug-related hepatic disorders- narrow |
| Injection site reaction | 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) | CMQ10643 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye irritation, Eye inflammation, Giant papillary conjunctivitis] [a] |
| Keratitis (FDA) | 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

The following summaries will be provided:

- All TEAEs, by selected standardized MedDRA query (SMQ)/Customized MedDRA query (CMQ) and PT or by laboratory values (as in alanine aminotransferase (ALT) elevation), 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.

- All TEAEs, by selected SMQ/CMQ including risk differences and hazard ratios with corresponding 95% CIs.
- 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 participants with any specific TEAE adjusted by the exposure duration
  - Time to onset of first TEAE and cumulative incidence at specified time points (K-M estimates 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.

### 4.7.3 Additional safety assessments

#### *4.7.3.1 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.
- **Hepatitis screen:** hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab) will be tested at screening (V1). In case of results showing HBs Ag (negative) and HBc Ab (positive), an hepatitis B virus (HBV) deoxyribonucleic acid (DNA) testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCV Ab (positive), an HCV ribonucleic acid (RNA) testing will be performed and should be confirmed negative prior to randomization.
- **HIV screen:** Anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1

- Urinalysis:
  - **Urinalysis** will include specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen and bilirubin. In case the urine dipstick test result is abnormal, a urine sample should be sent into the central laboratory for microscopic and macroscopic examination.
- Vital signs: heart rate (beats per minute), systolic and diastolic blood pressure (mmHg) in a semi-supine or sitting position after 5 minutes rest, weight, respiratory rate (breaths per minute), temperature (degrees Celsius) and height (screening only)
- ECG variables: ECG assessments will be described as normal or abnormal

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**

For all laboratory variables and vital signs variables above, descriptive statistics for results and changes from baseline will be provided for each analysis window, the last value and the worst value during the on-treatment period. These analyses will be performed using central measurements only (when available) 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 variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

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

***Additional analyses for suspect drug-induced liver injury***

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

- Time to onset of the initial ALT or aspartate aminotransferase (AST) elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) during the treatment-emergent period will be analyzed using Kaplan-Meier method.
- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (e.g., ALT), participants having a PCSA (e.g., 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).

## 4.8 OTHER ANALYSES

### 4.8.1 PK analyses

Predose serum dupilumab concentrations at Visit 2 (Day 1), dupilumab trough levels at Week 12, Week 24/EOT and posttreatment serum dupilumab at Week 36 will be provided.

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

### 4.8.2 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/EOT and follow up at Week 36 will be provided. The neutralizing antibody status for ADA positive samples will be provided.

Incidence will be provided for the following ADA response categories:

Pre-existing immunoreactivity is defined as:

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

Treatment-emergent ADA responses are defined as:

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

Treatment-emergent ADA responses are further classified as Persistent, Indeterminate or Transient

a) Persistent Response- defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days), with no ADA negative samples in between.
b) Indeterminate Response- defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
c) 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 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.

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

**Impact of ADA on clinical efficacy endpoints**

Associations between the ADA variables (e.g., 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)

Associations between ADA variables (e.g., ADA peak titers, neutralizing antibody status, treatment-emergent, persistent and treatment-boosted) and safety may be explored.

### 4.8.3 Pharmacodynamic/genomics endpoints

Venous blood samples will be collected at Visit 2 (Week 0), Visit 3 (Week 12), Visit 4 (Week 24/EOT), and Visit 5 (Week 36), for measurement of total serum IgE. Total IgE will be measured using validated quantitative methods.

For those participants (with exception of adolescent) who consent to the optional pharmacogenetic/pharmacogenomic sample collection section of the ICF, serum/plasma for archival samples for possible future analysis of potential biomarkers of drug response, disease activity, safety, and the Type 2 inflammation pathway, and blood samples for exploratory genetic analysis of DNA or RNA will be collected and stored for possible future use. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

For those participants (with exception of adolescent) who consent to the optional basophil activation (substudy), samples will be taken at Visit 2, Visit 3 (Week 12) and Visit 4 (Week 24/EOT).

Total IgE will be summarized in the safety population defined as participants who actually received at least 1 dose or part of a dose of the IMP. 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 will be summarized.

Summary plots (median+/- standard error of the mean) on values at each visit, absolute changes from baseline and percent changes from baseline will be provided for the total IgE by intervention group and visit.

Exploratory analysis of DNA/RNA will be addressed in a separate document.

The analyses of the basophil activation substudy will be addressed in a separate document.

## 4.9 INTERIM ANALYSES

No interim analysis is planned.

A primary database lock will be performed when all randomized participants in this study have completed their 24-week treatment phase. Analysis will be based on all data collected up to the database cut-off date and will be considered as the final analyses in the CSR.

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. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

# 5 SUPPORTING DOCUMENTATION

## 5.1 APPENDIX 1 LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA: | anti-drug antibody |
| AE: | adverse event |
| AESIs: | adverse events of special interest |
| ALT: | alanine aminotransferase |
| ANCOVA: | analysis of covariance |
| AST: | aspartate aminotransferase |
| ATC: | anatomic category |
| CDG: | customized drug grouping |
| CDLQI: | Children's Dermatology Life Qualtiy Index |
| CI: | confidence interval |
| CLcr: | Creatinine clearance |
| CSU: | Chronic Spontaneous Urticaria |
| DLQI: | Dermatology Life Quality Index |
| DNA: | deoxyribonucleic acid |
| ECG: | electrocardiogram |
| eCRF: | electronic case report form |
| EOT: | end of treatment |
| HBc Ab: | hepatitis B core antibody |
| HBs Ab: | hepatitis B surface antibody |
| HBs Ag: | hepatitis B surface antigen |
| HBV: | hepatitis B virus |
| HCV Ab: | hepatitis C virus antibodies |
| HLGT: | high level group term |
| HLT: | high level term |
| HRQoL: | health-related quality of life |
| IMP: | investigational medicinal product |
| ITT: | intent-to-treat |
| LLT: | lower-level term |
| LS: | least squares |
| MedDRA: | medical dictionary for regulatory activities |
| OCS: | oral corticosteroids |
| PCSA: | potentially clinically significant abnormality |
| PGIS: | Patient Global Impression of Severity |
| PT: | preferred term |
| RNA: | ribonucleic acid |
| SAP: | statistical analysis plan |
| SDG: | standardized drug grouping |
| SDGs: | Standardized drug groupings |
| SMQ: | standardized MedDRA query |
| SOC: | system organ class |

TEAE: treatment-emergent adverse event
UCT: urticaria control test
ULN: upper limit of normal
WHO-DD: World Health Organization-Drug Dictionary

## 5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This Statistical Analysis Plan (SAP) for study EFC16720 is based on the protocol amendment 01 dated 27 September 2022. For the details of major statistical changes, see protocol amendment summary of changes table in study protocol.

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

***Demographics, baseline characteristics, medical surgical history***

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

Demographic variables are

- Age in years (quantitative and qualitative variable: 12-<18, 18-<40, 40-<65, 65-<75 and ≥75 years),
- 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)
- Region (**Asia:** Japan; **Latin America:** Argentina; **Western Countries**: Canada, USA**,** Germany)
- Weight in kg (quantitative and qualitative variable: <60, ≥60 kg)
- BMI in $kg/m^2$ (quantitative and qualitative variable: <30, ≥30 $kg/m^2$)

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

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

This information will be coded using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Comorbidity will be summarized separately. The following comorbid diseases will be summarized from electronic case report form (eCRF) pages which were filled in by investigators based on participant reporting. Angioedema history will be further summarized under disease characteristics at baseline.

CSU (Yes, Ongoing condition)

Atopic Dermatitis (Yes, Ongoing condition)

Allergic rhinitis (Yes, Ongoing condition)

Allergic Conjunctivitis (Yes, Ongoing condition)

Asthma (Yes, Ongoing condition)

Food allergy (Yes, Ongoing condition)

Chronic Rhinosinusitis (Yes, Ongoing condition)

Nasal Polyps (Yes, Ongoing condition)

Eosinophilic Esophagitis (Yes, Ongoing condition)

***Disease characteristics at baseline***

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

- Age at onset of cold urticaria (years)
- Duration of cold urticaria before screening visit (years) to be derived as
- (Year of screening visit – Year of first diagnosis of cold urticaria) + (month of screening visit-month of first diagnosis of cold urticaria)/12
- Number of patients who had cold urticaria events within 12 months before screening visit requiring Hospitalization/emergency care [n (%)], Epinephrine [n (%)] and OCS [n (%)], resulting in anaphylactic reaction [n (%)] and oropharyngeal edema [n (%)]
- Number of patients who experienced cold urticaria symptoms including Skin (e.g. Localized Urticaria) [n (%)], Angioedema (e.g. Oropharyngeal angioedema) [n (%)], Skin (e.g. Generalized Urticaria) [n (%)], Skin (e.g. Generalized Urticaria) [n (%)], Generalized Angioedema [n (%)], Respiratory distress (e.g. Wheezing or shortness of breath) [n (%)], Hypotension (e.g. Dizziness, sensation of fainting, disorientation, or shock) [n (%)], Gastrointestinal discomfort (e.g. Diarrhea or vomiting) [n (%)], Other symptoms [n (%)]
- Baseline urticaria control test (UCT)
- Baseline Wheal intensity Likert scale
- Baseline peak pruritus NRS
- Baseline peak pain NRS

- Baseline peak burning sensation NRS
- Baseline number of cold urticaria sign and symptom free days, Baseline number of cold exposure days, Baseline number of days of avoidance to cold (all measured by ColdUAS)
- Baseline proportion of cold urticaria sign and symptom free days (measured by ColdUAS)
- Baseline cold urticaria signs and symptoms severity on cold exposure (measured by ColdUAS)
- Baseline Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI)
- Baseline ColdU-QoL
- Baseline Patient Global Impression of Severity (PGIS)
- Screening ACUSI
- Baseline EQ-5D-5L and EQ-VAS
- Baseline IgE (quantitative and qualitative variable : <100 vs ≥100)
- Baseline H1-AH use (regular vs per-need) and dose (<1-fold, 1-fold, 2-3-fold, 4-fold)
- Prior cold urticaria medication use (LTRAs, H2-blockers, Omalizumab)

***Prior or concomitant medications***

All medications taken within 1 month before screening and until the end of the study, including all prior medications taken for ColdU are to be reported in the case report form pages.

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

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

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

Medications will be summarized by intervention group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the

first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, participants may be counted several times for the same medication.

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

Concomitant medication received 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.

***Rescue medications***

The following rescue medications may be used:

- Additional doses of H1-AH up to 4-fold the recommended dose (2-fold in Japan)
- Short course of OCS

The use of rescue medications should be delayed, if possible, for at least 8 weeks following the initiation of IMP. The following specific medications will be summarized:

- Rescue medications taken during the study will be summarized separately overall and by type (additional doses of H1-AH medications, OCS therapy).
- The total number of days rescue medication was taken by type will be summarized.

## 5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

**Demographic formulas**

Age of onset of cold urticaria is calculated as:

Year of cold urticaria diagnosis – Year of birth

BMI is calculated as:

Weight in kg / (height$^2$ in meters)

**Renal function formulas**

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

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

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

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

where the coefficient k = 0.55 for children <12; k = 0.65 for male adolescent participants or k = 0.55 for female adolescent participants

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

Age = age collected at screening + integer part of (lab sampling analysis day / 365.25)

**Data handling conventions for other secondary endpoints**

For the UCT, in case of missing items the score for that participant will be left missing.

For the DLQI, handing of missing items is as follows:

a) If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
b) If two or more questions are left unanswered the questionnaire is not scored.
c) If question 7 is answered ‘yes’, this is scored 3 even if in the same question one of the other boxes is ticked.
d) If question 7 is answered ‘no’ or ‘not relevant’ but either ‘a lot’ or ‘a little’ is ticked, this is then scored 2 or 1.
e) If two or more response options are ticked for one question, the response option with the highest score should be recorded.

For the CDLQI, handling of missing items is as follows:

a) If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
b) If two or more questions are left unanswered the questionnaire is not scored.
c) If two or more response options are ticked for one question, the response option with the highest score should be recorded.

For the ColdU-QoL total score, the raw total score will be converted to a 0 to 100 score for analysis using the following formula:

ColdU-QoL total score = Sum of the score of all completed items/Maximum possible sum of the score of all completed items*100.

For the ColdUAS, there are two endpoints:

1. (E1) Proportion of sign and symptom free days over the exposure days in the 14-day window
2. (E2) MEAN SCORE of Q1+Q2 adjusted for exposure in the 14-day window

To define E1, first take all the days in the 14-day window with Q3>0 (called A1). For those days, look at how many days when the patient answers Q1=0 and Q2=0 (A2). The proportion is defined as A2/A1. It will be set to missing if A1=0.

To define E2, first take all the days in the 14-day window with Q3>0 (called A1). For those days, calculate the total score Q1+Q2 for each day and then sum the total scores together (called B2). The MEAN SCORE of Q1+Q2 adjusted for exposure in the 14-day window is defined as B2/A1. It will be set to missing if A1=0.

Example:

| Day | ColdUAS Completed | Q3 | Note for programming | Q1 | Q2 | Q1+Q2 |
|---|---|---|---|---|---|---|
| 1 | Y | 0 | Not exposed, not counted in A1 | 1 | 1 | 2* |
| 2 | N | NA | Missing ediary, not counted in A1 | NA | NA | NA |
| 3 | Y | 1 | counted in A1 | 0 | 0 | 0 |
| 4 | Y | 2 | counted in A1 | 2 | 1 | 3 |
| 5 | Y | 2 | counted in A1 | 2 | 3 | 5 |
| 6 | Y | 1 | counted in A1 | 0 | 1 | 1 |
| 7 | N | NA | Missing ediary, not counted in A1 | NA | NA | NA |
| 8 | N | NA | Missing ediary, not counted in A1 | NA | NA | NA |
| 9 | Y | 1 | counted in A1 | 1 | 0 | 1 |
| 10 | Y | 1 | counted in A1 | 0 | 0 | 0 |
| 11 | Y | 0 | Not exposed, not counted in A1 | 1 | 2 | 3* |
| 12 | Y | 2 | counted in A1 | 2 | 1 | 3 |
| 13 | N | NA | Missing ediary, not counted in A1 | NA | NA | NA |
| 14 | Y | 1 | counted in A1 | 1 | 0 | 1 |

A1=8

A2=2 (within the 8 days of exposure, only 2 days with Q1+Q2=0)

B2=(0+3+5+1+1+0+3+1)=14 (the values 2 and 3 with superscript "*" are not counted as they belong to days without exposure)

E1=A2/A1=2/8=0.25

E2=B2/A1=14/8=1.75

Note: The e-diary completion days should be no less than 6 and exposure days should be no less than 1 in the 14-day window, otherwise the proportion of sign and symptom free days and mean score will be considered as missing. Additionally, analyses based on exposure days no less than 3 will be conducted.

For the EQ-5D-5L health status, it will be converted into a single index value according to the new crosswalk algorithm developed by Hernandez Alava et al (1) and using the UK value set.

**Daily e-diary weekly scores**

For the daily efficacy endpoints (ColdUAS), the time period used to calculate the bi-weekly score at each designated study day is summarized in Table 8. Randomization day is used as the reference day (Day 1).

**Table 8 - Weekly efficacy assessments from daily e-diary**

| Analysis visit | Day range for calculating weekly score | Target day |
|---|---|---|
| Baseline (Week 0) | -14- -1 | -1 |
| Week 2 | 2-15 | 15 |
| Week 4 | 16-29 | 29 |
| Week 6 | 30-43 | 43 |
| Week 8 | 44-57 | 57 |
| Week 10 | 58-71 | 71 |
| Week 12 | 72-85 | 85 |
| Week 14 | 86-99 | 99 |
| Week 16 | 100-113 | 113 |
| Week 18 | 114-127 | 127 |
| Week 20 | 128-141 | 141 |
| Week 22 | 142-155 | 155 |
| Week 24 | 156-169 | 169 |
| Week 26 | 170-183 | 183 |
| Week 28 | 181-197 | 197 |
| Week 30 | 198-211 | 211 |
| Week 32 | 212-225 | 225 |
| Week 34 | 226-239 | 239 |
| Week 36 | 240-253 | 253 |

### Analysis windows for time points

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

**Table 9 - Time window for safety endpoints**

| | | Time windows for | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit** | **Target Day** | **Vital signs** | **Hematology, biochemistry, urinalysis** | **Hepatitis, HIV serology** | **Serum pregnancy** | **Urine pregnancy** | **Physical exam** | **ECG** |
| Visit 1 | -28 to -14 | <-14 | <-14 | 1- | <-14 | | <-14 | 1- |
| Visit 2 (Week 0) | 1 | -14-1- | -14-1- | | | -14-1- | -14-1- | |
| Week 4 | 29 | | | | | 1+-42 | | |
| Week 8 | 57 | | | | | 43-70 | | |
| Visit 3 (Week 12) | 85 | 1+-126 | 1+-126 | | | 71-98 | | |
| Week 16 | 113 | | | | | 99-126 | | |
| Week 20 | 141 | | | | | 127-154 | | |
| Visit 4 (Week 24) | 169 | 127-210 | 127-210 | | | 155-182 | 1+-210 | |
| Week 28 | 197 | | | | | 183-210 | | |
| Week 32 | 225 | | | | | 211-238 | | |
| Visit 5 (Week 36) | 253 | >210 | >210 | | | >238 | >210 | |

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

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

**Table 10 - Time window for efficacy variables**

| Visit | Target Day | Time windows for | | | | |
|---|---|---|---|---|---|---|
| | | Ice cube, UCT | Likert, NRS | ColdUAS, PGIS | PGIC | DLQI/CDLQI, ColdU-QoL, EQ-5D-5L, [redacted] |
| Visit 1 | -28 to -14 | <-14 | | <-14 | | |
| Visit 2 (Week 0) | 1 | -14-1$^{-}$ | <1$^{-}$ | -14-1$^{-}$ | | <1$^{-}$ |
| Visit 3 (Week 12) | 85 | 1$^{+}$-126 | 1$^{+}$-126 | 1$^{+}$-126 | 1$^{+}$-126 | |
| Visit 4 (Week 24) | 169 | 127-210 | 127-210 | >126 | >126 | ≥1$^{+}$ |
| Visit 5 (Week 36) | 253 | >210 | >210 | | | |

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

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

**Table 11 - Time window for pharmacokinetics/pharmacodynamics variables**

| Visit | Target Day | Serum dupilumab, ADA, Total IgE | Basophil activation (optional) |
|---|---|---|---|
| Visit 1 | -28 to -14 | | |
| Visit 2 (Week 0) | 1 | <1$^{-}$ | <1$^{-}$ |
| Visit 3 (Week 12) | 85 | 1$^{+}$-126 | 1$^{+}$-126 |
| Visit 4 (Week 24) | 169 | 127-210 | >126 |
| Visit 5 (Week 36) | 253 | >210 | |

1-: up to 1st dose date/time or randomization if participant is not treated; 1+: after 1st dose date/time or randomization date if participant is not treated;

### Unscheduled visits

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

## 5.5 APPENDIX 5 SELECTION CRITERIA FOR AE/MEDICATION GROUPINGS

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

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

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

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

# 6 REFERENCES

1. Hernández Alava, M., Pudney, S. and Wailoo, A. (2020) Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English population study. Policy Research Unit in Economic Evaluation of Health and Care Interventions. Universities of Sheffield and York. Report 063.

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