STATISTICAL ANALYSIS PLAN

Protocol title:	**Master protocol of two randomized, double-blind, placebo-controlled, multi-center, parallel-group studies of dupilumab in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine treatment in patients naïve to omalizumab and in patients who are intolerant or incomplete responders to omalizumab**
Protocol number:	**EFC16461A**
Compound number (INN/Trademark):	**SAR231893/REGN668 dupilumab/Dupixent**
Study phase:	**Phase 3**
Short title:	**Dupilumab for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine and who are naïve to omalizumab.** **LIBERTY-CSU CUPID (Chronic Urticarial Pruritus Itch Dupilumab Trial)**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**16-Jun-2021**

Regulatory agency identifier number(s):

IND:	105379
EudraCT:	2019-003775-19
NCT:	NCT04180488
WHO:	U1111-1241-8208
Other:	Not applicable

Total number of pages: 49

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

TABLE OF CONTENTS

VV-CLIN-0695993 2.0

LIST OF TABLES

VV-CLIN-0696293 2.0

VERSION HISTORY

This Statistical Analysis Plan (SAP) only includes the plan for EFC16461 Study A (in omalizumab naïve patients), which is based on the protocol dated 29 April 2021 (amended protocol 4). A separate SAP is prepared for Study B. This section summarizes the major changes to the SAP.

The first participant was randomized on 06 February 2020.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	14-Jan-2021	Not Applicable	Original version
2	16-Jun-2021	Sensitivity analysis adding a delta to the WOCF values added.	To check robustness by applying worse scores than WOCF.
		Supplementary analysis using a worst possible score added.	An analysis using worst possible score was requested by the US FDA.
		Added blinded medical review to confirm the medications/procedures that are considered as treatment failure.	Per FDA recommendation to define the intercurrent event for those medications/procedures considered treatment failure
		Added summaries and analysis of cumulative number of itch and/or hive-free days.	This additional analysis adds value to provide a total summary over the entire planned treatment period
		Replaced additional analysis of proportion of angioedema-free days from Week 4-12 and 13-24 with cumulative number of angioedema-free days from Week 4-12, 13-24 and 4-24 in all participants and participants with angioedema at baseline.	For consistency with above additional analysis
		Added exposure adjusted AE summaries with risk differences and hazard ratios to select AE summaries.	Per FDA recommendation
		Added “Keratitis FDA” to other AE groupings.	For consistency with other dupilumab studies

VV-CLIN-0696293 2.0

1 INTRODUCTION

1.1 STUDY DESIGN

This is a master protocol composed of 2 studies of identical design, 1 in participants who are omalizumab naïve (Study A) and 1 in participants who are omalizumab intolerant or incomplete responders (Study B). Study A will include adults, adolescents (≥12 to <18 years) and children (≥6 to <12 years). Study B will include adults and adolescents. Both studies are 24-week, double-blind, randomized, placebo-controlled studies to evaluate the use of dupilumab in participants with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1-antihistamines (H1-AH).

After a screening period of 2 to 4 weeks, participants are centrally randomized (using permuted block randomization schedule) via interactive response technology (IRT) in a 1:1 randomization ratio to duplilumab (300 mg q2w for adults and adolescents ≥60 kg after a loading dose of 600 mg on Day 1; 200 mg q2w for adolescents <60 kg and children ≥30 kg after a loading dose of 400 mg on Day 1; or 300 mg q4w for children <30 kg and ≥15 kg after a loading dose of 600 mg on Day 1) or placebo over a 24 week treatment period. Randomization is stratified first by age (adults versus adolescents versus children) in Study A and adults versus adolescents in Study B; with up to approximately 5% of the total sample size planned for children in Study A and approximately 5% of the total sample size for adolescents in Studies A and B, separately. In adults, randomization is stratified further by country. In adolescents/children, randomization is not stratified further.

Approximately 234 participants (130 participants in Study A and 104 participants in Study B) will be randomized.

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-AH (Study A: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders)	• Change from baseline in weekly itch severity score (ISS7) at Week 24 (except EU and EU reference countries). • For EU and EU reference countries only: Change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24.

Objectives	Endpoints
Secondary	
To demonstrate the efficacy of dupilumab on urticaria activity composite endpoint and itch or hives, separately, at various time points	• Change from baseline in weekly urticaria activity score (UAS7) at Week 12 [a] and Week 24 (except EU and EU reference countries). • Change from baseline in ISS7 at Week 12 [a] and at Week 24 (in EU and EU reference countries). • Change from baseline in weekly hives severity score (HSS7) at Week 12 and Week 24. • Time to ISS7 minimally important difference (MID) (ISS7 ≥5) response. • Proportion of ISS7 MID (≥5 points) responders at Week 12 [a] and Week 24 [a]. • Change from baseline in ISS7 at all time points (onset of action is assessed by the first p <0.05 that remains significant at subsequent measures until Week 24). • Proportion of patients with UAS7 ≤ 6 at Week 12 [a] and Week 24 [a]. • Proportion of patients with UAS7 = 0 at Week 12 [a] and Week 24 [a].
To demonstrate the efficacy of dupilumab on angioedema	• Change from baseline in angioedema activity score over 7 days (AAS7) at Week 12 and Week 24.
To demonstrate the efficacy of dupilumab on urticaria control	• Change from baseline in urticaria control test (UCT) at Week 12 and Week 24. • Proportion of well-controlled patients (UCT ≥12) at Week 12 and Week 24.
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 patients ≥16 years old, and in Children's Dermatology Life Quality Index (CDLQI) in patients ≥6 to <16 years old at Week 12 and Week 24. • Patient Global Impression of Change (PGIC) of CSU at Week 12 and Week 24. • Change from baseline in Patient Global Impression of Severity (PGIS) of CSU at Week 12 and Week 24.
To evaluate the ability of dupilumab in reducing the proportion of patients who require treatment with oral corticosteroids (OCS)	• Time-to-event and proportion of patients receiving OCS for CSU during the planned treatment period.
To evaluate safety outcome measures	• Percentages of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs).
To evaluate immunogenicity of dupilumab	• Incidence of treatment-emergent anti-drug antibodies (ADA) against dupilumab over time.

VV-CLIN-0695993 2.0

Objectives	Endpoints
Tertiary/exploratory	
• To demonstrate exploratory outcome measures in the urticaria composite score and or its components	• Time to UAS7 MID response (9.5 to 10.5 points) by Week 12 and Week 24. • Change from baseline in the number of itch-free days and/or hive-free days at Week 12 and Week 24. • Change in UAS7 in well-controlled patients (UAS ≤6) from Weeks 24 to 36.
• To demonstrate exploratory health-related quality-of-life and health status measures	• Change from baseline in EQ-5D-5L (or EQ-5D-Y 5L for ≥6 to <16 years old) at Week 12 and Week 24. • Change from baseline in CU-Q2oL at Week 12 and Week 24. • Missed school/work days from baseline at Week 12 and Week 24.
• To demonstrate reduction in use of rescue medication	• Use of antihistamine rescue medication. • Total OCS rescue dose prescribed (in mg) during the treatment period. • Total OCS rescue intake in days during the treatment period.
Pharmacokinetic • To evaluate PK and pharmacodynamic (PD) outcome measures	• Functional dupilumab concentrations in serum and PK profile. • Pharmacodynamic response for selected biomarkers (total IgE).

a Key secondary endpoints

1.2.1 Estimands

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

Table 3 - Summary of primary estimand for main endpoints

Endpoint Category	Estimands			
	Endpoint(s) [a]	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary objective: The primary objective of this study is to demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-AH (Study A: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders).				
Primary endpoint – Continuous	Change from baseline in ISS7 at Week 24 (except EU and EU reference countries) Change from baseline in UAS7 at Week 24 (EU and EU reference countries)	ITT	The intercurrent events will be handled as follows: • Discontinuing the study intervention (but not taking selected prohibited and/or rescue medications [b] prior to Week 24): all data collected after discontinuation will be used in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications [b] prior to Week 24: data will be set to missing values after the medication usage, and the participant's worst postbaseline value on or before the time of the medication usage will be used to impute missing endpoint value (for participants whose postbaseline values are all missing, the participant's baseline value will be used to impute the missing endpoint value) (hypothetical strategy) In addition, the missing data imputation rules are as follows: • After discontinuation due to lack of efficacy prior to Week 24: WOCF approach will be used to impute missing data if needed. • After discontinuation due to reasons other than lack of efficacy prior to Week 24: multiple imputation (MI) approach will be used to impute missing endpoint value, and this multiple imputation will use all participants excluding participants who have taken the selected prohibited medications and/or rescue medications prior to Week 24 and excluding participants who discontinue due to lack of efficacy prior to Week 24.	ANCOVA model with intervention group, presence of angioedema at baseline, region (combined countries), and relevant baseline measurement as covariates. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule.

Endpoint Category	Estimands			
	Endpoint(s) [a]	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Secondary objective: To demonstrate the efficacy of dupilumab on urticaria activity composite endpoint and itch or hives, separately, at various time points				
Secondary endpoint – Proportion	Proportion of ISS7 MID (≥5 points) responders at Week 12 and Week 24; Proportion of patients with UAS7 ≤6 at Week 12 and Week 24 Proportion of patients with UAS7 = 0 at Week 12 and Week 24	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention (but not taking selected prohibited and/or rescue medications [b] prior to Week 24): Off-study intervention data will be included in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications [b] before Week 24 (or Week 12): Participants will be considered as non-responders (composite strategy). In addition, the missing data imputation rules are as follows: • Having missing data at Week 24 (or Week 12): Participants will be considered as non-responders.	CMH test adjusted by presence of angioedema at baseline, region (combined countries), and baseline disease severity (UAS7 <28, ≥28)
Secondary endpoint – Time-to-event	Time to ISS7 MID response	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention before Week 24 (but not taking selected prohibited and/or rescue medications [b] prior to Week 24): Off-study intervention data up to Week 24 will be included in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications [b] prior to Week 24: Analyses will be censored at Week 24 (composite strategy) In addition, the missing data imputation rules are as follows: • Discontinuing the study follow-up before Week 24: Analyses will be censored at the time of last ISS7 assessment.	This time-to-event endpoint will be analyzed using the Cox proportional hazards model, including intervention, the corresponding baseline value presence of angioedema at baseline, and region. The hazards ratio, its 95% confidence interval and p-value will be reported.

a Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (ie Continuous, proportion, time-to-event) at other weeks

b Selected prohibited medications and/or rescue medications are listed in Table 5.

2 SAMPLE SIZE DETERMINATION

For Study A (omalizumab naïve): An effect size of 0.7 or higher is assumed. An absolute change of 5 in the weekly itch severity score (ISS7) is considered the minimal clinically important difference (MCID) and an absolute change of 10 in the weekly urticaria activity score (UAS7) is considered the MCID. Based upon a SD of 7, a change of 5 in the ISS7 would correspond to an effect size of approximately 0.7. Based upon a standard deviation (SD) of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7. Based on this assumption, plus the assumption of a 15% dropout rate and inclusion of children, a 2-sided t-test with alpha = 0.05 has a power of 96% (to reject the null hypothesis of equal group means) if the effect size is 0.7 (between the Dupilumab arm and placebo) and 65 patient per group are included. This sample size estimate applies to both ISS7 (primary endpoint for all countries except European Union (EU) and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

The sample size calculations were performed using nQuery Advisor.

VV-CLIN-0695993 2.0

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 4 - 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. 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. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who accidentally receive a different intervention from that which was planned, the actual intervention allocation for as-treated analysis will be the dupilumab group. 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: ADA = antidrug antibody; ICF = Informed consent form, IRT = Interactive response technology; PD = Pharmacodynamic

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 EFC16461 Study A (omalizumab naïve) only. Study B (omalizumab intolerant or incomplete responders) will be described separately in a different SAP. If any pooled safety analyses are performed, they will be described in a separate SAP.

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

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 (+28 days for children <30 kg)
  - 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 observation 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 4 will be summarized.

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

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

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation 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 (ie, 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 efficacy endpoint is change from baseline in ISS7 at Week 24 (except EU and EU reference countries).

For EU and EU reference countries, the primary efficacy endpoint is change from baseline in UAS7 at Week 24.

The once daily UAS is the sum of the daily HSS (ranging from 0 = None to 3 = more than 50 hives) and the daily ISS (ranging from 0 = None to 3 = intense), the 2 key urticaria signs and symptoms which are wheals and itch. The daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create the UAS7, ranging from 0 to 42, and is composed of the HSS7 and ISS7 components.

For daily e-diary endpoints, the baseline value is the sum of the 7 measurements obtained within the 7 days prior to randomization. Note: To be eligible for the study, participants must have no missing e-diary (UAS7 and ISS7) in the 7 days before randomization.

For the Week 24 score, the sum of the 7 days on and prior to the target visit day will be used (ie, sum of days 163 through 169). If there are less than 7 but at least 4 non-missing scores available, the weekly score is the sum of the available scores in the 7 days, divided by the number of days that have a non-missing score, multiplied by 7. If there are less than 4 non-missing scores, the weekly score is missing. This same rule will be applied for other weekly scores.

VV-CLIN-0696293 2.0

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 change from baseline in ISS7 at Week 24 (except EU and EU reference countries), and the primary endpoint of change from baseline in UAS7 at Week 24 for EU and EU reference countries 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.

For efficacy analysis, Table 5 presents the prohibited and rescue medications where data may be set to missing and imputed after taking the medication in the main statistical analysis approach due to the impact these medications have on efficacy. Blinded medical review of participants that receive the treatment listed in Table 5 will be implemented before database lock to make sure the medication was used due to CSU treatment failure and not an unrelated condition.

Table 5 - Selected prohibited and/or rescue medications impact on efficacy

Medication	Comment	Intervention in the main statistical analysis (Yes/No) [a] / Selection criteria
Systemic immunosuppressants (immunosuppressive/immunomodulating drugs) eg, 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)
Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid		No
Other monoclonal antibodies (which are biological response modifiers).		Yes (SDG Monoclonal antibodies Narrow)
Phototherapy, including tanning beds.		No
IVIG		Yes (CDG00488 Intravenous immunoglobulin therapy - See Section 5.6)
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 CSU.		Yes for LTRAs; No for H2 receptor antagonists (SDG Leukotriene receptor antagonists for obstructive airway diseases Narrow)

Medication	Comment	Intervention in the main statistical analysis (Yes/No) [a] / Selection criteria
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 the estimand for the intercurrent event handling strategy will be as follows: hypothetical for continuous endpoints, and composite for responder and time-to-event endpoints. When no, a treatment policy strategy will be applied.

The primary estimand for the primary endpoint is the treatment policy/hypothetic approach.

The primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region 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 taking selected prohibited medications and/or rescue medications (see Table 5), their data after the medication start date will be set to missing, and the worst postbaseline value on or before the time of the medication usage will be used to impute missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute). Participants who discontinue the intervention prematurely are encouraged to follow the planned clinical visits and in these participants who did not take the selected prohibited medications and/or rescue medications, all data collected after intervention discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts to collect the data after intervention discontinuation. 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 (ie due to study discontinuation). 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 selected prohibited medications and/or 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 ANCOVA model as described above. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) 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.

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

4.3.3 Sensitivity analysis

The following sensitivity analyses will be performed targeting the same estimand as the primary estimand to assess the impact of the missing data handling strategy.

Tipping point analysis on WOCF

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

- A positive amount *d* is added to the imputed WOCF values, with the resulting score not to exceed the worst possible score (ie 21 on ISS7 and 42 on UAS7)
- Change from baseline in endpoint will be analyzed using ANCOVA model same as the one in primary analysis. A multiple imputation approach will be used for missing Week 24 data.

The above will be repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated is >0.05 or all participants with data imputed by WOCF are assigned the worst possible score. Pattern mixture model with copy increment from placebo after WOCF

After using the WOCF approach to impute data after taking the select prohibited/rescue medications and to impute missing data for participants who discontinue treatment due to lack of efficacy (as described for the primary analysis) the primary endpoint will be analyzed with imputed missing Week 24 values using a pattern mixture model with copy increment from placebo (1). This copy increment from placebo implies that when participants discontinue intervention early, they continue to take advantage of their previous therapy, but they progress in the same way as participants in the placebo group.

The imputed dataset will be analyzed by fitting an ANCOVA model same as the one in primary analysis. 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.

Pattern mixture model with copy increment from placebo without WOCF

All data after taking the select prohibited/rescue medications will be set to missing. The primary endpoint will be analyzed with imputed missing Week 24 values using a pattern mixture model with copy increment from placebo (1). This copy increment from placebo implies that when participants discontinue intervention early or take select prohibited/rescue medications, they continue to take advantage of their previous therapy, but they progress in the same way as participants in the placebo group.

The imputed dataset will be analyzed by fitting an ANCOVA model same as the one in primary analysis. 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.

Tipping point analysis

After using the WOCF approach to impute data after taking select prohibited/rescue medications and to impute missing data for participants who discontinue treatment due to lack of efficacy (as described for the primary analysis), a tipping point analysis will be performed for the primary endpoint with imputed missing Week 24 values as follows:

- **Step 1.** Monotone missing pattern will be 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 response variable, intervention groups, angioedema at baseline, region, and baseline value of the corresponding 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 set.
- **Step 4.** The imputed values in placebo group are subtracted by a positive amount p for each imputed data set.
- **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 treatment effect of dupilumab compared to placebo estimated in Step 5 is >0.05.

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

4.3.4 Supplementary analyses

The following supplementary analysis will be performed:

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

The data collected after taking the select prohibited medications and/or rescue medications will be included in the sensitivity analysis to evaluate the robustness of the primary analysis results with respect to the intercurrent event handling strategy while taking selected prohibited medications and/or rescue medications (eg, treatment policy strategy). For missing data, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants.

The change from baseline and percent change from baseline will be summarized and analyzed by week using the same approach as the primary endpoint. 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. Figures over time will also be presented.

Worst possible score

For participants taking selected prohibited and/or rescue medications (see Table 5), their data after the medication start date will be excluded from the analysis, and the worst possible score (ie, 21 for ISS7 and 42 for UAS7) will be assigned to the Week 24 value. In case there is missing data, 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 selected prohibited medications and/or rescue medications on or before Week 24.

Each of the imputed complete data will be analyzed by fitting an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region as covariates. 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.

4.3.5 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; <65, ≥65 years)
- Gender (Male, Female)
- Baseline weight (< median, ≥ median, <60, ≥60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m^2)
- Region (see Section 5.3)
- Territory (see Section 5.3)
- Race (White, all the Others)
- Ethnicity (Hispanic, non-Hispanic)
- Angioedema at baseline (Yes, No)
- Baseline UAS7 score (<28, ≥28)
- Baseline ISS7 score (<13, ≥13)
- Duration of disease (<2, 2-10, >10 years)
- H1-AH baseline dose (1-fold, 2-4-fold)
- Baseline serum Total IgE (<100 kU/L, ≥100 kU/L)

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, 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 for the primary endpoint, 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.

In addition, the primary endpoint will be analyzed in the subgroup of adults and adolescent participants.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Supportive secondary endpoint(s)

The change from baseline in AAS7 at Week 12 and Week 24 will be analyzed in those participants who have angioedema at baseline defined as a baseline AAS7 score >0. The change from baseline and percent change from baseline in continuous endpoints will be summarized and analyzed by week using the same approach as the primary endpoint. 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. Figures over time will also be presented.

The endpoint change from baseline in DLQI/CDLQI will be summarized and analyzed in participants ≥16 years old who completed the DLQI at baseline.

Proportion type efficacy endpoints will be analyzed similar to the key secondary endpoints above. The response rates at each week up to Week 24 will be summarized and plotted by intervention groups using the same method as other proportion type endpoints.

Time-to-event endpoints will be analyzed using the Cox proportional hazards model, including intervention, the corresponding baseline value, presence of angioedema at baseline, and region as covariates. The hazards ratio, its 95% confidence interval and p-value will be reported. Kaplan-Meier curves will be also provided.

For time to first ISS7 MID (ISS7 ≥5) response defined as time to reduction from baseline of 5 points or more, participants who receive selected prohibited medications and/or rescue

medications (see Table 5), data prior to start of the medication will be used, but after medication start, the participant will be censored at Week 24 (ie Day 169). For other participants, all available data up to Week 24 (ie, Day 169) including those collected during the off-treatment period will be used. Participants without events will be censored at Day 169 or their last ISS7 assessment date if discontinued from the study, whichever is earlier.

For time to participants receiving first OCS for CSU during the planned treatment period, participants who receive selected prohibited medications and/or rescue medications other than OCS for CSU, data prior to start of the medication will be used, but after medication start, the participant will be censored at time of start of medication. Participants who don't receive OCS during the treatment period will be censored at Day 169 or their status date collected on the completion of study/follow-up eCRF form, whichever is earlier. This endpoint will be analyzed using a Cox proportional hazards model, including intervention, presence of angioedema at baseline, and region as covariates.

In addition, secondary endpoints included in the multiplicity procedure (Section 4.6) will be analyzed in the subgroup of adults and adolescent participants.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

Additional details are provided below for specific exploratory efficacy endpoints.

Time to UAS7 MID response (9.5 to 10.5 points) by Week 12 and Week 24

Time to first UAS7 reduction from baseline of 10.5 points or greater or 9.5 points or greater will be analyzed similar to time to ISS7 MID (ISS7 ≥5) response. Proportion of participants with each of these MID responses (10.5 and 9.5) by week will also be provided.

Change from baseline in the number of itch-free days and/or hive-free days at Week 12 and Week 24

Three endpoints will be summarized at each Week using descriptive statistics (mean, SD, min, max). Change from baseline in number of itch-free days, number of hive-free days, and number of itch and hive-free days over the 7 days.

Change in UAS7 in well-controlled patients (UAS ≤6) from Week 24 to 36.

For those participants who were well-controlled (UAS ≤6) at Week 24, the change in UAS7 from Week 24 to Week 36 will be summarized using descriptive statistics (mean, SD, min, max)

Use of antihistamine rescue medication

The number (%) of participants who received antihistamine as rescue medication during the planned treatment period (ie, up to Day 169) will be summarized by intervention group.

VV-CLIN-0695993 2.0

Total OCS rescue dose prescribed (in mg) during the treatment period

The total cumulative prescribed dose of OCS rescue medication will be summarized by descriptive statistics (mean, SD, min, max) over the planned treatment period.

Total OCS rescue intake in days during the treatment period

The total number of days that OCS rescue medication was taken during the planned treatment period will be summarized by intervention group.

The endpoint, change from baseline in EQ-5D-5L/EQ-5D-Y 5L will be summarized and analyzed in participants ≥16 years old who completed the EQ-5D-5L at baseline.

Proportion of participants with ISS7 = 0 and HSS7 = 0 at Week 12 and Week 24 will be summarized and analyzed similar to the key secondary endpoint of UAS7 = 0. Cumulative number of itch and/or hive-free days from Week 4-12, 13-24, and Week 4-24 will be summarized and analyzed. This will be calculated as the number of days for which the participant indicated a 'No' response divided by the total number of days with a non-missing response during the period multiplied by the number of days in the period. Participants who withdrew before the Week 4 visit or who have missing responses for >40% of the daily entries during the period will not be included in the analysis. The same analysis will be done for cumulative number of angioedema-free days in all participants and participants with angioedema at baseline.

An additional exploratory endpoint of time to first select prohibited/rescue medication that impact efficacy will be provided. This includes medications where WOCF will be applied (see Table 5).

4.5.2 Main analytical approach

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

Time to first UAS7 change from baseline of ≥9.5 and ≥10.5 will be analyzed similar to time to ISS7 MID (ISS7 ≥5) response. For participants not receiving selected prohibited medications and/or rescue medications, all available data up to Week 24 (ie, Day 169) including those collected during the off-treatment period will be used. Participants without events will be censored at Day 169 or their last UAS7 assessment date on or before Day 169 if discontinued from the study, whichever is earlier.

4.5.3 Key/Confirmatory secondary endpoint(s)

4.5.3.1 Definition of endpoint(s)

Key secondary endpoints are indicated in Table 2 with an asterisk and are presented below.

- Change from baseline in UAS7 at Week 12
- Change from baseline in ISS7 at Week 12
- Proportion of ISS7 MID (≥5 points) responders at Week 12 and Week 24

Note: This endpoint is defined as the proportion of participants with a reduction from baseline of 5 points or more.

- Proportion of patients with UAS7 ≤6 at Week 12 and Week 24
- Proportion of patients with UAS7 = 0 at Week 12 and Week 24

As described for the primary endpoint, only data before taking select prohibited and rescue medications will be included (See Table 5). All data after intervention discontinuation will be used in the analysis.

4.5.3.2 Main analytical approach

Continuous secondary endpoints will be analyzed using the same approach as the primary efficacy endpoint.

Responder endpoints will be analyzed using the CMH test adjusted by baseline disease severity, presence of angioedema at baseline, and region. The baseline disease severity will be defined according to UAS7 <28 or ≥28. Comparisons of the response rates between dupilumab dose and placebo will be derived. Participants who receive selected prohibited medications and/or rescue medications will be considered as non-responders for time points after medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the responder/non-responder status. Missing data will be considered as non-responders.

4.6 MULTIPLICITY ISSUES

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

In non-EU and non-EU reference countries:

1. Change from baseline in ISS7 at Week 24
2. Change from baseline in UAS7 at Week 24
3. Proportion of patients with UAS7 ≤6 at Week 24
4. Proportion of patients with UAS7 = 0 at Week 24
5. Change from baseline in HSS7 at Week 24
6. Change from baseline in ISS7 at Week 12
7. Change from baseline in UAS7 at Week 12
8. Proportion of patients with UAS7 ≤6 at Week 12
9. Proportion of patients with MID (ISS7 ≥5) response at Week 24
10. Proportion of patients with MID (ISS7 ≥5) response at Week 12
11. Change from baseline in HSS7 at Week 12
12. Proportion of patients with UAS7 = 0 at Week 12
13. Change from baseline in UCT at Week 24
14. Change from baseline in UCT at Week 12

In EU and EU reference countries:

1. Change from baseline in UAS7 at Week 24
2. Change from baseline in ISS7 at Week 24
3. Proportion of patients with UAS7 ≤6 at Week 24
4. Proportion of patients with UAS7 = 0 at Week 24
5. Change from baseline in HSS7 at Week 24
6. Change from baseline in ISS7 at Week 12
7. Change from baseline in UAS7 at Week 12
8. Proportion of patients with UAS7 ≤6 at Week 12
9. Proportion of patients with MID (ISS7 ≥5) response at Week 24
10. Proportion of patients with MID (ISS7 ≥5) response at Week 12
11. Change from baseline in HSS7 at Week 12
12. Proportion of patients with UAS7 = 0 at Week 12
13. Change from baseline in UCT at Week 24
14. Change from baseline in UCT at Week 12

Study A is considered positive when the primary endpoint (change from baseline in ISS7 at Week 24 in non-EU and non-EU reference countries or change from baseline in UAS7 at Week 24 in EU and EU reference countries) achieves statistical significance.

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 (eg, 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 (or + 29 days for children <30 kg), 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 (or less than 25 days for children <30 kg) 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 (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period

- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

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

The primary 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 day is missing, it will be imputed using 01 (except if the same month and year of 1st IMP, then the day of first IMP will be used). If month is missing, the AE start date will remain missing.

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 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.

Table 7 - 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 (≥2% and ≥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 overview table, and common TEAEs (PT ≥2% 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 6 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 8. Number (%) of participants experiencing at least one event will be provided for each event of interest. 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 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 5.6) [a] and "Severe" ticked in Adverse Events eCRF page
Any severe type of blepharitis	CMQ10497 based on HLT as "Lid, lash and lacrimal infections, irritations and inflammations" and "Severe" ticked in Adverse Events eCRF page
Keratitis	CMQ10642 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, herpes ophthalmic, ophthalmic herpes simplex, corneal infection] [a]
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms) [b]	CMQ10641 based on HLT = Eosinophilic disorders or PT = Eosinophil count increased
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; 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	
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% CIsFor 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

VV-CLIN-0696293 2.0

- 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, calcium, 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, nitrate, 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: pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg) in a semi-supine or sitting position after 5 minutes, weight, respiratory rate (breaths per minute), temperature (degrees Celsius) and height (screening only),
- ECG variables: heart rate, PR, QRS, QT, and QTc intervals after 10 minutes of rest in the supine position.

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, vital signs and ECG 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.

VV-CLIN-0695993 2.0

- 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 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).

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), one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three significant figures. For participants in the placebo group, concentration values 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.

VV-CLIN-0696293 2.0

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

Impact of ADA on clinical efficacy endpoints

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

Association of ADA with clinical safety endpoints

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

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

Associations between ADA variables (eg, 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 and children) 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

VV-CLIN-0696293 2.0

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 and children) 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).

For those participants (with exception of adolescent and children) who consent to the optional skin biopsy (substudy), the sample will be taken from lesion and non-lesion skin using punch biopsy at Visit 2 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 and skin biopsy substudy will be addressed in a separate document.

4.9 INTERIM ANALYSES

No interim analysis is planned.

For Study A, 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 Study A 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.

VV-CLIN-0695993 2.0

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AAS7:	angioedema activity score over 7 days
ADA:	anti-drug antibody
AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance, analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomic category
CDG:	customized drug grouping
CDLQI:	children's dermatology life qualtiy index
CI:	confidence interval, confidence interval
CLcr:	creatinine clearance
CMH:	Cochran-Mantel Haenszel
CSU:	chronic spontaneous urticaria
CU-Q2oL:	chronic urticaria quality of life questionnaire
DLQI:	dermatology life quality index
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
eCRF:	electronic case report form
EMA:	European Medicines Agency
EOT:	end of treatment
EQ-5D-5L:	5-level EuroQol 5-dimensional questionnaire
EQ-5D-Y 5L:	EuroQol 5-dimensional questionnaire youth
EU:	European Union
FDA:	Food and Drug Administration
H1-AH:	H1-antihistamines
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
HSS7:	weekly hives severity score
IMP:	investigational medicinal product
IRT:	interactive response technology
ISS7:	weekly itch severity score
ITT:	intent-to-treat
LLT:	lower-level term

VV-CLIN-0695993 2.0

LS:	least squares, least squares
MCID:	minimal clinically important difference
MCMC:	Markov Chain Monte Carlo
MedDRA:	medical dictionary for regulatory activities
MI:	multiple imputation
MID:	minimal important difference
OCS:	oral corticosteroids
PCSA:	potentially clinically significant abnormality
PGIC:	patient global impression of change
PGIS:	patient global impression of severity
PK:	pharmacokinetic
PT:	preferred term
RNA:	ribonucleic acid
SAE:	serious adverse event
SAP:	statistical analysis plan, statistical analysis plan
SD:	standard deviation
SDG:	standardized drug grouping
SDGs:	Standardized drug groupings
SMQ:	standardized MedDRA query
SOC:	system organ class
TEAE:	treatment-emergent adverse event
UAS7:	weekly urticaria activity score
UCT:	urticaria control test
ULN:	upper limit of normal
WHO-DD:	World Health Organization-Drug Dictionary
WOCF:	worst-observation carried forward

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This Statistical Analysis Plan (SAP) for study EFC16461 is based on the protocol dated 29 April 2021 (amended protocol 4). This section summarizes major statistical changes in the protocol amendment(s).

The primary purpose of Amended protocol 2 was to increase the sample size of Study A (omalizumab naïve population) based on recommendation from Food and Drug Administration (FDA) to power the studies using conservative assumptions with regard to treatment effect and variability and to include children aged ≥6 to <12 years, and to switch the primary and the key secondary endpoints to establish the UAS7 as the primary endpoint for EU and EU reference countries based on recommendations from European Medicines Agency (EMA).

VV-CLIN-0696293 2.0

Table 9 - Major statistical changes in protocol amendment(s)

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	30-Apr-2020	FDA request to power the study using conservative assumptions with regards to treatment effect and variability and include children	Sample size was increased in Study A from 80 to 130 with a more conservative effect size and up to 5% of participants will now be children. Power increased from 90% to 96%.
		EMA request to change the primary and key secondary endpoints for EU and EU reference countries	For EU and EU references countries only, primary endpoint is now change from baseline in UAS7 at Week 24 and key secondary endpoint is change from baseline in ISS7 at Week 24.
		Efficacy analysis was modified to include covariates	Presence of angioedema at baseline was added as a covariate to the primary endpoint analysis and by baseline disease severity, and presence of angioedema at baseline were added to Cochran-Mantel Haenszel (CMH) test. The corresponding baseline value and presence of angioedema at baseline was added as covariates for time-to-event endpoints.

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, 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:** China, Japan; **Latin America:** Argentina; **Western Countries**: Canada, USA**,** France, Germany, Spain, United Kingdom, **East Europe:** Hungary, Russia)
- Territory (**North America:** Canada, USA**; European Union and UK:** France, Germany, Spain, United Kingdom, Hungary; **Rest of Word:** China, Japan, Argentina, Russia)
- Weight in kg (quantitative and qualitative variable: <60, ≥60 kg)
- BMI in kg/m^2 (quantitative and qualitative variable: <30, ≥30 kg/m^2)

VV-CLIN-0696293 2.0

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 history (Yes, Ongoing condition)

Angioedema (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 CSU (years)
- Time since first diagnosis of CSU (years) to be derived as
  (Year of randomization – Year of first diagnosis of CSU) + (month of randomization-month of first diagnosis of CSU)/12
- Presence of angioedema at baseline
  - Number of episodes in past 6 months
  - Time since last episode (months)
- Baseline ISS7 score (quantitative and qualitative variable: <13, ≥13)
- Baseline UAS7 score (quantitative and qualitative variable: <28, ≥28)

- Baseline weekly hives severity score (HSS7)
- Baseline angioedema activity score over 7 days (AAS7) for participants with angioedema
- Baseline urticaria control test (UCT)
- Baseline Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI)
- Baseline Patient Global Impression of Severity (PGIS)
- Frequency of alcohol drinking in the past 12 months (never, occasional, at least monthly, at least weekly, at least daily) and number of drinks on a typical day (1 or 2, >2)
- Baseline IgE (quantitative and qualitative variable: <100 vs ≥100)
- Baseline H1-AH dose (1-fold, 2-3-fold, 4-fold)

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 CSU 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 CSU 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.

VV-CLIN-0696293 2.0

Concomitant medication received during first IMP to last IMP +14 days (+28 days for children <30 kg) 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 CSU is calculated as:

Year of CSU 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:

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

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

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

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.

i. For the DLQI, handing of missing items is as follows: 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
ii. If two or more questions are left unanswered the questionnaire is not scored
iii. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked
iv. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1
v. 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:

i. 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
ii. If two or more questions are left unanswered the questionnaire is not scored
iii. If two or more response options are ticked for one question, the response option with the highest score should be recorded

For the CU-Q2oL total score, the raw total score will be converted to a 0 to 100 score for analysis using the following formula:

CU-Q2oL total score = (raw score – 23)*100/92

Daily e-diary weekly scores

For the daily efficacy endpoints (ISS, UAS, HSS, and AAS), the time period used to calculate the weekly score at each designated study day is summarized in Table 10. Randomization day is used as the reference day (Day 1).

Table 10 - Weekly efficacy assessments from daily e-diary

Analysis visit	Day range for calculating weekly score	Target day
Week 1	2-8	8
Week 2	9-15	15
Week 3	16-22	22
Week 4	23-29	29
Week 5	30-36	36
Week 6	37-43	43
Week 7	44-50	50
Week 8	51-57	57
Week 9	58-64	64
Week 10	65-71	71
Week 11	72-78	78
Week 12	79-85	85
Week 13	86-92	92
Week 14	93-99	99
Week 15	100-106	106
Week 16	107-113	113
Week 17	114-120	120
Week 18	121-127	127
Week 19	128-134	134
Week 20	135-141	141
Week 21	142-148	148
Week 22	149-155	155
Week 23	156-162	162
Week 24	163-169	169
Week 25	170-176	176
Week 26	177-183	183
Week 27	184-190	190
Week 28	191-197	197
Week 29	198-204	204
Week 30	205-211	211
Week 31	212-218	218
Week 32	219-225	225
Week 33	226-232	232
Week 34	233-239	239
Week 35	240-246	246
Week 36	247-253	253

VV-CLIN-0696293 2.0

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 11 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 11 - 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	1+
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 12. 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 12 - Time window for efficacy variables

Visit	Target Day	Time windows for			
		UCT, DLQI/CDLQI, CU-Q2oL	PGIC	PCIS	EQ-5D-5L/EQ-5D-L, missed school/work days
Visit 1	-28 to -14			<-14	
Visit 2 (Week 0)	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	>126	>126	127-210
Visit 5 (Week 36)	253	>210			>210

1-: up to randomization and before 1st dose date/time; 1+: after randomization or 1st 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 13 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 13 - Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target Day	Serum dupilumab, ADA, Total IgE	Skin biopsy (substudy)	Basophil activation(substudy)
Visit 1	-28 to -14			
Visit 2 (Week 0)	1	<1-	<1-	<1-
Visit 3 (Week 12)	85	1+-126		1+-126
Visit 4 (Week 24)	169	127-210	>1+	>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 SAMPLE SAS CODE

The multiple imputation and analysis model for the primary analysis approach 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 taken selected prohibited medications and/or rescue medications or have not discontinued study intervention due to lack of efficacy prior to Week 24.

```
proc mi data=dat_etd seed=16461 nimpute=40 out=dat_mc;
    mcmc impute=monotone;
    var angiobl region trt01p iss7bl chg1iss …  chg24iss;
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 intervention groups, region, angioedema status at baseline and baseline value of the response variable.

```
proc mi data=dat_mc nimpute=1 seed=16461 out=dat_mi;
    by _imputation_;
    class angiobl region trt01p;
    monotone method=reg;
    var angiobl region trt01p iss7bl chg1iss … chg24iss;
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;
```


VV-CLIN-0695993 2.0

```
proc glm data= dat_imp;
      by _imputation_;
      class region angiobl trt01p;
      model  chg24iss = iss7bl angiobl region trt01p;
      lsmeans trt01p / 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 SELECTION CRITERIA FOR AE/MEDICATION GROUPINGS

Table 14 - 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

VV-CLIN-0695993 2.0

Grouping	Preferred Term/ Medication Code	Preferred Term/ Medication
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
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

VV-CLIN-0696293 2.0

6 REFERENCES

1. Carpenter JR, Roger JH, Kenward MG. Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and inference via Multiple Imputation. J Biopharm Stat. 2013;23:1352-71.

Signature Page for VV-CLIN-0587243 v2.0
efc16461a-16-1-9-sap

Approve & eSign	[redacted]
Approve & eSign	

STATISTICAL ANALYSIS PLAN

Protocol title:	**Master protocol of two randomized, double-blind, placebo-controlled, multi-center, parallel-group studies of dupilumab in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine treatment in patients naïve to omalizumab and in patients who are intolerant or incomplete responders to omalizumab**
Protocol number:	**EFC16461B**
Compound number (INN/Trademark):	**SAR231893/REGN668 dupilumab/Dupixent**
Study phase:	**Phase 3**
Short title:	**Dupilumab for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine and who are intolerant of, or incomplete responders to omalizumab.** **LIBERTY-CSU CUPID (Chronic Urticarial Pruritus Itch Dupilumab Trial)**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**07-Dec-2021**

Regulatory agency identifier number(s):

IND:	105379
EudraCT:	2019-003775-19
NCT:	NCT04180488
WHO:	U1111-1241-8208
Other:	Not applicable

Total number of pages: 51

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

TABLE OF CONTENTS

VV-CLIN-0695997 2.0

LIST OF TABLES

VERSION HISTORY

This Statistical Analysis Plan (SAP) only includes the plan for EFC16461 Study B, which is based on the protocol dated 29 April 2021 (amended protocol 4). A separate SAP is prepared for Study A.

This section summarizes the major changes to the SAP. The SAP history table below gives the timing, rationale, and key details for the major changes to the statistical analysis features in the SAP. It includes the major changes in SAP version 2.0 from the most recent approved protocol (amended protocol 4). The first participant was randomized on 03 March 2020. This SAP is approved before the first interim analysis is conducted.

The major changes to the statistical analysis features from a protocol version to another are to be described under Appendix 2.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
2	07-Dec-2021	Sensitivity analysis adding a delta to the WOCF values added	To check robustness by applying worse scores than WOCF
		Supplementary analysis using a worst possible score added	An analysis using worst possible score was requested by a Health Authority
		Added blinded medical review to categorize the medications/procedures that constitute a treatment failure	In line with Health Authority recommendation, to safeguard unbiased definition of intercurrent events for those medications/procedures that constitute treatment failure
		Added summaries and analysis of cumulative number of itch and/or hive-free days	This additional analysis adds value to provide a total summary over the entire planned treatment period
		Added exposure adjusted AE summaries with risk differences and hazard ratios to select AE summaries	Per a Health Authority recommendation, to consider potentially different exposure of different patients
		Added “Keratitis FDA” to other AE groupings	For consistency with other dupilumab studies
		Change “key secondary endpoints” to “secondary endpoints” except for Change from baseline in weekly urticaria activity score (UAS7) at Week 24 (except EU and EU reference countries). Change from baseline in ISS7 at Week 24 (in EU and EU reference countries)	This change is proposed to harmonize with regional Health Authority requirements

SAP Version	Approval Date	Changes	Rationale
		Removed week 12 endpoints in hierarchy	Based on the data from study A, the treatment effect of dupilumab continued to improve over time through Week 24, and therefore changes in the hierarchy were updated
		Added interim analysis when the first 83 randomized patients would have completed their Week 24 visit	For an earlier assessment of efficacy or stop for futility in this population
		Revised the number of patients at IA to be 83 and added wording to show the actual number of randomized patients is 108 in total	108 patients are randomized, compared to the planned 104. To preserve the ratio of number of patients at IA to total sample size at final, and alpha spending at IA 0.021, the sample size of IA is increased from 80 to 83

1 INTRODUCTION

1.1 STUDY DESIGN

The master protocol is comprised of 2 studies of identical design, 1 in participants who are omalizumab naïve (Study A) and 1 in participants who are omalizumab intolerant or incomplete responders (Study B). Study A will include adults, adolescents (≥12 to <18 years) and children (≥6 to <12 years). Study B will include adults and adolescents. Both studies are 24-week, double-blind, randomized, placebo-controlled studies to evaluate the use of dupilumab in participants with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1-antihistamines (H1-AH).

After a screening period of 2 to 4 weeks, participants are centrally randomized (using permuted block randomization schedule) via interactive response technology (IRT) in a 1:1 randomization ratio to duplilumab (300 mg q2w for adults and adolescents ≥60 kg after a loading dose of 600 mg on Day 1; 200 mg q2w for adolescents <60 kg and children ≥30 kg after a loading dose of 400 mg on Day 1; or 300 mg q4w for children <30 kg and ≥15 kg after a loading dose of 600 mg on Day 1) or placebo over a 24 week treatment period. Randomization is stratified first by age (adults versus adolescents versus children) in Study A and adults versus adolescents in Study B; with up to approximately 5% of the total sample size planned for children in Study A and approximately 5% of the total sample size for adolescents in Studies A and B, separately. In adults, randomization is stratified further by country. In adolescents/children, randomization is not stratified further.

Approximately 234 participants (130 participants in Study A and 104 participants in Study B) will be randomized.

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-AH (Study A: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders)	• Change from baseline in weekly itch severity score (ISS7) at Week 24 (except EU and EU reference countries). • For EU and EU reference countries only: Change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24.

VV-CLIN-0698297 2.0

Objectives	Endpoints
Secondary	
To demonstrate the efficacy of dupilumab on urticaria activity composite endpoint and itch or hives, separately, at various time points	• Change from baseline in weekly urticaria activity score (UAS7) at Week 24[a] (except EU and EU reference countries). • Change from baseline in ISS7 at Week 24[a] (in EU and EU reference countries). • Change from baseline in weekly urticaria activity score (UAS7) at Week 12. • Change from baseline in ISS7 at Week 12. • Change from baseline in weekly hives severity score (HSS7) at Week 12 and Week 24. • Time to ISS7 minimally important difference (MID) (ISS7 ≥5) response. • Proportion of ISS7 MID (≥5 points) responders at Week 12 and Week 24. • Change from baseline in ISS7 at all time points (onset of action is assessed by the first p <0.05 that remains significant at subsequent measures until Week 24). • Proportion of patients with UAS7 ≤ 6 at Week 12 and Week 24. • Proportion of patients with UAS7 = 0 at Week 12 and Week 24.
To demonstrate the efficacy of dupilumab on angioedema	• Change from baseline in angioedema activity score over 7 days (AAS7) at Week 12 and Week 24.
To demonstrate the efficacy of dupilumab on urticaria control	• Change from baseline in urticaria control test (UCT) at Week 12 and Week 24. • Proportion of well-controlled patients (UCT ≥12) at Week 12 and Week 24.
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 patients ≥16 years old, and in Children's Dermatology Life Quality Index (CDLQI) in patients ≥6 to <16 years old at Week 12 and Week 24. • Patient Global Impression of Change (PGIC) of CSU at Week 12 and Week 24. • Change from baseline in Patient Global Impression of Severity (PGIS) of CSU at Week 12 and Week 24.
To evaluate the ability of dupilumab in reducing the proportion of patients who require treatment with oral corticosteroids (OCS)	• Time-to-event and proportion of patients receiving OCS for CSU during the planned treatment period.
To evaluate safety outcome measures	• Percentages of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs).
To evaluate immunogenicity of dupilumab	• Incidence of treatment-emergent anti-drug antibodies (ADA) against dupilumab over time.

Objectives	Endpoints
Tertiary/exploratory	
• To demonstrate exploratory outcome measures in the urticaria composite score and or its components	• Time to UAS7 MID response (9.5 to 10.5 points) by Week 12 and Week 24. • Change from baseline in the number of itch-free days and/or hive-free days at Week 12 and Week 24. • Change in UAS7 in well-controlled patients (UAS ≤6) from Weeks 24 to 36.
• To demonstrate exploratory health-related quality-of-life and health status measures	• Change from baseline in EQ-5D-5L (or EQ-5D-Y 5L for ≥6 to <16 years old) at Week 12 and Week 24. • Change from baseline in CU-Q2oL at Week 12 and Week 24. • Missed school/work days from baseline at Week 12 and Week 24.
• To demonstrate reduction in use of rescue medication	• Use of antihistamine rescue medication. • Total OCS rescue dose prescribed (in mg) during the treatment period. • Total OCS rescue intake in days during the treatment period.
Pharmacokinetic	
• To evaluate PK and pharmacodynamic (PD) outcome measures	• Functional dupilumab concentrations in serum and PK profile. • Pharmacodynamic response for selected biomarkers (total IgE).

a Key secondary endpoints

1.2.1 Estimands

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

VV-CLIN-0695997 2.0

Table 3 - Summary of primary estimand for main endpoints

Endpoint Category	Estimands			
	Endpoint(s)[a]	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Primary objective: The primary objective of this study is to demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-AH (Study A: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders)				
Primary endpoint – Continuous	Change from baseline in ISS7 at Week 24 (except EU and EU reference countries) Change from baseline in UAS7 at Week 24 (EU and EU reference countries)	ITT	The intercurrent events will be handled as follows: • Discontinuing the study intervention (but not taking selected prohibited and/or rescue medications[b] prior to Week 24): all data collected after discontinuation will be used in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications[b] prior to Week 24: data will be set to missing values after the medication usage, and the participant's worst postbaseline value on or before the time of the medication usage will be used to impute missing endpoint value (for participants whose postbaseline values are all missing, the participant's baseline value will be used to impute the missing endpoint value) (hypothetical strategy) In addition, the missing data imputation rules are as follows: • After discontinuation due to lack of efficacy prior to Week 24: WOCF approach will be used to impute missing data if needed. • After discontinuation due to reasons other than lack of efficacy prior to Week 24: multiple imputation (MI) approach will be used to impute missing endpoint value, and this multiple imputation will use all participants excluding participants who have taken the selected prohibited medications and/or rescue medications prior to Week 24 and excluding participants who discontinue due to lack of efficacy prior to Week 24.	ANCOVA model with intervention group, presence of angioedema at baseline, region (combined countries), and relevant baseline measurement as covariates. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule.

Endpoint Category	Estimands			
	Endpoint(s)[a]	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Secondary objective: To demonstrate the efficacy of dupilumab on urticaria activity composite endpoint and itch or hives, separately, at various time points				
Secondary endpoint – Proportion	Proportion of ISS7 MID (≥5 points) responders at Week 12 and Week 24; Proportion of patients with UAS7 ≤6 at Week 12 and Week 24 Proportion of patients with UAS7 = 0 at Week 12 and Week 24	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention (but not taking selected prohibited and/or rescue medications[b] prior to Week 24): Off-study intervention data will be included in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications[b] before Week 24 (or Week 12): Participants will be considered as non-responders (composite strategy). In addition, the missing data imputation rules are as follows: • Having missing data at Week 24 (or Week 12): Participants will be considered as non-responders.	CMH test adjusted by presence of angioedema at baseline, region (combined countries), and baseline disease severity (UAS7 <28, ≥28)
Secondary endpoint – Time-to-event	Time to ISS7 MID response	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention before Week 24 (but not taking selected prohibited and/or rescue medications[b] prior to Week 24): Off-study intervention data up to Week 24 will be included in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications[b] prior to Week 24: Analyses will be censored at Week 24 (composite strategy) In addition, the missing data imputation rules are as follows: • Discontinuing the study follow-up before Week 24: Analyses will be censored at the time of last ISS7 assessment.	This time-to-event endpoint will be analyzed using the Cox proportional hazards model, including intervention, the corresponding baseline value presence of angioedema at baseline, and region. The hazards ratio, its 95% confidence interval and p-value will be reported.

a Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (ie Continuous, proportion, time-to-event) at other weeks

b Selected prohibited medications and/or rescue medications are listed in Table 5.

2 SAMPLE SIZE DETERMINATION

For Study B (omalizumab intolerant or incomplete responders): An effect size of 0.7 or higher is assumed. An absolute change of 5 in the weekly itch severity score (ISS7) is considered the minimal clinically important difference (MCID) and an absolute change of 10 in the weekly urticaria activity score (UAS7) is considered the MCID. Based upon a SD of 7, a change of 5 in the ISS7 would correspond to an effect size of approximately 0.7. Based upon a SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7. Based on this assumption, plus the assumption of a 15% dropout rate, a 2-sided t-test with alpha = 0.05 has a power of 90% (to reject the null hypothesis of equal group means) if the effect size is 0.7 (between the dupilumab arm and placebo) and 52 patients per group are included. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

There are 108 patients in total actually randomized.

Considering the reduced drop-out rate of 10% observed during the study, an interim analysis will be performed when the first 83 randomized patients would have completed their Week 24 visit by the interim analysis cut-off date. Using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis will be 0.021, and the alpha spending at the final analyses when all 108 patients complete the study will be 0.043.

At the interim analysis, it is estimated that 42 patients per group will provide 77% power to detect a treatment effect of 5 or higher with SD 7 and minimal detectable difference (MDD) of approximately 3.7 for ISS7 and a treatment effect of 10 or higher with SD 14 and MDD of approximately 7.4 for UAS7 between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.021.

With the decision process outlined in section 4.9, the overall power for the study will be approximately 88%.

The sample size calculations and the alpha spending by O'Brien-Fleming approach were calculated by nQuery Advisor and nTerim 4.0.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 4 - 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. 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.
Intent-to-treat24 (ITT24) (For interim analysis)	First 83 participants who were randomized and would have completed the Week 24 visit.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who accidentally receive a different intervention from that which was planned, the actual intervention allocation for as-treated analysis will be the dupilumab group. 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.
Antidrug 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: ADA = antidrug antibody; ICF = Informed consent form, IRT = Interactive response technology; PD = Pharmacodynamic

Participants exposed to study intervention 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 ie, 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.

VV-CLIN-0695997 2.0

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 EFC16461 Study B (omalizumab intolerant or incomplete responders) only. Study A (omalizumab naïve) will be summarized separately in a different SAP. If any pooled safety analyses are performed, they will be described in a separate SAP.

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

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 observation 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 4 will be summarized.

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

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

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation 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 (ie, 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 efficacy endpoint is change from baseline in ISS7 at Week 24 (except EU and EU reference countries).

For EU and EU reference countries, the primary efficacy endpoint is change from baseline in UAS7 at Week 24.

The once daily UAS is the sum of the daily HSS (ranging from 0 = None to 3 = more than 50 hives) and the daily ISS (ranging from 0 = None to 3 = intense), the 2 key urticaria signs and symptoms which are wheals and itch. The daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create the UAS7, ranging from 0 to 42, and is composed of the HSS7 and ISS7 components.

For daily e-diary endpoints, the baseline value is the sum of the 7 measurements obtained within the 7 days prior to randomization. Note: To be eligible for the study, participants must have no missing e-diary (UAS7 and ISS7) in the 7 days before randomization.

For the Week 24 score, the sum of the 7 days on and prior to the target visit day will be used (ie, sum of days 163 through 169). If there are less than 7 but at least 4 non-missing scores available, the weekly score is the sum of the available scores in the 7 days, divided by the number of days that have a non-missing score, multiplied by 7. If there are less than 4 non-missing scores, the weekly score is missing. This same rule will be applied for other weekly scores.

VV-CLIN-0696297 2.0

4.3.2 Main analytical approach

The primary analysis population for the efficacy endpoints will be the ITT24 population for the interim analysis and the ITT population for the final analysis. The statistical hypotheses for comparing dupilumab against placebo on the primary endpoint of change from baseline in ISS7 at Week 24 (except EU and EU reference countries), and the primary endpoint of change from baseline in UAS7 at Week 24 for EU and EU reference countries 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.

For efficacy analysis, Table 5 presents the prohibited and rescue medications where data may be set to missing and imputed after taking the medication in the main statistical analysis approach due to the impact these medications have on efficacy. Blinded medical review of participants that receive the treatment listed in Table 5 will be implemented before database lock to confirm that the medication was used due to CSU treatment failure and not an unrelated condition. The selected prohibited and/or rescue medications list in Table 5 is same as for study A SAP.

Table 5 - Selected prohibited and/or rescue medications impact on efficacy

Medication	Comment	Intervention in the main statistical analysis (Yes/No)[a] / Selection criteria
Systemic immunosuppressants (immunosuppressive/immunomodulating drugs) eg, 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)
Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid		No
Other monoclonal antibodies (which are biological response modifiers).		Yes (SDG Monoclonal antibodies Narrow)
Phototherapy, including tanning beds.		No
IVIG		Yes (CDG00488 Intravenous immunoglobulin therapy - See Section 5.6)
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

Medication	Comment	Intervention in the main statistical analysis (Yes/No)[a] / Selection criteria
LTRAs and H2 receptor antagonists, unless stable and taken for diseases other than CSU.		Yes for LTRAs; No for H2 receptor antagonists (SDG Leukotriene receptor antagonists for obstructive airway diseases Narrow)
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 the estimand for the intercurrent event handling strategy will be as follows: hypothetical for continuous endpoints, and composite for responder and time-to-event endpoints. When no, a treatment policy strategy will be applied.

The primary estimand for the primary endpoint is the treatment policy/hypothetical approach.

The primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region 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 taking selected prohibited medications and/or rescue medications (see Table 5), their data after the medication start date will be set to missing, and the worst postbaseline value on or before the time of the medication usage will be used to impute missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute). Participants who discontinue the intervention prematurely are encouraged to follow the planned clinical visits and in these participants who did not take the selected prohibited medications and/or rescue medications, all data collected after intervention discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts to collect the data after intervention discontinuation. 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 (ie due to study discontinuation). 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 selected prohibited medications and/or 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 ANCOVA model as described above. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) 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.

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

4.3.3 Sensitivity analysis

The following sensitivity analyses will be performed targeting the same estimand as the primary estimand to assess the impact of the missing data handling strategy.

Tipping point analysis on WOCF

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

- A positive amount *d* is added to the imputed WOCF values, with the resulting score not to exceed the worst possible score (ie, 21 on ISS7 and 42 on UAS7)
- Change from baseline in endpoint will be analyzed using ANCOVA model same as the one in primary analysis. A multiple imputation approach will be used for missing Week 24 data.

The above will be repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated is >0.021 at IA or >0.043 at final analysis, or all participants with data imputed by WOCF are assigned the worst possible score.

Pattern mixture model with copy increment from placebo after WOCF

After using the WOCF approach to impute data after taking the select prohibited/rescue medications and to impute missing data for participants who discontinue treatment due to lack of efficacy (as described for the primary analysis) the primary endpoint will be analyzed with imputed missing Week 24 values using a pattern mixture model with copy increment from placebo (1). This copy increment from placebo implies that when participants discontinue intervention early, they continue to take advantage of their previous therapy, but they progress in the same way as participants in the placebo group.

The imputed dataset will be analyzed by fitting an ANCOVA model same as the one in primary analysis. 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.

Pattern mixture model with copy increment from placebo without WOCF

All data after taking the select prohibited/rescue medications will be set to missing. The primary endpoint will be analyzed with imputed missing Week 24 values using a pattern mixture model with copy increment from placebo (1). This copy increment from placebo implies that when participants discontinue intervention early or take select prohibited/rescue medications, they continue to take advantage of their previous therapy, but they progress in the same way as participants in the placebo group.

The imputed dataset will be analyzed by fitting an ANCOVA model same as the one in primary analysis. 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.

Tipping point analysis for missing data

After using the WOCF approach to impute data after taking select prohibited/rescue medications and to impute missing data for participants who discontinue treatment due to lack of efficacy (as described for the primary analysis), a tipping point analysis will be performed for the primary endpoint with imputed missing Week 24 values as follows:

- **Step 1.** Monotone missing pattern will be 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 response variable, intervention groups, angioedema at baseline, region, and baseline value of the corresponding 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 set.
- **Step 4.** The imputed values in placebo group are subtracted by a positive amount *p* for each imputed data set.
- **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 treatment effect of dupilumab compared to placebo estimated in Step 5 is >0.021 at IA or >0.043 at final analysis.

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

4.3.4 Supplementary analyses

The following supplementary analysis will be performed:

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

The data collected after taking the select prohibited medications and/or rescue medications will be included in the sensitivity analysis to evaluate the robustness of the primary analysis results with respect to the intercurrent event handling strategy while taking selected prohibited medications and/or rescue medications. (eg, treatment policy strategy). For missing data, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants.

Worst possible score

For participants taking selected prohibited and/or rescue medications (see Table 5), their data after the medication start date will be excluded from the analysis, and the worst possible score (ie, 21 for ISS7 and 42 for UAS7) will be assigned to the Week 24 value. In case there is missing data, 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 selected prohibited medications and/or rescue medications on or before Week 24.

Each of the imputed complete data will be analyzed by fitting an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region as covariates. 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.

The change from baseline and percent change from baseline will be summarized and analyzed by week using the same approach as the primary endpoint. 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. Figures over time will also be presented.In addition, descriptive summaries by week up to Week 36 and figures over time will be provided using the ITT population, while WOCF/MI and other imputation approach will not impute visits a participant would not have reached by the cutoff date.

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; <65, ≥65 years)
- Gender (Male, Female)
- Baseline weight (<median, ≥median, <60, ≥60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m^2)
- Region (see Section 5.3)
- Territory (see Section 5.3)
- Race (White, all the Others)
- Ethnicity (Hispanic, non-Hispanic)
- Angioedema at baseline (Yes, No)
- Baseline UAS7 score (<28, ≥28)
- Baseline ISS7 score (<13, ≥13)
- Duration of disease (<2, 2-10, >10 years)
- H1-AH baseline dose (1-fold, 2-4-fold)
- Baseline Total serum IgE (<median, ≥median)

VV-CLIN-0695997 2.0

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, 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 for the primary endpoint, 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.

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 indicated in Table 1 with an asterisk and are presented below.

- Change from baseline in weekly urticaria activity score (UAS7) at Week 24 (except EU and EU reference countries).
- Change from baseline in ISS7 at Week 24 (in EU and EU reference countries).

As described for the primary endpoint, only data before taking select prohibited and rescue medications will be included (See Table 5). All data after intervention discontinuation (but before taking select prohibited and rescue medications) will be used in the analysis.

4.4.1.2 Main analytical approach

Continuous secondary endpoints will be analyzed using the same approach as the primary efficacy endpoint.

4.4.2 Supportive secondary endpoint(s)

The change from baseline in AAS7 at Week 12 and Week 24 will be analyzed in those participants who have angioedema at baseline defined as a baseline AAS7 score >0. The change from baseline and percent change from baseline in continuous endpoints will be summarized and analyzed by week using the same approach as the primary endpoint. 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. Figures over time will also be presented.

The endpoint change from baseline in DLQI will be summarized and analyzed in participants ≥16 years old who completed the DLQI at baseline.

Responder endpoints will be analyzed using the CMH test adjusted by baseline disease severity, presence of angioedema at baseline, and region. The baseline disease severity will be defined according to UAS7 <28 or ≥28. Comparisons of the response rates between dupilumab dose and placebo will be derived. Participants who receive selected prohibited medications and/or rescue medications will be considered as non-responders for time points after medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the responder/non-responder status. Missing data will be considered as non-responders.

Time-to-event endpoints will be analyzed using the Cox proportional hazards model, including intervention, the corresponding baseline value, presence of angioedema at baseline, and region as covariates. The hazards ratio, its 95% confidence interval and p-value will be reported. Kaplan-Meier curves will be also provided.

For time to first ISS7 MID (ISS7 ≥5) response defined as time to reduction from baseline of 5 points or more, participants who receive selected prohibited medications and/or rescue medications (see Table 5), data prior to start of the medication will be used, but after medication start, the participant will be censored at Week 24 (ie, Day 169). For other participants, all available data up to Week 24 (ie, Day 169) including those collected during the off-treatment period will be used. Participants without events will be censored at Day 169 or their last ISS7 assessment date if discontinued from the study whichever is earlier, for ITT24 population at IA and for ITT population at the final analysis.

For time to participants receiving first OCS for CSU during the planned treatment period, participants who receive selected prohibited medications and/or rescue medications other than OCS for CSU, data prior to start of the medication will be used, but after medication start, the participant will be censored at time of start of medication. Participants who don't receive OCS during the treatment period will be censored at Day 169 or their status date collected on the completion of study/follow-up eCRF form or cut-off date, whichever is earlier. This endpoint will be analyzed using a Cox proportional hazards model, including intervention, presence of angioedema at baseline, and region as covariates.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

Additional details are provided below for specific exploratory efficacy endpoints.

Time to UAS7 MID response (9.5 to 10.5 points) by Week 12 and Week 24

Time to first UAS7 reduction from baseline of 10.5 points or greater and 9.5 points or greater will be analyzed similar to time to ISS7 MID (ISS7 ≥5) response. Proportion of participants with each of these MID responses (10.5 and 9.5) by week will also be provided.

Change from baseline in the number of itch-free days and/or hive-free days at Week 12 and Week 24

Three endpoints will be summarized at each Week using descriptive statistics (mean, SD, min, max). Change from baseline in number of itch-free days, number of hive-free days, and number of itch and hive-free days over the 7 days.

Change in UAS7 in well-controlled patients (UAS ≤6) from Week 24 to 36. (only provide for final analysis)

For those participants who were well-controlled (UAS ≤6) at Week 24, the change in UAS7 from Week 24 to Week 36 will be summarized using descriptive statistics (mean, SD, min, max)

Use of antihistamine rescue medication

The number (%) of participants who received antihistamine as rescue medication during the planned treatment period (ie, up to Day 169) will be summarized by intervention group.

Total OCS rescue dose prescribed (in mg) during the treatment period

The total cumulative prescribed dose of OCS rescue medication will be summarized by descriptive statistics (mean, SD, min, max) over the planned treatment period.

Total OCS rescue intake in days during the treatment period

The total number of days that OCS rescue medication was taken during the planned treatment period will be summarized by intervention group.

The endpoint change from baseline in EQ-5D-5L/EQ-5D-Y 5L will be summarized and analyzed in participants ≥16 years old who completed the EQ-5D-5L at baseline.

Proportion of participants with ISS7 = 0 and HSS7 = 0 at Week 12 and Week 24 will be summarized and analyzed similar to the secondary endpoint of UAS7 = 0. Cumulative number of itch and/or hive-free days from Week 4-12, 13-24, and Week 4-24 will be summarized and analyzed. This will be calculated as the number of days for which the participant indicated a 'No' response divided by the total number of days with a non-missing response during the period multiplied by the number of days in the period. Participants who withdrew before the Week 4 visit or who have missing responses for >40% of the daily entries during the period will not be included in the analysis.

An additional exploratory endpoint of time to first select prohibited/rescue medication that impact efficacy will be provided. This includes medications where WOCF will be applied (see Table 5).

4.5.2 Main analytical approach

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

Time to first UAS7 change from baseline of ≥9.5 and ≥10.5 will be analyzed similar to time to ISS7 MID (ISS7 ≥5) response. For participants not receiving selected prohibited medications

and/or rescue medications, all available data up to Week 24 (ie, Day 169) including those collected during the off-treatment period will be used. Participants without events will be censored at Day 169 or their last UAS7 assessment date on or before Day 169 if discontinued from the study, whichever is earlier.

4.6 MULTIPLICITY ISSUES

A multiplicity procedure is proposed to control the overall type-I error rate for testing the primary and selected secondary endpoints. The overall type-I error is controlled at 0.05. The alpha spending at the interim analysis (details are provided in Section 4.9) will be 0.021, and the alpha spending at the final analyses when all 108 patients complete the study will be 0.043.

At the interim analysis, the comparisons with placebo will be tested based on the hierarchical order below at 2-sided alpha=0.021.

At the final analysis, the comparisons with placebo will be tested based on the hierarchical order below at 2-sided alpha=0.043.

In non-EU and non-EU reference countries:

1. Change from baseline in ISS7 at Week 24
2. Change from baseline in UAS7 at Week 24
3. Change from baseline in HSS7 at Week 24
4. Proportion of patients with MID (ISS7 ≥5) response at Week 24
5. Proportion of patients with UAS7 ≤6 at Week 24
6. Proportion of patients with UAS7 = 0 at Week 24
7. Change from baseline in UCT at Week 24

In EU and EU reference countries:

1. Change from baseline in UAS7 at Week 24
2. Change from baseline in ISS7 at Week 24
3. Change from baseline in HSS7 at Week 24
4. Proportion of patients with MID (ISS7 ≥5) response at Week 24
5. Proportion of patients with UAS7 ≤6 at Week 24
6. Proportion of patients with UAS7 = 0 at Week 24
7. Change from baseline in UCT at Week 24

Study B is considered positive when the primary endpoint (change from baseline in ISS7 at Week 24 in non-EU and non-EU reference countries or change from baseline in UAS7 at Week 24 in EU and EU reference countries) achieves statistical significance.

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 (eg, 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. At the interim analysis, the date of the last dose of IMP is the last injection date for the analysis of IA for those participants who are ongoing.

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 (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

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

The primary 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 day is missing, it will be imputed using 01 (except if the same month and year of 1st IMP, then the day of first IMP will be used). If month is missing, the AE start date will remain missing.

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.

VV-CLIN-0695997 2.0

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 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 grouping
- Any TEAE related to IMP

The AE summaries of Table 7 will be generated with number (%) of participants experiencing at least one event.

Table 7 - 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 (≥2% and ≥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

Type of AE	MedDRA levels
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 overview table, and common TEAEs (PT ≥2% 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 6 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 8. Number (%) of participants experiencing at least one event will be provided for each event of interest. 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 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

AE Grouping	Criteria
Helminthic infections	CMQ10544 based on HLGT as "Helminthic disorder"
Any severe type of conjunctivitis	CMQ10498 based on PTs (See Section 5.6)[a] and "Severe" ticked in Adverse Events eCRF page
Any severe type of blepharitis	CMQ10497 based on HLT as "Lid, lash and lacrimal infections, irritations and inflammations" and "Severe" ticked in Adverse Events eCRF page
Keratitis	CMQ10642 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, herpes ophthalmic, ophthalmic herpes simplex, corneal infection][a]
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)[b]	CMQ10641 based on HLT = Eosinophilic disorders or PT = Eosinophil count increased
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; 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

VV-CLIN-0695997 2.0

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 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, calcium, bicarbonate
  - **Renal function**: creatinine, blood urea nitrogen, uric acid

VV-CLIN-0696297 2.0

- **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, nitrate, 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: pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg) in a semi-supine or sitting position after 5 minutes, weight, respiratory rate (breaths per minute), temperature (degrees Celsius) and height (screening only)
- ECG variables: heart rate, PR, QRS, QT, and QTc intervals after 10 minutes of rest in the supine position

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, vital signs and ECG 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 (eg, ALT), participants having 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).

4.8 OTHER ANALYSES

4.8.1 PK analyses

Pre-dose dupilumab concentrations in serum at Visit 2 (Day 1), dupilumab trough levels at Week 12, Week 24/EOT and post-treatment dupilumab concentrations in serum at Week 36 will be provided.

Concentrations of dupilumab (SAR231893; REGN668) in serum 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), one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three significant figures. For participants in the placebo group, concentration values are below the LLOQ will be taken into account with a concentration in serum 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

VV-CLIN-0695997 2.0

- 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

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

Impact of ADA on clinical efficacy endpoints

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

Association of ADA with clinical safety endpoints

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

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

Associations between ADA variables (eg, 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 IgE in serum. Total IgE will be measured using validated quantitative methods.

For those participants (with exception of adolescents) 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).

For those participants (with exception of adolescent) who consent to the optional skin biopsy (substudy), the sample will be taken from lesion and non-lesion skin using punch biopsy at Visit 2 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 +/- interquartile range) 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 and skin biopsy substudy will be addressed in a separate document.

4.9 INTERIM ANALYSES

An interim analysis (IA) will be performed when the first 83 randomized participants would have completed their 24-week treatment period by the interim analysis cut-off date. This interim analysis will use the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, with an alpha spending at the interim analysis of 0.021, and an alpha spending at the final analysis (when all 108 patients complete the study) of 0.043.

The possible outcomes from this interim analysis are summarized below and in Table 6.

Efficacy at IA:

In case p-value at interim analysis is ≤0.021 for both ISS7 and UAS7, Study B will be considered "Efficacy at IA for ISS7 and UAS7" (as shown in Table 6).

VV-CLIN-0698297 2.0

In case p-value at interim analysis is ≤0.021 in ISS7 and >0.1 for UAS7, Study B will be considered "Efficacy at IA for ISS7" (as shown in Table 6).

In case of "Efficacy at IA", the interim analysis will be considered as the primary database lock, the study treatment will continue, and a final database lock will occur when all participants have completed the last visit in the study. Additional data between this database lock and last participant completing last visit will be analyzed using the same approach in a CSR addendum.

Stop for futility:

In case p-value at interim analysis is >0.1 for both ISS7 and UAS7, Study B will be considered "Stop for futility" (as shown in Table 6).

In case of stop for futility, the study treatment will be stopped for all current participants. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

Continue up to EOT for the primary analysis:

For all other situations the decision is to continue the study (as shown in Table 6) until 108 patients (54 patients per group) complete the study treatment and the final analysis will be conducted with an alpha of 0.043.

In this case Study B will continue up to the EOT for the primary analysis, a second database lock will be performed when all randomized participants have completed their treatment phase and a final database lock will occur when all participants have completed the last visit in the study.

Table 9 - Possible outcomes from the interim analysis

UAS7 (treatment effect)	ISS7 (treatment effect)		
	≤0.021	**p>0.021 and p≤0.1**	**p>0.1**
≤0.021	Efficacy at IA for ISS7 and UAS7	Continue up to EOT for final analysis	Continue up to EOT for final analysis
p>0.021 and p≤0.1	Continue up to EOT for final analysis	Continue up to EOT for final analysis	Continue up to EOT for final analysis
p>0.1	Efficacy at IA for ISS7	Continue up to EOT for final analysis	Stop for futility

To maintain study integrity with respect to the subsequent visits and analyses after the Study B interim analysis, a dissemination plan will be written. This plan will clearly identify two independent study teams (blinded and unblinded teams), an independent statistical group (ISG, ACI clinic will serve as ISG in this study), and an independent committee (including a statistician).

Sanofi will transfer blinded clinical study data to the ISG (ACI), as well as instruct the IVRS vendor (ALMAC) to send unblinding scheme to ACI (directly), so ACI can perform the pre-specified interim analysis and produce the data displays for the independent committee.

The independent committee will be in charge of analyzing and reviewing the interim analysis and providing guidance about the above described scenarios (continue, success or futility).

Two independent study teams, unblinded and blinded study team, will be put in place in case of efficacy IA outcome. Specific steps will be setup to maintain the blind of the study to all individuals involved in the conduct of the study and/or analysis, and to protect the overall blinding and integrity of the study data, after the interim analysis has been performed. Details will be provided in the dissemination plan.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AAS7:	angioedema activity score over 7 days
ADA:	anti-drug antibody
AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance, analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomic category
CDG:	customized drug grouping
CDLQI:	Children's Dermatology Life Qualtiy Index
CI:	confidence interval, confidence interval
CLcr:	Creatinine clearance
CMH:	Cochran-Mantel Haenszel
CU-Q2oL:	chronic urticaria quality of life questionnaire
DLQI:	Dermatology Life Quality Index
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
eCRF:	electronic case report form
EMA:	European Medicines Agency
EOT:	end of treatment
EQ-5D-5L:	5-level EuroQol 5-dimensional questionnaire
EQ-5D-Y 5L:	EuroQol 5-dimensional questionnaire youth
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
HSS7:	weekly hives severity score
IMP:	investigational medicinal product
IRT:	interactive response technology
ISS7:	weekly itch severity score
ITT:	intent-to-treat
LLT:	lower-level term
LS:	least squares, least squares
MCMC:	Markov Chain Monte Carlo
MedDRA:	medical dictionary for regulatory activities
MID:	minimal important difference

VV-CLIN-0696297 2.0

OCS:	oral corticosteroids
PCSA:	potentially clinically significant abnormality
PGIC:	Patient Global Impression of Change
PGIS:	Patient Global Impression of Severity
PK:	pharmacokinetic
PT:	preferred term
RNA:	ribonucleic acid
SAE:	serious adverse event
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
WOCF:	worst-observation carried forward

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This Statistical Analysis Plan (SAP) for study EFC16461 is based on the protocol dated 29 April 2021 (amended protocol 4). This section summarizes major statistical changes in the protocol amendment(s).

One of the purposes of Amended protocol 2 was to switch the primary and the key secondary endpoints to establish the UAS7 as the primary endpoint for EU and EU reference countries based on recommendations from European Medicines Agency (EMA).

The primary purpose of Amended protocol 4 is to plan for an interim analysis for Study B when 80 randomized participants would have completed their 24-week treatment period.

Since finally 108 patients are randomized, to preserve the ratio of number of patients at IA to total sample size at final (will allow the same alpha spending as defined in the protocol), the sample size of IA is increased from 80 to 83.

VV-CLIN-0696297 2.0

Table 10 - Major statistical changes in protocol amendment(s)

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	30-Apr-2020	EMA request to change the primary and key secondary endpoints for EU and EU reference countries	For EU and EU references countries only, primary endpoint is now change from baseline in UAS7 at Week 24 and key secondary endpoint is change from baseline in ISS7 at Week 24
		Efficacy analysis was modified to include covariates	Presence of angioedema at baseline was added as a covariate to the primary endpoint analysis and by baseline disease severity, and presence of angioedema at baseline were added to Cochran-Mantel Haenszel (CMH) test. The corresponding baseline value and presence of angioedema at baseline was added as covariates for time-to-event endpoints.
4	29-Apr-2021	Due to COVID impact and associated difficulties to enroll patients in Study B (intolerant or incomplete responders to omalizumab), an interim analysis of Study B will be performed to allow an earlier assessment of efficacy or stop for futility in this population. This protocol amendment describes the details of this interim analysis with possible scenarios for study discontinuation for considering efficacy, continuation or stopping the study. Blinding and integrity of the study will be ensured by appropriate measures	Considering the reduced drop-out rate of 10% observed during the study, an interim analysis will be performed when the first 80 randomized patients would have completed their Week 24 visit by the interim analysis cut-off date. Using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis will be 0.021, and the alpha spending at the final analysis when all 104 patients complete the study will be 0.043.

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. Demographics and baseline characteristics will also be summarized using descriptive statistics in the ITT24 population.

Demographic variables are

- Age in years (quantitative and qualitative variable: <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:** China, Japan; **Latin America:** Argentina; **Western Countries**: Canada, USA**,** France, Germany, Spain, United Kingdom, **East Europe:** Hungary, Russia),
- Territory (**North America:** Canada, USA**; European Union and UK:** France, Germany, Spain, United Kingdom, Hungary; **Rest of Word:** China, Japan, Argentina, Russia),
- 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 history (Yes, Ongoing condition)

Angioedema (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 CSU (years)
- Time since first diagnosis of CSU (years) to be derived as
  (Year of randomization – Year of first diagnosis of CSU) + (month of randomization-month of first diagnosis of CSU)/12
- Presence of angioedema at baseline
  - Number of episodes in past 6 months
  - Time since last episode (months)
- Baseline ISS7 score (quantitative and qualitative variable: <13, ≥13)
- Baseline UAS7 score (quantitative and qualitative variable: <28, ≥28)
- Baseline weekly hives severity score (HSS7)
- Baseline angioedema activity score over 7 days (AAS7) for participants with angioedema
- Baseline urticaria control test (UCT)
- Baseline Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI)
- Baseline Patient Global Impression of Severity (PGIS)
- Frequency of alcohol drinking in the past 12 months (never, occasional, at least monthly, at least weekly, at least daily) and number of drinks on a typical day (1 or 2, >2)
- Baseline IgE (quantitative and qualitative variable: <100 vs ≥100)
- Baseline H1-AH dose (1-fold, 2-3-fold, 4-fold)
- Incomplete response to Omalizumab vs Intolerant to Omalizumab
- Duration of prior Omalizumab treatment (<6 months, 6-12 months, >12 months)
- Prior Omalizumab dose (300 mg q4w vs other doses)

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 CSU 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 CSU 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.

VV-CLIN-0695997 2.0

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Demographic formulas

Age of onset of CSU is calculated as:

Year of CSU 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:

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

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

GFR (mL/min/1.73 m²) = k × height (cm) / sCr (mg/dL),

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

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

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.

i. For the DLQI, handing of missing items is as follows: 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
ii. If two or more questions are left unanswered the questionnaire is not scored
iii. If question 7 is answered ‘yes’ this is scored 3 even if in the same question one of the other boxes is ticked
iv. If question 7 is answered ‘no’ or ‘not relevant’ but then either ‘a lot’ or ‘a little’ is ticked this is then scored 2 or 1
v. 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:

i. 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
ii. If two or more questions are left unanswered the questionnaire is not scored
iii. If two or more response options are ticked for one question, the response option with the highest score should be recorded

For the CU-Q2oL total score, the raw total score will be converted to a 0 to 100 score for analysis using the following formula:

$$\text{CU-Q2oL total score} = (\text{raw score} - 23)*100/92$$

Daily e-diary weekly scores

For the daily efficacy endpoints (ISS, UAS, HSS, and AAS), the time period used to calculate the weekly score at each designated study day is summarized in Table 11. Randomization day is used as the reference day (Day 1).

Table 11 - Weekly efficacy assessments from daily e-diary

Analysis visit	Day range for calculating weekly score	Target day
Week 1	2-8	8
Week 2	9-15	15
Week 3	16-22	22
Week 4	23-29	29
Week 5	30-36	36
Week 6	37-43	43
Week 7	44-50	50
Week 8	51-57	57
Week 9	58-64	64
Week 10	65-71	71
Week 11	72-78	78
Week 12	79-85	85
Week 13	86-92	92
Week 14	93-99	99
Week 15	100-106	106
Week 16	107-113	113
Week 17	114-120	120
Week 18	121-127	127
Week 19	128-134	134
Week 20	135-141	141
Week 21	142-148	148
Week 22	149-155	155
Week 23	156-162	162
Week 24	163-169	169
Week 25	170-176	176
Week 26	177-183	183

Analysis visit	Day range for calculating weekly score	Target day
Week 27	184-190	190
Week 28	191-197	197
Week 29	198-204	204
Week 30	205-211	211
Week 31	212-218	218
Week 32	219-225	225
Week 33	226-232	232
Week 34	233-239	239
Week 35	240-246	246
Week 36	247-253	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 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	Target Day	Time windows for						
		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	1+
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;

VV-CLIN-0695997 2.0

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 13. 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 13 - Time window for efficacy variables

Visit	Target Day	Time windows for			
		UCT, DLQI/CDLQI, CU-Q2oL	PGIC	PCIS	EQ-5D-5L/EQ-5D-L, missed school/work days
Visit 1	-28 to -14			<-14	
Visit 2 (Week 0)	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	>126	>126	127-210
Visit 5 (Week 36)	253	>210			>210

1-: up to randomization and before 1st dose date/time; 1+: after randomization or 1st 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 14 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 14 - Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target Day	Serum dupilumab, ADA, Total IgE	Skin biopsy (substudy)	Basophil activation (substudy)
Visit 1	-28 to -14			
Visit 2 (Week 0)	1	<1-	<1-	<1-
Visit 3 (Week 12)	85	1+-126		1+-126
Visit 4 (Week 24)	169	127-210	>1+	>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 SAMPLE SAS CODE

The multiple imputation and analysis model for the primary analysis approach 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 taken selected prohibited medications and/or rescue medications or have not discontinued study intervention due to lack of efficacy prior to Week 24.

```
proc mi data=dat_etd seed=16461 nimpute=40 out=dat_mc;
    mcmc impute=monotone;
    var angiobl region trt01p iss7bl chg1iss …  chg24iss;
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 intervention groups, region, angioedema status at baseline and baseline value of the response variable.

```
proc mi data=dat_mc nimpute=1 seed=16461 out=dat_mi;
    by _imputation_;
     class angiobl region trt01p;
     monotone method=reg;
     var angiobl region trt01p iss7bl chg1iss … chg24iss;
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 region angiobl trt01p;
      model  chg24iss = iss7bl angiobl region trt01p;
      lsmeans trt01p / 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 SELECTION CRITERIA FOR AE/MEDICATION GROUPINGS

Table 15 - 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
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

VV-CLIN-0695997 2.0

6 REFERENCES

1. Carpenter JR, Roger JH, Kenward MG. Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and inference via Multiple Imputation. J Biopharm Stat. 2013;23:1352-71.

Signature Page for VV-CLIN-0587244 v2.0
efc16461b-16-1-9-sap

Approve & eSign	[redacted]
Approve & eSign	

STATISTICAL ANALYSIS PLAN

Protocol title:	**Master protocol of three randomized, double-blind, placebo-controlled, multi-center, parallel-group studies of dupilumab in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine treatment in patients naïve to omalizumab and in patients who are intolerant or incomplete responders to omalizumab**
Protocol number:	**EFC16461C**
Compound number (INN/Trademark):	**SAR231893/REGN668 dupilumab/Dupixent**
Study phase:	**Phase 3**
Short title:	**Dupilumab for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine and who are naïve to omalizumab** **LIBERTY-CSU CUPID (Chronic Urticarial Pruritus Itch Dupilumab Trial)**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**12-Apr-2024**

Regulatory agency identifier number(s):

IND:	105379
EudraCT:	2019-003775-19
NCT:	NCT04180488
WHO:	U1111-1241-8208
Other:	Not applicable

Total number of pages: 47

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

TABLE OF CONTENTS

VV-CLIN-0699997 1.0

LIST OF TABLES

VV-CLIN-0699907 1.0

VERSION HISTORY

This Statistical Analysis Plan (SAP) only includes the plan for EFC16461 Study C (in omalizumab naïve patients), which is based on the protocol dated 17 March 2022 (amended protocol 5). There are no major changes to the statistical analysis features in this SAP compared to the protocol. Separate SAPs were prepared for Study A and B.

The first participant was randomized on 02 Aug 2022.

VV-CLIN-0699907 1.0

1 INTRODUCTION

1.1 STUDY DESIGN

This is a master protocol composed of 3 studies of similar design, 2 studies in participants who are omalizumab naïve (Study A and Study C) and 1 study in participants who are omalizumab intolerant or incomplete responders (Study B). Study A and Study C will include adults, adolescents (≥12 to <18 years) and children (≥6 to <12 years). Study B will include adults and adolescents. The three studies are 24-week, double-blind, randomized, placebo-controlled studies to evaluate the use of dupilumab in participants with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1-antihistamines (H1-AH).

After a screening period of 2 to 4 weeks, participants are centrally randomized (using permuted block randomization schedule) via interactive response technology (IRT) in a 1:1 randomization ratio to dupilumab (300 mg q2w for adults and adolescents ≥60 kg after a loading dose of 600 mg on Day 1; 200 mg q2w for adolescents <60 kg and children ≥30 kg after a loading dose of 400 mg on Day 1; or 300 mg q4w for children <30 kg and ≥15 kg after a loading dose of 600 mg on Day 1) or placebo over a 24-week treatment period. Randomization is stratified first by age (adults versus adolescents versus children in Study A and Study C, adults versus adolescents in Study B; up to approximately 5% of total sample size for children and approximately 5% of total sample size for adolescents). In adults, randomization is stratified further by country (Studies A, B, and C) and presence of angioedema at baseline (Study C only). In adolescents/children ≥6 to <12 years of age, randomization is not stratified further.

The total anticipated number of participants across the 3 studies is approximately 384 randomized participants (130 participants in Study A, 104 participants in Study B and 150 participants in Study C).

1.2 OBJECTIVE AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-AH (Study A and Study C: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders)	• Change from baseline in weekly itch severity score (ISS7) at Week 24 (except EU and EU reference countries). • For EU and EU reference countries only: Change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24.

VV-CLIN-0699992 1.0

Objectives	Endpoints
Secondary	
To demonstrate the efficacy of dupilumab on urticaria activity composite endpoint and itch or hives, separately, at various time points	• Change from baseline in weekly urticaria activity score (UAS7) at Week 12[a] and Week 24[b] (except EU and EU reference countries). • Change from baseline in ISS7 at Week 12[a] and Week 24[b] (in EU and EU reference countries). • Change from baseline in weekly hives severity score (HSS7) at Week 12 and Week 24. • Time to ISS7 minimally important difference (MID) (ISS7 ≥5) response. • Proportion of ISS7 MID (≥5 points) responders at Week 12[a] and Week 24[a]. • Change from baseline in ISS7 at all time points (onset of action is assessed by the first p <0.05 that remains significant at subsequent measures until Week 24). • Proportion of patients with UAS7 ≤ 6 at Week 12[a] and Week 24[a]. • Proportion of patients with UAS7 = 0 at Week 12[a] and Week 24[a].
To demonstrate the efficacy of dupilumab on angioedema	• Change from baseline in angioedema activity score over 7 days (AAS7) at Week 12 and Week 24.
To demonstrate the efficacy of dupilumab on urticaria control	• Change from baseline in urticaria control test (UCT) at Week 12 and Week 24. • Proportion of well-controlled patients (UCT ≥12) at Week 12 and Week 24.
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 patients ≥16 years old, and in Children's Dermatology Life Quality Index (CDLQI) in patients ≥6 to <16 years old at Week 12 and Week 24. • Patient Global Impression of Change (PGIC) of CSU at Week 12 and Week 24. • Change from baseline in Patient Global Impression of Severity (PGIS) of CSU at Week 12 and Week 24.
To evaluate the ability of dupilumab in reducing the proportion of patients who require treatment with oral corticosteroids (OCS)	• Time-to-event and proportion of patients receiving OCS for CSU during the planned treatment period.
To evaluate safety outcome measures	• Percentages of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs).
To evaluate immunogenicity of dupilumab	• Incidence of treatment-emergent anti-drug antibodies (ADA) against dupilumab over time.

Objectives	Endpoints
[redacted]	
• To demonstrate exploratory outcome measures in the urticaria composite score and or its components	• Time to UAS7 MID response (9.5 to 10.5 points) by Week 12 and Week 24. • Change from baseline in the number of itch-free days and/or hive-free days at Week 12 and Week 24. • Change in UAS7 in well-controlled patients (UAS ≤6) from Weeks 24 to 36.
• To demonstrate exploratory health-related quality-of-life and health status measures	• Change from baseline in EQ-5D-5L (or EQ-5D-Y 5L for ≥6 to <16 years old) at Week 12 and Week 24. • Change from baseline in CU-Q2oL at Week 12 and Week 24. • Missed school/work days from baseline at Week 12 and Week 24.
• To demonstrate reduction in use of rescue medication	• Use of antihistamine rescue medication. • Total OCS rescue dose prescribed (in mg) during the treatment period. • Total OCS rescue intake in days during the treatment period.
Pharmacokinetic	
• To evaluate PK and pharmacodynamic (PD) outcome measures	• Functional dupilumab concentrations in serum and PK profile. • Pharmacodynamic response for selected biomarkers (total IgE).

a Key secondary endpoints for Study A and B

b Key secondary endpoint for Study C: UAS7 at Week 24 (except EU and EU reference countries, where ISS7 at Week 24 is key secondary endpoint)

1.2.1 Estimands

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

VV-CLIN-0[redacted] 1.0

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category	Estimands			
	Endpoint(s)[a]	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Primary objective: The primary objective of this study is to demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-AH (Study A and Study C: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders)				
Primary endpoint – Continuous	Change from baseline in ISS7 at Week 24 Change from baseline in UAS7 at Week 24 (EU and EU reference countries)	ITT	The intercurrent events will be handled as follows: • Discontinuing the study intervention (but not taking selected prohibited and/or rescue medications[b] prior to Week 24): all data collected after discontinuation will be used in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications[b] prior to Week 24: data will be excluded after the medication usage, and the participant's worst post-baseline value on or before the time of the medication usage will be assigned to the Week 24 value (for participants whose post-baseline values are all missing, the participant's baseline value will be used for the Week 24 value) (composite strategy) After applying the rules for intercurrent events, if there is still missing data, then the missing data imputation rules are as follows: • After study intervention discontinuation due to lack of efficacy prior to Week 24: WOCF approach (as described above) will be used to impute missing data if needed. • After study intervention discontinuation due to reasons other than lack of efficacy prior to Week 24: multiple imputation (MI) approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants excluding participants who have taken the selected prohibited medications and/or rescue medications prior to Week 24 and excluding participants who discontinue study intervention due to lack of efficacy prior to Week 24.	ANCOVA model with intervention group, presence of angioedema at baseline, region (combined countries), and relevant baseline measurement as covariates. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule.

Endpoint Category	Estimands			
	Endpoint(s)[a]	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Secondary objective: To demonstrate the efficacy of dupilumab on urticaria activity composite endpoint and itch or hives, separately, at various time points				
Secondary endpoint – Proportion	Proportion of ISS7 MID (≥5 points) responders at Week 12 and Week 24; Proportion of patients with UAS7 ≤6 at Week 12 and Week 24 Proportion of patients with UAS7 = 0 at Week 12 and Week 24	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention (but not taking selected prohibited and/or rescue medications[b] prior to Week 24): Off-study intervention data will be included in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications[b] before Week 24 (or Week 12): Participants will be considered as non-responders (composite strategy). After applying the rules for intercurrent events, if there is still missing data, then the missing data imputation rules are as follows: • Having missing data at Week 24 (or Week 12): Participants will be considered as non-responders.	CMH test adjusted by presence of angioedema at baseline, region (combined countries), and baseline disease severity (UAS7 <28, ≥28)
Secondary endpoint – Time-to-event	Time to ISS7 MID response	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention before Week 24 (but not taking selected prohibited and/or rescue medications[b] prior to Week 24): Off-study intervention data up to Week 24 will be included in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications[b] prior to Week 24: Analyses will be censored at Week 24 (composite strategy) After applying the rules for intercurrent events, if there is still missing data, then the missing data imputation rules are as follows: • Discontinuing the study follow-up before Week 24: Analyses will be censored at the time of last ISS7 assessment.	This time-to-event endpoint will be analyzed using the Cox proportional hazards model, including intervention, the corresponding baseline value, presence of angioedema at baseline, and region. The hazards ratio, its 95% confidence interval and p-value will be reported.

a Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (ie Continuous, proportion, time-to-event) at other weeks

b Selected prohibited medications and/or rescue medications are listed in Table 4.

2 SAMPLE SIZE DETERMINATION

For Study C (omalizumab naive): Assumptions for sample size calculations for Study C were based on Study A results. An effect size of 0.564 or higher is assumed. Based upon an SD of 7.5 (pooled SD from the observed data in Study A), a treatment difference of[redacted] in the ISS7 would correspond to an effect size of approximately[redacted] Based upon an SD of[redacted] (pooled SD from the observed data in Study A), a treatment difference of [redacted] in the UAS7 would correspond to an effect size of approximately[redacted]. Based on this assumption, plus the assumption of a 10% dropout rate, it is estimated that 75 participants per group will provide 90% power to detect an effect size of [redacted]or higher between the dupilumab arm and placebo using a 2-sided t-test with alpha =[redacted]. This sample size estimate applies to both ISS7 and UAS7 (primary endpoint for EU and EU reference countries).

The sample size calculations were calculated by nQuery Advisor and 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. 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. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who accidentally receive a different intervention from that which was planned, the actual intervention allocation for as-treated analysis will be the dupilumab group. 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.
Antidrug 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: ADA = antidrug antibody; ICF = Informed consent form, IRT = Interactive response technology; PD = Pharmacodynamic

Participants exposed to study intervention 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 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% of 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 the COVID-19 pandemic.

VV-CLIN-0699987 1.0

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 EFC16461 Study C (omalizumab naïve) only. Study A (omalizumab naïve) and Study B (omalizumab intolerant or incomplete responders) were summarized separately in different SAPs.

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

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 (+28 days for children <30 kg)
  - 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 observation 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 DISPOSITION

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

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

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

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation 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 (ie, 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 efficacy endpoint is the change from baseline in ISS7 at Week 24.

For EU and EU reference countries, the primary efficacy endpoint is the change from baseline in UAS7 at Week 24.

The once daily UAS is the sum of the daily HSS (ranging from 0 = None to 3 = more than 50 hives) and the daily ISS (ranging from 0 = None to 3 = intense), assessing the 2 key urticaria signs and symptoms which are wheals and itch. The daily UAS scores range from 0 to 6 point/day. The daily UAS scores are summed over 7-day period to create the UAS7, ranging from 0 to 42, and is composed of the HSS7 and ISS7 components.

For daily e-diary endpoints, the baseline values are the sum of the 7 measurements obtained within the 7 days prior to randomization. Note: To be eligible for the study, participants must have no missing e-diary (UAS7 and ISS7) entries in the 7 days prior to randomization.

For the Week 24 score, the sum of the 7 days on and prior to the target visit day will be used (ie, sum of days 163 through 169). If there are less than 7 but at least 4 non-missing scores available, the weekly score is the sum of the available scores in the 7 days, divided by the number of days that have a non-missing score, multiplied by 7. If there are less than 4 non-missing scores, the weekly score is missing. This same rule will be applied for other weekly scores.

VV-CLIN-0699992 1.0

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 change from baseline in ISS7 at Week 24, and the primary endpoint of change from baseline in UAS7 at Week 24 for EU and EU reference countries 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

For efficacy analysis, Table 4 presents the prohibited and rescue medications where data may be excluded and WOCF values assigned after taking the medication in the main statistical analysis approach due to the impact these medications could have on efficacy. Blinded medical review of participants that receive treatments listed in Table 4 will be implemented before database lock to confirm that the medication was used due to CSU treatment failure and not an unrelated condition. The selected prohibited and/or rescue medications listed in Table 4 are the same as for Study A and Study B SAPs.

Table 4 - Selected prohibited and/or rescue medications impact on efficacy

Medication	Comment	Intervention in the main statistical analysis (Yes/No)[a] / Selection criteria
Systemic immunosuppressants (immunosuppressive/immunomodulating drugs) eg, 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).
Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid.		No
Other monoclonal antibodies (which are biological response modifiers).		Yes (SDG Monoclonal antibodies Narrow).
Phototherapy, including tanning beds.		No
IVIG		Yes (CDG00488 Intravenous immunoglobulin therapy - See Section 5.6).
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

Medication	Comment	Intervention in the main statistical analysis (Yes/No)[a] / Selection criteria
LTRAs and H2 receptor antagonists, unless stable and taken for diseases other than CSU.		Yes for LTRAs; No for H2 receptor antagonists (SDG Leukotriene receptor antagonists for obstructive airway diseases Narrow).
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 the estimand for the intercurrent event handling strategy will be composite. When no, a treatment policy strategy will be applied.

The primary estimand for the primary endpoint is the treatment policy/composite approach.

The primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region 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 taking selected prohibited medications and/or rescue medications (see Table 4), their data after the medication start date will be excluded, and the worst postbaseline value on or before the time of the medication usage will be assigned to the Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used). Participants who discontinue the intervention prematurely are encouraged to follow the planned clinical visits and in these participants who did not take the selected prohibited medications and/or rescue medications, all data collected after intervention discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts to collect the data after intervention discontinuation. 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 (ie due to study discontinuation). For participants who discontinued study intervention for reasons other than lack of efficacy, a multiple imputation approach will be used to impute the missing Week 24 value. This multiple imputation will include all participants except participants who have taken the selected prohibited medications and/or rescue medications on or before Week 24 and will also exclude participants who discontinued study intervention due to lack of efficacy on or before Week 24.

Each of the imputed complete data will be analyzed by fitting an ANCOVA model as described above. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) 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.

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

4.3.3 Sensitivity analysis

The following sensitivity analyses will be performed targeting the same estimand as the primary estimand to assess the impact of the missing data handling strategy.

Pattern mixture model with copy increment from placebo after WOCF

After using the WOCF approach to impute data after taking the select prohibited/rescue medications and to impute missing data for participants who discontinue study intervention due to lack of efficacy (as described for the primary analysis), the primary endpoint will be analyzed with imputed missing Week 24 values using a pattern mixture model with copy increment from placebo (1). This copy increment from placebo implies that when participants discontinue intervention early, they continue to take advantage of their previous therapy, but they progress in the same way as participants in the placebo group.

The imputed dataset will be analyzed by fitting an ANCOVA model with same covariates as the primary analysis. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) means will be reported. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be reported along with the p-values.

Tipping point analysis for missing data

After using the WOCF approach to impute data after taking select prohibited/rescue medications and to impute missing data for participants who discontinue study intervention due to lack of efficacy (as described for the primary analysis), a tipping point analysis will be performed for the primary endpoint with imputed missing Week 24 values as follows:

- **Step 1.** Monotone missing pattern will be 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 response variable, intervention groups, angioedema at baseline, region, and baseline value of the corresponding 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 set.
- **Step 4.** The imputed values in placebo group are subtracted by a positive amount *p* for each imputed data set.
- **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.

VV-CLIN-0600002 1.0

Step 3 to Step 5 will be repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated in Step 5 is >0.021 at IA or >0.043 at final analysis.

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

4.3.4 Supplementary analyses

The following supplementary analysis will be performed:

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

The data collected after taking the select prohibited medications and/or rescue medications will be included in the sensitivity analysis to evaluate the robustness of the primary analysis results with respect to the intercurrent event handling strategy while taking selected prohibited medications and/or rescue medications. (eg, treatment policy strategy). For missing data, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants.

Worst possible score

For participants taking selected prohibited and/or rescue medications (see Table 4), their data after the medication start date will be excluded from the analysis, and the worst possible score (ie, 21 for ISS7 and 42 for UAS7) will be assigned to the Week 24 value. In case there is missing data, 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 selected prohibited medications and/or rescue medications on or before Week 24.

Each of the imputed complete data will be analyzed by fitting an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region as covariates. 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.

The change from baseline and percent change from baseline will be summarized and analyzed by week using the same approach as the primary endpoint. 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. Figures over time will also be presented. In addition, descriptive summaries by week up to Week 36 and figures over time will be provided using the ITT population, while WOCF/MI and other imputation approach will not impute visits a participant would not have reached by the cutoff date.

4.3.5 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary endpoint (ISS7 and UAS7) across the following subgroups:

- Age group (<median, ≥median; <65, ≥65 years)
- Gender (Male, Female)
- Baseline weight (<median, ≥median, <60, ≥60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m^2)
- Region (see Section 5.3)
- Territory (see Section 5.3)
- Race (White, all the Others)
- Ethnicity (Hispanic, non-Hispanic)
- Angioedema at baseline (Yes, No)
- Baseline UAS7 score (<28, ≥28)
- Baseline ISS7 score (<13, ≥13)
- Duration of disease (<2, 2-10, >10 years)
- H1-AH baseline dose (1-fold, 2-4-fold)
- Baseline Total serum IgE (<100 IU/mL, ≥100 IU/mL)

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, 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 for the primary endpoint, 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.

In addition, the primary endpoint will be analyzed in the subgroups of adults and adolescent participants.

China subpopulation will be considered for primary efficacy, key secondary efficacy, and important safety analyses (which are for China submission and may be performed outside of the main Clinical Study Report).

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 indicated in Table 1 and are presented below.

- Change from baseline in weekly urticaria activity score (UAS7) at Week 24 (primary for EU and EU reference countries).
- Change from baseline in ISS7 at Week 24 (in EU and EU reference countries).

The same intercurrent event handling strategy and missing data handling will be applied as the primary endpoint.

4.4.1.2 Main analytical approach

Continuous secondary endpoints will be analyzed using the same approach as the primary efficacy endpoint.

4.4.2 Supportive secondary endpoint(s)

The change from baseline in AAS7 at Week 12 and Week 24 will be analyzed in those participants who have angioedema at baseline defined as a baseline AAS7 score >0. The change from baseline and percent change from baseline in continuous endpoints will be summarized and analyzed by week using the same approach as the primary endpoint. 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. Figures over time will also be presented.

The endpoint change from baseline in DLQI will be summarized and analyzed in participants ≥16 years old who completed the DLQI at baseline.

Responder endpoints will be analyzed using the CMH test adjusted by baseline disease severity, presence of angioedema at baseline, and region. The baseline disease severity will be defined according to UAS7 <28 or ≥28. Comparisons of the response rates between dupilumab dose and placebo will be derived. Participants who receive selected prohibited medications and/or rescue medications will be considered as non-responders for time points after medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the responder/non-responder status. Missing data will be considered as non-responders.

Time-to-event endpoints will be analyzed using the Cox proportional hazards model, including intervention, the corresponding baseline value, presence of angioedema at baseline, and region as covariates. The hazards ratio, its 95% confidence interval and p-value will be reported. Kaplan-Meier curves will be also provided.

For time to first ISS7 MID (ISS7 ≥5) response defined as time to reduction from baseline of 5 points or more, participants who receive selected prohibited medications and/or rescue

medications (see Table 4), data prior to start of the medication will be used, but after medication start, the participant will be censored at Week 24 (ie, Day 169). For other participants, all available data up to Week 24 (ie, Day 169) including those collected during the off-treatment period will be used. Participants without events will be censored at Day 169 or their last ISS7 assessment date if discontinued from the study whichever is earlier.

For time to participants receiving first OCS for CSU during the planned treatment period, participants who receive selected prohibited medications and/or rescue medications other than OCS for CSU, data prior to start of the medication will be used, but after medication start, the participant will be censored at time of start of medication. Participants who don't receive OCS during the treatment period will be censored at Day 169 or their status date collected on the completion of study/follow-up eCRF form, whichever is earlier. This endpoint will be analyzed using a Cox proportional hazards model, including intervention, presence of angioedema at baseline, and region as covariates.

Categorical summaries by visit will be provided for PGIC and PGIS.

In addition, secondary endpoints included in the multiplicity procedure (Section 4.6) will be analyzed in the subgroup of adults and adolescent participants.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

Additional details are provided below for specific exploratory efficacy endpoints.

Time to UAS7 MID response (9.5 to 10.5 points) by Week 12 and Week 24

Time to first UAS7 reduction from baseline of 10.5 points or greater and 9.5 points or greater will be analyzed similar to time to ISS7 MID (ISS7 ≥5) response. Proportion of participants with each of these MID responses (10.5 and 9.5) by week will also be provided.

Change from baseline in the number of itch-free days and/or hive-free days at Week 12 and Week 24

Three endpoints will be summarized at each Week using descriptive statistics (mean, SD, min, max). Change from baseline in number of itch-free days, number of hive-free days, and number of itch and hive-free days over the 7 days.

Change in UAS7 in well-controlled patients (UAS ≤6) from Week 24 to 36. (only provide for final analysis)

For those participants who were well-controlled (UAS ≤6) at Week 24, the change in UAS7 from Week 24 to Week 36 will be summarized using descriptive statistics (mean, SD, min, max).

Use of antihistamine rescue medication

The number (%) of participants who received antihistamine as rescue medication during the planned treatment period (ie, up to Day 169) will be summarized by intervention group.

VV-CLIN-0[redacted] 1.0

Total OCS rescue dose prescribed (in mg) during the treatment period

The total cumulative prescribed dose of OCS rescue medication will be summarized by descriptive statistics (mean, SD, min, max) over the planned treatment period.

Total OCS rescue intake in days during the treatment period

The total number of days that OCS rescue medication was taken during the planned treatment period will be summarized by intervention group.

EQ-5D-5L

The endpoint change from baseline in EQ-5D-5L index score (UK tariffs using the crosswalk method developed by Van Hout (2)) and EQ VAS will be summarized and analyzed in participants ≥16 years old who completed the EQ-5D-5L at baseline.

Proportion of participants with ISS7 = 0 and HSS7 = 0 at Week 12 and Week 24 will be summarized and analyzed similar to the secondary endpoint of UAS7 = 0. Cumulative number of itch and/or hive-free days from Week 4-12, 13-24, and Week 4-24 will be summarized and analyzed. This will be calculated as the number of days for which the participant indicated a 'No' response divided by the total number of days with a non-missing response during the period multiplied by the number of days in the period. Participants who withdrew before the Week 4 visit or who have missing responses for >40% of the daily entries during the period will not be included in the analysis.

The following additional exploratory analyses will be provided:

- Time to first select prohibited/rescue medication that impact efficacy (including medications where WOCF will be applied (see Table 4).
- A summary of the number (%) of participants with UAS7 categories (complete control (UAS7 = 0), well-controlled (UAS7 = 1 to 6), mild (UAS7 = 7 to 15), moderate (UAS7 = 16 to 27), and severe(UAS7 = 28 to 42)) at Week 24 by baseline UAS7 status (moderate or severe).

4.5.2 Main analytical approach

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

Time to first UAS7 change from baseline of ≥9.5 and ≥10.5 will be analyzed similar to time to ISS7 MID (ISS7 ≥5) response. For participants not receiving selected prohibited medications and/or rescue medications, all available data up to Week 24 (ie, Day 169) including those collected during the off-treatment period will be used. Participants without events will be censored at Day 169 or their last UAS7 assessment date on or before Day 169 if discontinued from the study, whichever is earlier.

4.6 MULTIPLICITY ISSUES

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

1. Change from baseline in ISS7 at Week 24
2. Change from baseline in UAS7 at Week 24
3. Change from baseline in HSS7 at Week 24
4. Proportion of patients with MID (ISS7 ≥5) response at Week 24
5. Proportion of patients with UAS7 ≤6 at Week 24
6. Proportion of patients with UAS7 = 0 at Week 24
7. Change from baseline in UCT at Week 24

In EU and EU reference countries:

1. Change from baseline in UAS7 at Week 24
2. Change from baseline in ISS7 at Week 24
3. Change from baseline in HSS7 at Week 24
4. Proportion of patients with MID (ISS7 ≥5) response at Week 24
5. Proportion of patients with UAS7 ≤6 at Week 24
6. Proportion of patients with UAS7 = 0 at Week 24
7. Change from baseline in UCT at Week 24

Study C is considered positive when the primary endpoint (change from baseline in ISS7 at Week 24 in non-EU countries or change from baseline in UAS7 at Week 24 in EU and EU reference countries) achieves statistical significance.

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 (eg, 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.

VV-CLIN-0[illegible] 1.0

Duration of IMP exposure

Duration of IMP exposure is defined as last dose date – first dose date + 15 days (or +29 days for children < 30 kg), 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 (or less than 25 days for children < 30 kg) will be summarized.

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

VV-CLIN-0699992 1.0

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

The AEs will be analyzed in the following 3 categories:

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

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

The primary 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 day is missing, it will be imputed using 01 (except if the same month and year of 1st IMP, then the day of first IMP will be used). If month is missing, the AE start date will remain missing.

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 (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 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 (≥2% and ≥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 overview table, and common TEAEs (PT ≥2% 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 5.6)[a] and "Severe" ticked in Adverse Events eCRF page.
Any severe type of blepharitis	CMQ10497 based on HLT as "Lid, lash and lacrimal infections, irritations and inflammations" and "Severe" ticked in Adverse Events eCRF page.
Keratitis	CMQ10642 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, herpes ophthalmic, ophthalmic herpes simplex, corneal infection][a].
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)[b]	CMQ10641 (based on HLT = Eosinophilic disorders or PT = Eosinophil count increased) and AESI is "Yes".
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.

AE Grouping	Criteria
Significant ALT elevation	ALT >5 × ULN in participants with baseline ALT ≤2 × ULN; OR ALT >8 × ULN if baseline ALT >2 × ULN.
Symptomatic overdose with IMP	Symptomatic Overdose is answered Yes, with Overdose of 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 to 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, calcium, 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, nitrate, 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: Pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg) in a semi-supine or sitting position after 5 minutes, weight, respiratory rate (breaths per minute), temperature (degrees Celsius) and height (screening only)
- ECG variables: Heart rate, PR, QRS, QT, and QTc intervals after 10 minutes of rest in the supine position

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, vital signs and ECG 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.

VV-CLIN-0[illegible] 1.0

- 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 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).

4.8 OTHER ANALYSES

4.8.1 PK analyses

Pre-dose dupilumab concentrations in serum at Visit 2 (Day 1), dupilumab trough levels at Week 12, Week 24/EOT and post-treatment dupilumab concentrations in serum at Week 36 will be provided.

Concentrations of dupilumab (SAR231893; REGN668) in serum 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), one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three significant figures. For participants in the placebo group, concentration values are below the LLOQ will be taken into account with a concentration in serum 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)

On-treatment ADA incidence will also be derived in the same way except that only on-treatment measurements (measurements during the treatment epoch) are considered post first dose.

The following summary will be provided based on ADA population for the on-treatment period and during the study:

- 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

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

Impact of ADA on clinical efficacy endpoints

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

Association of ADA with clinical safety endpoints

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

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

Associations between ADA variables (eg, 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 IgE in serum. Total IgE will be measured using validated quantitative methods.

VV-CLIN-0699997 1.0

For those participants (with exception of adolescents and children) 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 and children) 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).

For those participants (with exception of adolescent and children) who consent to the optional skin biopsy (substudy), the sample will be taken from lesion and non-lesion skin using punch biopsy at Visit 2 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 +/- interquartile range) 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 and skin biopsy substudy will be addressed in a separate document.

4.9 INTERIM ANALYSES

No interim analysis is planned.

For Study C, 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 this database lock and will be considered as the final analyses in the Study C 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.

VV-CLIN-0699997 1.0

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AAS7:	angioedema activity score over 7 days
ADA:	anti-drug antibody
AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance, analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomic category
CDG:	customized drug grouping
CDLQI:	Children's Dermatology Life Qualtiy Index
CI:	confidence interval, confidence interval
CLcr:	creatinine clearance
CU-Q2oL:	chronic urticaria quality of life questionnaire
DLQI:	Dermatology Life Quality Index
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
eCRF:	electronic case report form
EOT:	end of treatment
EQ-5D-5L:	5-level EuroQol 5-dimensional questionnaire
EQ-5D-Y 5L:	EuroQol 5-dimensional questionnaire youth
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
HSS7:	weekly hives severity score
IMP:	investigational medicinal product
IRT:	interactive response technology
ITT:	intent-to-treat
LLT:	lower-level term
LS:	least squares, least squares
MCMC:	Markov Chain Monte Carlo
MedDRA:	medical dictionary for regulatory activities
MID:	minimal important difference
OCS:	oral corticosteroids
PCSA:	potentially clinically significant abnormality
PGIC:	Patient Global Impression of Change

VV-CLIN-0699992 1.0

PGIS:	Patient Global Impression of Severity
PK:	pharmacokinetic
PT:	preferred term
RNA:	ribonucleic acid
SAE:	serious adverse event
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
WOCF:	worst-observation carried forward

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This Statistical Analysis Plan (SAP) for study EFC16461 Study C is based on the protocol dated 17 March 2022 (amended protocol 5). This section summarizes major statistical changes in the protocol amendment(s) relevant to Study C.

The primary purpose of Amended protocol 5 was to conduct a Study C with a study population and design similar to the completed Study A, to meet Health Authority requirements to provide data from two adequate and well-controlled clinical trials to support filing of a marketing application.

Table 8 - Major statistical changes in protocol amendment(s)

Amendment Number	Date Approved	Rationale	Description of statistical changes
5	17-Mar-2022	Add Study C with similar design to Study A to meet Health Authority requirements.	Study C is added with similar design and patient population as Study A. Study C is also stratified in adults by presence of angioedema.

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.

VV-CLIN-0699987 1.0

Demographic variables are:

- Age in years (quantitative and qualitative variable: < 12, 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:** China, Japan; **Latin America:** Argentina; **Western Countries**: Canada, USA**,** France, Germany, Spain **East Europe:** Hungary),
- Territory (**North America:** Canada, USA**; European Union:** France, Germany, Spain, Hungary; **Rest of World:** China, Japan, Argentina),
- 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 history (Yes, Ongoing condition)

Angioedema (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 CSU (years)
- Time since first diagnosis of CSU (years) to be derived as
  (Year of randomization – Year of first diagnosis of CSU) + (month of randomization-month of first diagnosis of CSU)/12
- Presence of angioedema at baseline
  - Number of episodes in past 6 months
  - Time since last episode (months)
- Baseline ISS7 score (quantitative and qualitative variable: <13, ≥13)
- Baseline UAS7 score (quantitative and qualitative variable: <28, ≥28)
- Baseline weekly hives severity score (HSS7)
- Baseline angioedema activity score over 7 days (AAS7) for participants with angioedema
- Baseline urticaria control test (UCT)
- Baseline Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI)
- Baseline Patient Global Impression of Severity (PGIS)
- Frequency of alcohol drinking in the past 12 months (never, occasional, at least monthly, at least weekly, at least daily) and number of drinks on a typical day (1 or 2, >2)
- Baseline IgE (quantitative and qualitative variable: <100 vs ≥100)
- Baseline H1-AH dose (1-fold, 2-3-fold, 4-fold)

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 CSU 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.

VV-CLIN-0699997 1.0

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 CSU 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 CSU is calculated as:

$$\text{Year of CSU diagnosis} - \text{Year of birth}$$

BMI is calculated as:

$$\text{Weight in kg} / (\text{height}^2 \text{ in meters})$$

VV-CLIN-0699997 1.0

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

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

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:

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

Data handling conventions for other secondary endpoints

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

i. For the DLQI, handing of missing items is as follows: 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,
ii. If two or more questions are left unanswered, the questionnaire is not scored,
iii. If question 7 is answered ‘yes’, this is scored 3 even if in the same question one of the other boxes is ticked,
iv. If question 7 is answered ‘no’ or ‘not relevant’ but then either ‘a lot’ or ‘a little’ is ticked, this is scored 2 or 1,
v. 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:

i. 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,
ii. If two or more questions are left unanswered, the questionnaire is not scored,
iii. If two or more response options are ticked for one question, the response option with the highest score should be recorded.

For the CU-Q2oL total score, the raw total score will be converted to a 0 to 100 score for analysis using the following formula:

$$\text{CU-Q2oL total score} = (\text{raw score} - 23)*100/92$$

VV-CLIN-0699987 1.0

Daily e-diary weekly scores

For the daily efficacy endpoints (ISS, UAS, HSS, and AAS), the time period used to calculate the weekly score at each designated study day is summarized in Table 9. Randomization day is used as the reference day (Day 1).

Table 9 - Weekly efficacy assessments from daily e-diary

Analysis visit	Day range for calculating weekly score	Target day
Week 1	2-8	8
Week 2	9-15	15
Week 3	16-22	22
Week 4	23-29	29
Week 5	30-36	36
Week 6	37-43	43
Week 7	44-50	50
Week 8	51-57	57
Week 9	58-64	64
Week 10	65-71	71
Week 11	72-78	78
Week 12	79-85	85
Week 13	86-92	92
Week 14	93-99	99
Week 15	100-106	106
Week 16	107-113	113
Week 17	114-120	120
Week 18	121-127	127
Week 19	128-134	134
Week 20	135-141	141
Week 21	142-148	148
Week 22	149-155	155
Week 23	156-162	162
Week 24	163-169	169
Week 25	170-176	176
Week 26	177-183	183
Week 27	184-190	190
Week 28	191-197	197
Week 29	198-204	204
Week 30	205-211	211
Week 31	212-218	218
Week 32	219-225	225
Week 33	226-232	232
Week 34	233-239	239
Week 35	240-246	246
Week 36	247-253	253

VV-CLIN-0699987 1.0

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 10 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 10 - Time window for safety endpoints

Visit	Target Day	Time windows for						
		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	1^+
Week 28	197					183-210		
Week 32	225					211-238		
Visit 5 (Week 36)	253	>210	>210			>238	>210	

1^-: up to 1^{st} dose date/time; 1^+: after 1^{st} 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 11. 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 11 - Time window for efficacy variables

Visit	Target Day	Time windows for			
		UCT, DLQI/CDLQI, CU-Q2oL	PGIC	PGIS	EQ-5D-5L/EQ-5D-L, missed school/work days
Visit 1	-28 to -14			<-14	
Visit 2 (Week 0)	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	>126	>126	127-210
Visit 5 (Week 36)	253	>210			>210

1-: up to randomization and before 1st dose date/time; 1+: after randomization or 1st 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 12 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 12 - Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target Day	Serum dupilumab, ADA, Total IgE	Skin biopsy (substudy)	Basophil activation (substudy)
Visit 1	-28 to -14			
Visit 2 (Week 0)	1	<1-	<1-	<1-
Visit 3 (Week 12)	85	1+-126		1+-126
Visit 4 (Week 24)	169	127-210	>1+	>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.

VV-CLIN-0699997 1.0

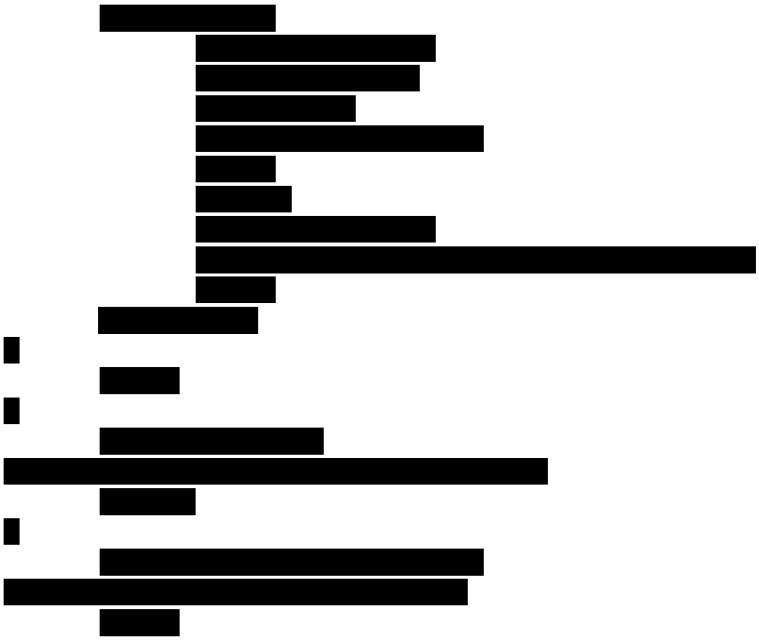
5.5 APPENDIX 5 SAMPLE SAS CODE

The multiple imputation and analysis model for the primary analysis approach 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 taken selected prohibited medications and/or rescue medications or have not discontinued study intervention due to lack of efficacy prior to Week 24.

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 intervention groups, region, angioedema status at baseline and baseline value of the response variable.

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.



[redacted]

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:

[redacted]

5.6 APPENDIX 6 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

Grouping	Preferred Term/ Medication Code	Preferred Term/ Medication
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
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. Carpenter JR, Roger JH, Kenward MG. Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and inference via Multiple Imputation. J Biopharm Stat. 2013;23:1352-71.

2. Van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012 Jul-Aug;15(5):708-15

Signature Page for VV-CLIN-0669600 v1.0
efc16461c-16-1-9-sap

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]