STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable**
Protocol number:	**EFC16459**
Compound number (INN/Trademark):	**SAR231893/REGN668 dupilumab/Dupixent**
Study phase:	**Phase 3**
Short title:	**Study of dupilumab for the treatment of patients with prurigo nodularis, inadequately controlled on topical prescription therapies or when those therapies are not advisable LIBERTY-PN PRIME**
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Statistical project leader:	[redacted]
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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study EFC16459 is based on Protocol Amendment 1 dated 20-May-2020 and a health authority's feedback on Protocol Amendment 2 dated 14-Apr-2021, after which, the Sponsor made the decision to complete the study as originally planned instead of resizing the study based on the results of EFC16460, and on Protocol Amendment 3 dated on 21-Oct-2021. This section summarizes major changes to the statistical analysis features in the SAP. All changes to the statistical analysis features from the original protocol to Amendment 3 are described in Appendix 2.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	04-Feb-2021	Not Applicable	Original version
2.0	20-Apr-2021	In the case of an early primary database lock prior to the last enrolled participant reaching the end of treatment (EOT), analyses for the endpoints up to Week 12 use ITT-Week-12 population and beyond Week 12 use the ITT-Week-24 population.	EFC16459 and EFC16460 are 2 pivotal Phase 3 studies of identical design with EFC16460 data that will be available prior to EFC16459 data. Using data from EFC16460, the sample size calculation will be revisited aiming for a statistical power of at least 90% at an alpha level of 0.05 for the primary and key secondary endpoints in the respective analysis populations and the database lock will be performed when the number of participants based on this revised sample size are expected to have reached their Week 24 visit. This revised estimation may result in database lock occurring earlier than last participant reaching the end of treatment. At a minimum, this will include at least 135 participants having Week 24 pertinent data included at the time of database lock. Based on the timing of the availability of the EFC16460 results, and to ensure a minimum of 135 participants have the opportunity to reach the Week 24 endpoint, the randomization cut-off dates have been assessed as 22 March 2021 for Week 24 and 14 June 2021 for Week 12.
		Add ITT-Week-12 and ITT-Week-24 populations	Same as above.
		In the case of an early primary database lock prior to the last enrolled participant reaching EOT, the additional exposure-adjusted adverse event incidence rate tables will provide the number of patients with at least 1 event per 100 patient-years.	Same as above
		Remove Appendix 7 in Section 5.7	A separate medication/procedure adjudication document for details

SAP Version	Approval Date	Changes	Rationale
3.0	08-Aug-2021	Remove all modifications specific to early database lock previously made in SAP version 2 to align with Protocol Amendment 2 including discussion on the criteria used to perform early database lock and reference to the ITT-Week 12 and ITT-Week 24 populations.	Based on a health authority's feedback on Protocol Amendment 2, the Sponsor made the decision to complete the study as originally planned instead of resizing the study based on the results of EFC16460
		Retain additional exposure-adjusted adverse event incidence rate tables that will provide the number of patients with at least 1 event per 100 patient-years previously made in SAP version 2.	As requested by a health authority to include exposure-adjusted incidence rate and patient years in the summaries for TEAEs and AESIs.
		Retain "Keratitis FDA" to other AE groupings previously made in SAP version 2	For consistency with other dupilumab studies
		Add objective "To demonstrate efficacy of dupilumab on both itch as well as skin lesions within the same participant" and multicomponent endpoint (Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24) as a key secondary endpoint for the US and US reference countries hierarchy.	To add this multicomponent endpoint as another measure of treatment success based on feedback from a health authority.
		Add supplementary analysis (tipping point analyses) for primary and key secondary endpoints	This additional supplementary analysis was recommended by a health authority to assess whether the estimate, and the inference thereof, was robust to departure from the strategies used in primary analysis for handling intercurrent events and missing data.
		Add subgroup analyses for key secondary endpoints.	To evaluate whether the treatment effect is consistent across pre-specified sub-groups on the key secondary endpoints in addition to the primary endpoint.
		Add subgroup analyses for participants who have been impacted (or not) by COVID-19	To address a health authority's request to assess the impact of the treatment effect by COVID-19.
		Modify hierarchical order for multiplicity procedure for US and US reference countries	To include the multicomponent endpoint in the hierarchy to address the health authority's feedback requesting assessment of this endpoint as another measure of treatment success.
		Add as-observed plus multiple imputation supplementary analysis for the secondary endpoint (percent change from baseline in WI-NRS at Week 24)	To explore the robustness of the estimate, and the inference thereof, with a different strategy for handling intercurrent events and missing data

SAP Version	Approval Date	Changes	Rationale
		Remove “selected” in the text including “selected prohibited and/or rescue medication”	Since a participant who takes any protocol specified prohibited medications/procedures and/or rescue medications is considered as a non-responder after medical adjudication/confirmation conducted in a blinded fashion, use of the word "selected" may be confusing.
		Add Appendix 7 back in Section 5.7	Add this medication/procedure adjudication algorithm back as it was inadvertently removed in SAP Version 2.
4.0	11-Nov-2021	To promote the “proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 24 as primary endpoint and to move the “proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 12” to a secondary endpoint	Based on the data from EFC16460, the treatment effect of dupilumab continued to improve over time through Week 24. Therefore, the Sponsor proposes to assess the proportion of participants with improvement (reduction) in WI-NRS by ≥4 at Week 24, which represents the effect more accurately and synchronizes the primary itch assessment with the primary lesion assessment. This is consistent with primary endpoint change in Protocol Amendment 3.
		To update hierarchical order in Section 4.6 by removing “Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 12”, “Proportion of participants with IGA PN-S 0 or 1 score at Week 12” and “Change from baseline in Sleep-NRS to Week 24”	Updated power calculations performed using data from study EFC16460 showed low power for demonstrating statistical significance for each of these three endpoints. Accordingly, the hierarchical order was revised to remove these endpoints.

The first participant was randomized on 2020-01-02.

1 INTRODUCTION

1.1 STUDY DESIGN

This study is a multi-center, 24-week treatment, parallel group, double-blind, randomized, placebo-controlled study to evaluate the use of dupilumab in participants with prurigo nodularis (PN) inadequately controlled on topical prescription therapies or when those therapies are not advisable. The study will assess the effect of dupilumab on itch improvement as well as its effect on PN lesions, on participants' health-related quality of life (HRQoL), anxiety and depression, sleep quality, skin pain, and overall health status.

After 2-4 weeks of screening, participants will be centrally randomized using a permuted block randomization schedule via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 1:1 randomization ratio to dupilumab 300 mg q2w or matching placebo. Randomization will be stratified by documented history of atopy (atopic or non-atopic), stable use of topical corticosteroids (TCS)/topical calcineurin inhibitors (TCI) (yes or no), and country/territory code.

A total of approximately 150 participants will be randomized to two treatment arms (75 participants/arm). The number of participants with active mild AD upon study entry will represent up to 10% of the atopic participants. Both the atopic and the non-atopic PN populations will each be capped at 60% of the total enrolled population.

The study duration consists of the following periods:

- Screening period (2-4 weeks)
- Randomized IMP intervention period (24 weeks)
- Follow-up period (12 weeks).

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of dupilumab on itch response in participants with PN, inadequately controlled on topical prescription therapies or when those therapies are not advisable.	• Proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 24.
Secondary	
• To demonstrate the efficacy of dupilumab on additional itch endpoints in participants with PN, inadequately controlled on topical prescription therapies or when those therapies are not advisable.	• Time to onset of effect on pruritus as measured by proportion of participants with an improvement (reduction) in WI-NRS by ≥4 from baseline during the 24-week treatment period. • Change from baseline in WI-NRS at Week 24. • Change from baseline in WI-NRS at Week 12.

Objectives	Endpoints
	• Percent change from baseline in WI-NRS at Week 24. • Percent change from baseline in WI-NRS at Week 12. • Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 12 • Percent change from baseline in WI-NRS at Week 4. • Percent change from baseline in WI-NRS at Week 2. • Percent change from baseline in WI-NRS over time until Week 24. • Proportion of participants with WI-NRS reduction ≥4 at Week 4. • Proportion of participants with WI-NRS reduction ≥4 over time until Week 24[a]. • Onset of action in change from baseline in WI-NRS (first p <0.05 difference from placebo in the daily WI-NRS that remains significant at subsequent measurements) until Week 12[b].
• To demonstrate efficacy of dupilumab on skin lesions of PN.	• Proportion of participants with Investigator's Global Assessment 0 or 1 score for PN-Stage (IGA PN-S) at Week 24 **[Key secondary endpoint]**. • Proportion of participants with IGA PN-S 0 or 1 score at Week 12. • Proportion of participants with IGA PN-S 0 or 1 score at Week 8[c]. • Proportion of participants with IGA PN-S 0 or 1 score at Week 4[c]. • Change from baseline in IGA PN-S score at Week 24. • Change from baseline in IGA PN-S score at Week 12. • Change from baseline in IGA PN-S score at Week 8. • Change from baseline in IGA PN-S score at Week 4. • Proportion of participants with Investigator's Global Assessment 0 or 1 score for PN-Activity (IGA PN-A) at Week 24. • Proportion of participants with IGA PN-A 0 or 1 score at Week 12. • Proportion of participants with IGA PN-A 0 or 1 score at Week 8. • Proportion of participants with IGA PN-A 0 or 1 score at Week 4.
• To demonstrate efficacy of dupilumab on both itch as well as skin lesions within the same participant	• Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24 **(key secondary endpoint** for US and US reference countries only)
• To demonstrate the improvement in health-related quality of life (HRQoL).	• Change from baseline in HRQoL, as measured by Dermatology Life Quality Index (DLQI) to Week 24. • Change from baseline in HRQoL, as measured by DLQI to Week 12.
• To evaluate safety outcome measures.	• Percentage of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) from baseline through Week 24.

Objectives	Endpoints
• To evaluate immunogenicity of dupilumab.	• Incidence of treatment-emergent antidrug antibodies (ADA) against dupilumab over time.
Tertiary/exploratory	
• To demonstrate a reduction in the use of rescue medication and systemic immunosuppressant	• Use of high potency or superpotent TCS rescue medication through Week 24 • Use of systemic immunosuppressants through Week 24, constituting treatment failure
• To evaluate exploratory outcome measures	• Change from baseline in Hospital Anxiety and Depression Scale (HADS) total score to Week 24. • Change from baseline in EQ5D-5L to Week 24. • Change from baseline in skin Pain numeric rating scale (NRS) to Week 4, Week 8, Week 12, and Week 24, respectively. • Change from baseline in Sleep NRS to Week 4, Week 8, Week 12, and Week 24, respectively. • Missed school/work days through Week 24. • Incidence of skin-infection TEAEs (excluding herpetic infections) through Week 24.
• To evaluate the efficacy of dupilumab on skin lesions using a modified PAS 5-item questionnaire	• Proportion of participants who achieve ≥75% healed lesions from Prurigo Activity Score (PAS) at Week 4, Week 8, Week 12, and Week 24, respectively. • Change from baseline in exact number of lesions in representative area (as determined from PAS) at Week 4, Week 8, Week 12, and Week 24, respectively.
• To evaluate the efficacy of dupilumab on other PN endpoints	• Change from baseline in Participant Global Impression of Severity (PGIS) of PN to Week 4, Week 8, Week 12, and Week 24, respectively. • Participant Global Impression of Change (PGIC) of PN at Week 4, Week 8, Week 12, and Week 24, respectively.
PK	
• To evaluate pharmacokinetic (PK) and pharmacodynamic (PD) outcome measures	• Serum functional dupilumab concentrations and PK profile. • Pharmacodynamic response for selected biomarkers (total IgE).

a The early onset for significant change in the proportion of responders with WI-NRS reduction ≥4 between dupilumab and placebo will be claimed at Week xx if the p-value for Week xx is <0.05 and the remaining timepoints also have nominal p-value ≤0.05 until Week 12.

b The early onset for significant change in WI-NRS from baseline between dupilumab and placebo will be claimed at Week xx if the p-value for Week xx is <0.05 and the remaining timepoints also have nominal p-value ≤0.05 until Week 12.

c The early onset for reaching IGA PN-S (0,1) between dupilumab and placebo will be claimed at Week xx if the p-value for Week xx is ≤0.05 and the remaining timepoints also have nominal p-value ≤0.05 until Week 12.

1.2.1 Estimands

The primary estimands 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) strategy and missing data handling**	**Population-level summary**
Primary objective: To demonstrate the efficacy of dupilumab on itch response in participants with PN, inadequately controlled on topical prescription therapies or when those therapies are not advisable.				
Primary endpoint	Proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI NRS) by ≥4 from baseline to Week 24	ITT	The intercurrent events will be handled as follows: • Discontinuation of study treatment before Week 24: Off-study treatment data up to Week 24 will be included in the analysis (treatment policy strategy). • Taking the prohibited medications/procedures and/or rescue medications[b] prior to Week 24: 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: Participants will be considered as non-responders	CMH test adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region (countries combined), and baseline antidepressant use (yes or no).
Secondary objective: To demonstrate the efficacy of dupilumab on additional itch endpoints in participants with PN, inadequately controlled on topical prescription therapies or when those therapies are not advisable.				
Secondary endpoint	Time to onset of effect on pruritus as measured by proportion of participants with an improvement (reduction) in WI-NRS by ≥4 from baseline during the 24-week treatment period	ITT	The intercurrent events will be handled as follows: • Discontinuation of study treatment before Week 24: Off-study treatment data up to Week 24 will be included in the analysis (treatment policy strategy). • Taking the prohibited medications/procedures 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 WI-NRS assessment.	This time-to-event endpoint will be analyzed using the Cox proportional hazards model, including intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region (countries combined), and baseline antidepressant use (yes or no). The hazards ratio, its 95% confidence interval and p-value will be reported. Kaplan-Meier curves will be also provided[b]

Endpoint Category	Estimands			
	Endpoint(s)[a]	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary**
Secondary endpoint	Change from baseline in WI-NRS at Week 24	• ITT	The intercurrent events will be handled as follows: • Discontinuing the study treatment: all data collected following schedule after treatment discontinuation will be used in the analysis (treatment policy strategy). • Taking the prohibited medications/procedures 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 will be used to impute the missing endpoint value) (hypothetical strategy) In addition, the missing data imputation rules are as follows: • After discontinuation of the study treatment due to lack of efficacy prior to Week 24: WOCF approach will be used to impute missing data if needed[2]. • After discontinuation of the study treatment 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 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, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region (countries combined), baseline antidepressant use (yes or no), and relevant baseline measurement as covariates is used. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule.

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 Prohibited medications and/or rescue medications are listed in Table 5.

2 SAMPLE SIZE DETERMINATION

The primary endpoint is the proportion of participants with WI-NRS reduction of ≥4 from baseline to Week 24. By assuming the response rate is [redacted] in the placebo and dupilumab arms, respectively, 56 participants/arm will provide 90% power to detect the difference of[redacted] between dupilumab and placebo with Fisher exact test at 2-sided level of 0.05. Assuming 15% drop out during treatment, the target is to randomize 75 participants/arm with a cap of up to 10% of participants in the atopic population having active mild AD.

The assumptions were based on the effect of dupilumab versus placebo in WI-NRS reduction ≥4 at Week 16 observed in participants with moderate to severe AD as seen in studies of AD-1334 (Solo1) and AD 1416 (Solo2).

Approximately 150 participants will be randomized to dupilumab or placebo in a 1:1 ratio with stratification factors of documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), and country/territory code. Both the atopic and the non-atopic PN population will be capped at 60% of the total enrolled population.

The sample size calculation was performed using SAS 9.4 power procedure.

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	The randomized population includes all participants with a treatment kit number allocated and recorded in the interactive response technology (IRT) database, and regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.
Intent-to-treat (ITT)	All randomized participants analyzed according to the intervention group allocated by randomization regardless if treatment kit is used or not
Efficacy	The ITT population
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who accidentally receive different treatment from the planned, the actual intervention allocation for as-treated analysis will be the dupilumab group. The 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 treatment. 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 treatment. Participants will be analyzed according to the intervention actually received.

ADA: antidrug antibody; ICF: informed consent form; ITT: intent to treat; PD: pharmacodynamics: PK: pharmacokinetic.

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

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

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention (placebo and dupilumab) during the study, the intervention group for as-treated analysis will be the dupilumab group.

Regarding the COVID-19 pandemic, additional summaries by COVID-19 subgroups (ie, impacted by the COVID-19 pandemic and NOT impacted by the COVID-19 pandemic) will be provided to assess the impact of COVID-19 on treatment effect. 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

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 before randomization and prior to the first dose of study medication unless below eDiary data (WI-NRS, skin Pain-NRS and Sleep-NRS) score or otherwise specified.

The baseline for weekly average WI-NRS (skin Pain-NRS and Sleep-NRS) score is defined as the average of daily non-missing scores obtained during the 7 days prior to randomization.

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 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 discontinued study treatment prior to Week 12 by main reason for permanent intervention discontinuation including due to COVID-19
- Participants who did not complete the study treatment period as per protocol and discontinued study treatment prior to Week 24 by main reason for permanent intervention discontinuation including due to COVID-19
- Participants who completed the study period as per protocol
- Participants who did not complete the study period as per protocol and discontinued study by main reason for study discontinuation including due to COVID-19.
- Vital status at last study contact

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

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

Protocol deviations

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

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint(s)

The primary endpoint for this study is the proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 24.

WI-NRS is a patient-reported outcome (PRO) comprised of a single item rated on a scale from 0 (“No itch”) to 10 (“Worst imaginable itch”). Participants are asked to rate the intensity of their worst pruritus (itch) over the past 24 hours using this scale.

The weekly average WI-NRS score at each week, which is defined as the average of daily non-missing scores within the week window of each week (see Section 5.4), will be used for analyses.

For efficacy analysis, Table 5 presents the prohibited and rescue medications/procedures which will be considered as intercurrent events if the last column indicates as "Yes" and therefore be handled in the estimands for endpoints defined in Table 3.

Table 5 - Prohibited medications/procedures and rescue medications that impact efficacy

Medication/procedure	Comment	Data to be set as non-responder after taking medication in the main statistical analysis (Yes/No)[a]/Selection criteria
Prohibited medications/procedures		
Systemic immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, hydroxychloroquine, dapsone, sulfasalazine, colchine, etc)	IMP to be discontinued	Yes (CDG[b] Immunosuppressant drugs Narrow and SDG[b]Corticosteroids Narrow)
Other monoclonal antibodies (that are biological response modifiers).	IMP to be discontinued	Yes (SDG[b] SDGMonoclonal antibodies Narrow)
Phototherapy, including tanning beds.	IMP to be discontinued	Yes (CMQ[b] HLT Phototherapies, CMQ[b] Tanning_single PT)
Naltrexone or other opioid antagonist	IMP to be discontinued	Yes (SDG[b] Analgesia producing opioids NARROW)
Gabapentin, pregabalin, and thalidomide	IMP to be discontinued	Yes (CDG[b] Gabapentin mono and multi ingredients, Pregabalin mono and multi ingredients, or Thalidomide mono and multi ingredients)
Paroxetine, fluvoxamine or other SSRIs.	No IMP discontinuation, see requirement in the footnote	Yes[c,d] (CDG[b] N06AB selective serotonin reuptake inhibitors)
SNRIs.	No IMP discontinuation, see requirement in the footnote	Yes[c, d] (CDG[b] serotonin and norepinephrine reuptake inhibitors)
Amitriptyline or other tricyclic or tetracyclic antidepressants	No IMP discontinuation, see requirement in the footnote	Yes[c, d] (CDG[b] N06AA non-selective monoamine reuptake inhibitors)
Intralesional corticosteroid injections and cryotherapy.	No IMP discontinuation	Yes[d] (CMQ[b] Injection_single pt, cryotherapy or skin cryotherapy PT)
Sedating antihistamine	No IMP discontinuation	Yes[d, e] (CDG[b] sedating antihistamines)
Non-sedating antihistamine if used specifically for the treatment of itch secondary to AD or PN	No IMP discontinuation	Yes[d, e] (CDG[b] non-sedating antihistamines)

Medication/procedure	Comment	Data to be set as non-responder after taking medication in the main statistical analysis (Yes/No)[a]/Selection criteria
Rescue medications		
Dermatological preparations of high potency or superpotent TCS and TCI	No IMP discontinuation	Yes[d] (CDG[b] calcineurin inhibitors and corticosteroids narrow, Ticked 'RESCUE THERAPY' in CRF page)

a When yes, 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.
b CDG=company drug groupings, CMQ=company MedDRA query, SDG= Standardized drug groupings.
c Only if the antidepressant is initiated during the study or its dose is increased from baseline provided that medication was taken at least 3 months prior to screening.
d As per medical adjudication, see Section 5.7 for details.
e Only if the medication is initiated at Week 12 or Week 24, or the dose is increased from Week 11 to Week 12 or from Week 23 to Week 24.

Blinded review of prohibited/rescue treatment (medication or procedure) based on Table 5 and a pre-specified algorithm (Section 5.7) will be implemented before database locks by considering the type of medication or procedure, indication, timing, frequency and the potential impact of the use of the prohibited medications/procedures and rescue medications.

4.3.2 Main analytical approach

The primary estimand for the primary endpoint is the treatment policy/composite approach as defined in Table 3.

The primary analysis population for the efficacy endpoints will be the ITT population.

The following null hypothesis H0 and alternative hypothesis H1 will be tested for dupilumab against placebo:

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

The primary analysis will be conducted by using Cochran–Mantel–Haenszel test (CMH) test adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, and baseline anti-depressant use (yes or no). Comparisons of the response rates between dupilumab and placebo will be derived. In addition, odds ratio and response rate difference as well as the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

As defined in Table 3 for participants discontinuing the study treatment before Week 24, their off-study treatment values measured up to Week 24 will be included in the analysis. Participants taking the prohibited medications/procedures and/or rescue medications (see Table 5) prior to Week 24 or having missing data at Week 24 will be considered non-responders.

4.3.3 Sensitivity analysis

For the primary estimand for the primary endpoint, no sensitivity analysis will be performed. However, three supplementary analyses will be performed as described in the section below.

4.3.4 Supplementary analyses

The following supplementary analyses will be performed:

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

The data collected after taking all prohibited medications and/or rescue medications will be included in the supplementary analysis to evaluate the robustness of the primary analysis results with respect to the method of handling data while taking the prohibited medications (eg, treatment policy strategy). In addition, for participants discontinuing the study treatment before Week 24, their off-study treatment values measured up to Week 24 will be included in the analysis. The participants having missing data at Week 24 regardless of reason(s) will be considered non-responders at that timepoint.

Hybrid method analysis (the worst-observation carried forward (WOCF) and multiple imputation (MI))

In the primary analysis of change from baseline in WI-NRS (continuous variable) at Week 24, the hybrid method of the WOCF and MI will be used (see Section 4.4.2). Similar to the continuous variable, the same imputation method will be used in the analysis of the proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24, which is consistent for the intercurrent event strategy and missing data handling in the binary variables and continuous variable. That is, after the imputation of continuous WI-NRS data at Week 24 using the hybrid method of the WOCF and MI (see Section 4.4.2), responders will be defined as patients with improvement in WI-NRS by ≥4 from baseline to Week 24 in each of the imputed datasets with about 40 imputations, and then the CMH test adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, and baseline anti-depressant use (yes or no) will be used. Statistical inference obtained from all imputed data will be combined using Rubin's rule.

Tipping point analysis

The intercurrent events will be handled as follows:

- Discontinuation of study treatment before Week 24: Off-study treatment data up to Week 24 will be included in the analysis (treatment policy strategy).
- Taking the prohibited medications/procedures and/or rescue medications prior to Week 24: Data after the intercurrent events will be censored and then imputed with the below tipping point method

In addition, the missing data imputation rules are as follows:

- Having missing data at Week 24: Data will be imputed with the following tipping point method.

Tipping point method:

- A sequence of analyses will be performed with the adjustment to artificially decrease the response rate in the dupilumab group and increase the response rate in the placebo group with a fixed and definite set of values for data imputation.
- For each combination of increasing response rate in placebo and decreasing response rate in dupilumab, multiple imputed datasets will be generated and analyzed using CMH test. The results obtained from multiple imputed datasets will be combined to generate statistical inference, ie, p-value and treatment difference between 2 treatment groups.
- A "tipping point" will be identified while the result is no longer statistically significant (ie, p-value >0.05).

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 (categories with fewer than 5 participants may be combined with other categories):

- Age group (<65, ≥65 years)
- Gender (Male, Female)
- Region
- Territory
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, Others)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline weight (<60, ≥60- <90, ≥90 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m^2)
- Participants without a current diagnosis of AD
- History of atopy (atopic or non-atopic)
- Stable use of TCS/TCI (yes or no)
- Antidepressant use (yes or no) at baseline
- Baseline IGA PN-S moderate versus severe (3 versus. 4)
- Participants who have not been impacted by COVID-19 vs impacted by COVID-19 (for participants who have been impacted by the COVID-19, the efficacy data will be descriptive only if the number of participants is not enough to perform statistical tests. 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.)

To test the interaction between intervention and subgroup factor, a logistic regression model incorporating subgroup-by-treatment interaction will be built for each subgroup factor except the

subgroup of participants without a current diagnosis of AD (very few AD participants will be excluded). The model will include all the covariates in the main statistical model plus the subgroup variable and the subgroup-by-treatment interaction. A p-value for the test of interaction will be provided.

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

4.4 SECONDARY ENDPOINT(S) ANALYSIS

The weekly average skin Pain-NRS or Sleep-NRS score at each week, which is defined as the average of non-missing daily scores within the week window of each week (see Section 5.4), will be used for analyses.

4.4.1 Key/Confirmatory secondary endpoint(s)

4.4.1.1 Definition of endpoint(s)

The key secondary endpoint is:

- Proportion of participants with IGA PN-S 0 or 1 score at Week 24.

In addition, for US and US reference countries only, there is another key secondary endpoint:

- Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24.

Investigator's global assessment for prurigo nodularis (IGA PN)

The IGA PN is a clinician-reported outcome (ClinRO) that allows clinicians to assess the activity of PN (IGA PN-A) using a 5-point scale from 0 (clear) to 4 (severe); and the stage of the disease (IGA PN-S) using a 5-point scale from 0 (clear) to 4 (severe).

4.4.1.2 Main analytical approach

For the key secondary efficacy endpoints, the analysis will be conducted by using CMH test adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, and baseline anti-depressant use (yes or no). The same estimand, ie, intercurrent event strategy and missing data handling method, as the primary endpoint is used.

The same supplementary and subgroup analyses used for the primary endpoint will also be performed for the key secondary efficacy endpoints.

4.4.2 Supportive secondary endpoint(s)

The other secondary endpoints are as follows:

- Proportion of participants with WI-NRS reduction ≥4 over time until Week 24.
- Proportion of participants with WI-NRS reduction ≥4 at Week 12
- Proportion of participants with WI-NRS reduction ≥4 at Week 4
- Proportion of participants with IGA PN-S 0 or 1 score at Week 12
- Proportion of participants with IGA PN-S 0 or 1 score at Week 8
- Proportion of participants with IGA PN-S 0 or 1 score at Week 4
- Proportion of participants with IGA PN-A 0 or 1 score at Week 24
- Proportion of participants with IGA PN-A 0 or 1 score at Week 12
- Proportion of participants with IGA PN-A 0 or 1 score at Week 8
- Proportion of participants with IGA PN-A 0 or 1 score at Week 4
- Time to onset of effect on pruritus as measured by proportion of participants with an improvement (reduction) in WI-NRS by ≥4 from baseline during the 24-week treatment period
- Change from baseline in WI-NRS at Week 24
- Change from baseline in WI-NRS at Week 12
- Percent change from baseline in WI-NRS at Week 24
- Percent change from baseline in WI-NRS at Week 12
- Percent change from baseline in WI-NRS at Week 4
- Percent change from baseline in WI-NRS at Week 2
- Percent change from baseline in WI-NRS over time until Week 24.
- Onset of action in change from baseline in WI-NRS (first $p < 0.05$ difference from placebo in the daily WI-NRS that remains significant at subsequent measurements) until Week 12
- Change from baseline in IGA PN-S score at Week 24
- Change from baseline in IGA PN-S score at Week 12
- Change from baseline in IGA PN-S score at Week 8
- Change from baseline in IGA PN-S score at Week 4
- Change from baseline in HRQoL, as measured by Dermatology Life Quality Index (DLQI) to Week 24
- Change from baseline in HRQoL, as measured by Dermatology Life Quality Index (DLQI) to Week 12.

Dermatology life quality index (DLQI)

The DLQI is a PRO developed to measure dermatology-specific HRQoL in adult participants. The instrument comprises 10 items assessing the impact of skin disease on participants' HRQoL over the previous week. The items cover symptoms, leisure activities, work/school or holiday time, personal relationships including intimate, the side effects of treatment, and emotional reactions to having a skin disease. It is a validated questionnaire used in clinical practice and clinical trials. Response scale is a 4-point Likert scale (0 = "not at all" and 3 = "very much") for nine items. The remaining one item about work/studying asks whether work/study has been prevented and then (if "No") to what degree the skin condition has been a problem at work/study; the item is rated on a 3-point Likert scale ("Not at all" to "A lot"). Overall scoring ranges from 0 to 30, with a high score indicative of a poor HRQoL.

Time-to-event secondary efficacy endpoint

Time to first onset of effect on pruritus defined as an improvement (reduction) in WI-NRS by ≥4 from baseline during the 24-week treatment period will be analyzed using the Cox proportional hazards model, including treatment, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, and baseline anti-depressant use (yes or no). The hazards ratio, its 95% confidence interval and p-value will be reported. Kaplan-Meier curves will be also provided.

For time to first WI-NRS response (WI-NRS by ≥4 from baseline), participants who receive the prohibited medications and/or rescue medications (see Table 5), data prior to start of the medications will be used, but after medication start, the participants' data will not be used and they will be censored at Week 24 (ie, Day 172). For other participants, all available data up to Week 24 (ie, Day 172) including those collected during the off-treatment period will be used. Participants without events will be censored at Day 172 or their last WI-NRS assessment date if discontinued from the study, whichever is earlier.

Secondary efficacy endpoints that measure binary responses

Secondary efficacy endpoints that measure binary responses will be analyzed in the same fashion as the primary endpoint using primary statistical model.

Continuous secondary efficacy endpoints

The primary estimand for continuous secondary efficacy endpoints is defined in Table 3 and will be analyzed using an analysis of covariance (ANCOVA) model with intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region (countries combined), baseline antidepressant use (yes or no), and relevant baseline measurement as covariate, with intercurrent event strategy and missing data handling as defined as in Table 3. Specifically, data of participants taking the prohibited medications/procedures and/or rescue medications will be set to missing after the medication usage, and the 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 baseline will be used to impute). Participants who discontinue the treatment prematurely are encouraged to follow the planned clinical visits and in those participants who did not take the prohibited medications/procedures

and/or rescue medications, all data collected after treatment discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts have been tried to collect the data after treatment discontinuation. For participants who discontinue 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 data if needed. For participants who discontinued not due to lack of efficacy, a multiple imputation (MI) approach will be used to impute missing endpoint value, and this MI method will use all participants excluding participants who have taken the prohibited medications/procedures and/or rescue medications prior to timepoint of endpoint of interest and excluding participants who discontinue due to lack of efficacy.

Each of the imputed complete data will be analyzed by fitting an ANCOVA model as described above. The imputation number will be about 40. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) will be provided. In addition, difference of the dupilumab group against placebo in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

See Section 5.5 for the sample SAS code for the imputation and the analysis.

For the endpoint of percent change from baseline in WI-NRS at week 24, we will also perform an as-observed plus multiple imputation supplementary analysis as described below.

The data collected after taking all prohibited medications and/or rescue medications will be included in the supplementary analysis to evaluate the robustness of the primary analysis results with respect to the method of handling data while taking the prohibited medications (eg, treatment policy strategy). In addition, for participants discontinuing the study treatment before Week 24, their off-study treatment values measured up to Week 24 will be included in the analysis. For participants having missing data at Week 24 regardless of reason(s), a multiple imputation (MI) approach will be used to impute the missing endpoint value.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

The exploratory endpoints are as follows:

- Use of high potency or superpotent TCS rescue medication through Week 24
- Use of systemic immunosuppressant through Week 24, constituting treatment failure
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) total score to Week 24
- Change from baseline in EQ-5D-5L Single Index score to Week 24
- Change from baseline in EQ-5D visual analog scale (VAS)to Week 24
- Change from baseline in skin Pain-NRS to Week 4, Week 8, Week 12, and Week 24, respectively

- Change from baseline in Sleep-NRS to Week 4, Week 8, Week 12, and Week 24, respectively
- Missed school/work days through Week 24
- Incidence of skin-infection TEAEs (excluding herpetic infections) through Week 24
- Proportion of participants who achieve ≥75% healed lesions from PAS at Week 4, Week 8, Week 12, and Week 24, respectively
- Change from baseline in exact number of lesions in representative area (as determined from PAS) at Week 4, Week 8, Week 12, and Week 24, respectively
- Change from baseline in Participant Global Impression of Severity (PGIS) of PN to Week 4, Week 8, Week 12, and Week 24 respectively
- Proportion of participants with PGIS score of "none" at Week 4, Week 8, Week 12, and Week 24 respectively
- Proportion of participants with PGIS score of "none" or "mild" at Week 4, Week 8, Week 12, and Week 24 respectively
- Participant Global Impression of Change (PGIC) of PN at Week 4, Week 8, Week 12, and Week 24, respectively
- Proportion of participants with PGIC score of "very much better" at Week 4, Week 8, Week 12, and Week 24 respectively
- Proportion of participants with PGIC score of "very much better" or "moderately better" at Week 4, Week 8, Week 12, and Week 24 respectively.

Hospital anxiety and depression scale (HADS)

The HADS is a PRO instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a participant's emotional state. The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales:

- 0 to 7: normal
- 8 to 10: borderline abnormal (borderline case)
- 11 to 21: abnormal.

Euroqol 5 dimensions questionnaire (EQ-5D)

The Euroqol-5 dimensions (EQ-5D) is a standardized PRO measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analog scale (VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of perceived problems: “no problem”, “slight problems”, “moderate problems”, “severe problems” and “inability to do the activity”. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent’s health state. The EQ VAS records the respondent’s self-rated health on a vertical VAS where the endpoints are labeled “best imaginable health state (100)” and “worst imaginable health state (0)”. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

Skin Pain and sleep numeric rating scales (skin Pain-NRS, Sleep-NRS)

Participants will be asked to rate their worst skin pain in the past 24 hours using a 0 to 10 NRS, with 0 = No pain to 10 = Worst pain possible.

In addition, participants will be asked to rate their sleep quality on their past night upon awakening, using a 0 to 10 NRS, with 0 = Worst possible sleep and 10 = Best possible sleep.

Participants will complete the skin pain NRS and sleep quality NRS once a day.

Prurigo activity score (PAS)

The PAS is a clinician-reported outcome (ClinRO) measurement. The original PAS questionnaire Version 0.9 consists of 7 items, developed by expert clinicians in PN.

A 5-item simplified version of the PAS will be used in the current study. Item 4 (exact number of pruriginous lesions in representative area) and Item 5b (percentage of healed prurigo lesions in all pruriginous lesions) will be used for analyses. In addition, Item 2 (number of prurigo lesions) may be used for analysis too.

Participant Global Impression of Change of disease (PGIC) and Participant Global Impression of Severity (PGIS)

The PGIC is a one-item questionnaire that asks participants to provide the overall self-assessment of change in their PN overall on a 7-point scale, compared to just before participant started taking the study injection. Response choices are: 0 = “Very much better”, 1 = “Moderately better”, 2 = “A little better”, 3 = “No change”, 4 = “A little worse”, 5 = “Moderately worse”, 6 = “Very much worse”.

The PGIS is a one-item questionnaire that asks participants to provide the overall self-assessment of their disease severity on a 4-point scale for the past week. Response choices are: 1 = “none”, 2 = “Mild”, 3 = “Moderate”, 4 = “Severe”.

Missed school/work days

Participants who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment.

Photography substudy

Participants in selected sites who decide to participate in this substudy need to provide separate consent. One or several lesions will be photographed at baseline. The same lesions will be photographed at subsequent visits to evaluate their progression.

4.5.2 Main analytical approach

Exploratory efficacy endpoints will be analyzed using the same methodology as secondary efficacy for similar data (continuous or proportion) except the endpoints below.

- Use of high potency or superpotent TCS rescue medication through Week 24
- Use of systemic immunosuppressant through Week 24, constituting treatment failure
- Missed school/work days through Week 24
- Incidence of skin-infection TEAEs (excluding herpetic infections) through Week 24.

The number of participants and percentage with the events for these endpoints will be provided in observed cases. In addition, the time (week) to first event for those participants will also be analyzed using Kaplan-Meier method and the duration of the rescue medication use may be summarized if applicable.

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).

4.6 MULTIPLICITY ISSUES

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

In US and US reference countries:

- Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24
- Proportion of participants with IGA PN-S 0 or 1 score at Week 24
- Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24
- Percent change from baseline in WI-NRS at Week 24
- Change from baseline in HRQoL, as measured by Dermatology Life Quality Index (DLQI) to Week 24
- Change from baseline in skin Pain-NRS to Week 24
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) total score to Week 24

In all other countries (including EU and EU reference countries, as well as Japan):

- Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24
- Proportion of participants with IGA PN-S 0 or 1 score at Week 24
- Percent change from baseline in WI-NRS at Week 24
- Change from baseline in HRQoL, as measured by Dermatology Life Quality Index (DLQI) to Week 24
- Change from baseline in skin Pain-NRS to Week 24
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) total score to Week 24.

The study is considered positive when the primary endpoint 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 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 + 14 days, regardless of unplanned intermittent discontinuations. Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

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

Additionally, the cumulative duration of treatment exposure 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) will be considered an AESI per dupilumab clinical programs 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 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]

AE presentation	Sorting rules
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

Type of AE	MedDRA levels
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

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

AE Grouping	Criteria
Pregnancy of a female participants entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP	"Pregnancy" or "Partner Pregnancy" checked on the Pregnancy eCRF page as reported by the investigator
Significant ALT elevation	"ALT increase" and AESI answer "Yes" checked on AE eCRF as reported by the investigator (ALT >5 x ULN in participants with baseline ALT ≤2 x ULN; OR ALT >8 x ULN if baseline ALT >2 x ULN)
Symptomatic overdose with IMP	Symptomatic Overdose is answered Yes, with Overdose of 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 reaction' and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥24 hours or ongoing
Severe or serious infection	Primary SOC = 'Infections and infestations' and with severe or serious status
Drug-related hepatic disorder	SMQ [20000006] Drug-related hepatic disorders- narrow
Injection site reaction	HLT = 'Injection site reaction'
Malignancy	SMQ [20000091]‑ Malignant or unspecified tumors narrow
Suicidal behavior	CMQ10639 based on the following PTs [Completed suicide, Suicidal ideation, Depression suicidal, Suicidal behavior, Suicide attempt][a]
Conjunctivitis (narrow)	CMQ10644 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis][a]
Conjunctivitis (broad)	CMQ10645 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia][a]
Conjunctivitis (FDA)[c]	CMQ10643 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye irritation, Eye inflammation, Giant papillary conjunctivitis][a]
Keratitis (FDA) [c]	CMQ30102 based on the following PTs in (keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex)

a The list of terms may be adjusted according to MedDRA version changes
b All cases of Eosinophilia will be included in the analysis, where cases associated with clinical symptoms will be further described in the CSR
c FDA requested for US labeling

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,
- For each AESI and other selected AE groupings,
  - Number (%) of participants with any specific TEAE
  - Number (%) of participants with any specific serious AE (regardless of treatment emergent status)
  - Number (%) of participants with any specific treatment emergent serious AE
  - Number (%) of participants with any specific AE leading to death
  - Number (%) of participants with any specific TEAE leading to permanent study drug discontinuation
  - Number (%) of participants with any specific TEAE related to IMP reported by investigator
  - Number (%) of participants with any specific TEAE by maximum intensity, corrective treatment, and final outcome
  - Number of any specific TEAE adjusted by the exposure duration
  - Number of participants with any specific TEAE adjusted by the exposure duration at risk. For each specific TEAE, Kaplan-Meier estimates of cumulative incidence at Week 12, and 24 and K-M plot may be provided to depict the course of onset over time if the number of events is large enough.
  - Number (%) of participants with injection site reactions by IMP injection.
  - Number (%) of participants with different number of injection site reactions.
- In addition, AESIs reported by the investigator in eCRF will be summarized separately.

In addition, the exposure-adjusted adverse event incidence rate tables will provide the number of patients with at least 1 event per 100 patient-years for the summaries of TEAEs, treatment emergent SAE, TEAE leading to permanent intervention discontinuation, and AESIs and other selected AE groups in Table 8.

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, red blood cell count, platelet count

  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils

- Clinical chemistry:
  - Metabolism: glucose, total cholesterol, total protein, creatine phosphokinase
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Renal function: creatinine, blood urea nitrogen, uric acid
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, albumin
  - Pregnancy test: Serum β-human chorionic gonadotropin (all female participants) will be performed at screening (V1) in women of childbearing potential, and a urine pregnancy test will be performed at V2 and every 4 weeks thereafter.
  - Hepatitis screen: hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab) will be tested at screening (V1). In case of results showing HBs Ag (negative) and HBc Ab (positive), an hepatitis B virus (HBV) deoxyribonucleic acid (DNA) testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCV Ab (positive), an HCV ribonucleic acid (RNA) testing will be performed and should be confirmed negative prior to randomization.
  - HIV screen: Anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1.
  - TB test (performed locally if required and results noted in the eCRF).
- Urinalysis:
  - Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin. If positive for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory. Creatinine, leukotriene and tetranor PGDM will be tested by the central laboratory.
- 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 QTcF intervals after 10 minutes of rest in the supine position. Data are locally collected and read at screening (V1) and Week 24 (V6).

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, vital signs and ECG 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

Analysis of potentially clinically significant abnormality (PCSA) will be performed based on the PCSA list 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 Pharmacokinetic analyses

Predose dupilumab concentrations in serum at Visit 2 (Day 1), dupilumab trough concentrations at Week 4, Week 8, Week 12, Week 24/EOT Visit and post-treatment dupilumab concentrations at Week 36/EOS Visit will be provided.

Concentrations of dupilumab 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 that are below the LLOQ will be taken into account with a plasma concentration considered equal to 0.

4.8.2 Immunogenicity analyses

Anti-drug antibody (ADA) status to dupilumab (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 response is 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 (1000 ≤ Titer ≤10 000)
- High (Titer >10 000)

The following summary will be provided based on ADA population:

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

Kinetics of treatment-emergent ADA response

Number (%) of participants with treatment-emergent ADA positive response at each visit will be summarized, including titer categories (lower, moderate, and high titer), by each intervention group.

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

Association of Immunogenicity with Exposure, Safety and Efficacy

The safety and efficacy analyses 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.

Association of ADA with PK

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and concentration of dupilumab in serum may be explored for each dupilumab dose group. A plot of

concentration of functional dupilumab versus visit will be provided by ADA classifications for the dupilumab dose group. Individual participant plots of dupilumab concentration according to ADA status will be provided to assess the impact of ADA on PK.

Association of ADA with clinical efficacy endpoints

Associations between the ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent and 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 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 24), and Visit 7 (Week 36), for measurement of total serum IgE. Total IgE will be measured using validated quantitative methods.

For those participants who consent to the optional pharmacogenetic/pharmacogenomic sample collection section of the ICF, blood (serum/plasma) 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 the optional skin biopsy (substudy), the sample will be taken from lesion and non-lesion skin using punch biopsy.

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. In addition, for participants who take the prohibited medications/procedures or rescue medications defined in Table 5, the data after the medications will be censored and then last observation carried forward (LOCF) method will be implemented for missing data imputation in the analysis.

Summary plots (median with 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 and urine biomarkers will be addressed in a separate document.

The analyses of the skin biopsy substudy will be addressed in a separate document.

4.9 INTERIM ANALYSES

No interim analysis is planned.

A primary database lock will be performed when all randomized participants in this study have completed their 24-week treatment phase. Final analyses in the CSR will be based on this database.

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

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomic category
CDG:	company drug grouping
CI:	confidence interval
CLcr:	Creatinine clearance
CMH:	Cochran-Mantel Haenszel
CSR:	clinical study report
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:	Euroqol 5 dimensions
EQ-5D-5L:	5-level EuroQol 5-dimensional questionnaire
FDA:	Food and Drug Administration
HADS:	hospital anxiety and depression scale
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
HGLT:	high level group term
HLT:	high level term
HRQoL:	health-related quality-of-life
IGA PN:	Investigator’s global assessment for prurigo nodularis
IGA PN-A:	IGA PN-Activity
IGA PN-S:	IGA PN-Stage
IMP:	investigational medicinal product
ITT:	intent-to-treat
LLT:	lower-level term
LS:	least squares
MedDRA:	medical dictionary for regulatory activities
NRS:	numeric rating scale
PCSA:	potentially clinically significant abnormality

PD: pharmacodynamic
PGIC: Participant Global Impression of Change
PGIS: Participant Global Impression of Severity
PK: pharmacokinetic
PN: prurigo nodularis
PT: preferred term
RNA: ribonucleic acid
SAE: serious adverse event
SAP: statistical analysis plan
SD: standard deviation
SDG: standardized drug grouping
SMQ: standardized MedDRA query
SOC: system organ class
TEAE: treatment-emergent adverse event
ULN: upper limit of normal
VAS: visual analog scale, visual analog scale
WHO-DD: World Health Organization-Drug Dictionary
WI-NRS: worst-itch numeric rating scale
WOCF: worst-observation carried forward

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendments. As mentioned previously, the Sponsor made the decision to complete the study as originally planned instead of resizing the study based on the results of EFC16460 after a health authority's feedback on Protocol Amendment 2 dated 14-Apr-2021.

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

Amendment Number	Approval Date	Changes	Rationale
1	20-May-2020	To add "proportion of participants with Investigator's Global Assessment 0 or 1 score for PN-Stage (IGA PN-S) at Week 24" as another key secondary endpoint	To include a lesion-related key secondary endpoint according to the health authority's recommendations
		To remove the endpoint "Change from baseline in PAS total score at Week 4, Week 8, Week 12, and Week 24" in the exploratory endpoint and modify the exploratory endpoint regarding the healed lesions from PAS questionnaire analysis	To clarify the analysis on efficacy evaluation of dupilumab on skin lesions using a modified prurigo activity score (PAS) 5-item questionnaire
		To break out the secondary endpoints with multiple measuring timepoints into individual endpoints.	To clearly define the timepoints of each endpoint according to health authority's recommendation

Amendment Number	Approval Date	Changes	Rationale
		To add the sensitivity analysis for secondary endpoints information, and to separate key secondary endpoints in a different row	To evaluate the robustness of the missing data imputation assumption by sensitivity analyses, and to clarify the endpoints analyses
		To add the covariate “baseline anti-depressant use (yes or no)” to primary and secondary endpoint analyses	To adjust for potential impact of anti-depressant use on the treatment effect in primary and secondary efficacy analyses
		The following wording was added: “Data collected regarding the impact of the COVID-19 or other pandemics, on the participants will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 or other pandemics requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP”.	To describe alternative temporary mechanism that can be implemented in the study conduct in case of pandemic requiring public health emergency eg, COVID-19
2	14-Apr-2021	Added 2 more populations for analyses in in the case an earlier primary database lock occurs. The ITT-Week-12 population consists of all participants who had been randomized by 14 June 2021. The ITT-Week-24 population consists of all participants who had been randomized by 22 March 2021.	To detail how the endpoints will be analyzed in the case of an early primary database lock. Based on the timing of the availability of the EFC16460 results, and to ensure a minimum of 135 participants have the opportunity to reach the Week 24 endpoint, the randomization cut-off dates have been assessed as 22 March 2021 for Week 24 and 14 June 2021 for Week 12.
		Added text: The analysis population for the efficacy endpoints will be the ITT population. In the case of an early primary database lock prior to the last enrolled participant reaching EOT, the analysis population will be the ITT-Week-12 population for endpoints which occur earlier than or equal to Week 12. The ITT-Week-12 population consists of all participants who had been randomized by 14 June 2021. The analysis population for Week 24 endpoints will be the ITT-Week-24 population. The ITT-Week-24 population consists of all participants who had been randomized by 22 March 2021. Modification in accordance with the above proposal will be documented in the SAP prior to the database lock.	To provide detail of how data from timepoint evaluations will be handled in the case of an early primary database lock.

Amendment Number	Approval Date	Changes	Rationale
		Added text: In the case of an early primary database lock prior to the last enrolled participant reaching EOT, the analysis of safety will be performed on all available and safety data collected up to the time of the primary database lock. Added text in Table 7: In addition, exposure-adjusted AE incidence rate tables will present by SOC and PT the number of patients with at least 1 event per 100 patient-years.	With an early primary analysis, participants may have different treatment exposure because of study design.
3	21-Oct-2021	To promote the "proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 24 as primary endpoint and to move the "proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 12" to a secondary endpoint	Based on the data from EFC16460, the treatment effect of dupilumab continued to improve over time through Week 24. Therefore, the Sponsor proposes to assess the proportion of participants with improvement (reduction) in WI-NRS by ≥4 at Week 24, which represents the effect more accurately and synchronizes the primary itch assessment with the primary lesion assessment
		To update the sample size calculation based on the observed effect sizes from EFC16460.	To assess a timepoint that reflects the optimal dupilumab treatment effect as a primary endpoint
		To update the primary analysis considerations to the Week 24 timepoint.	To be consistent with primary endpoint change
		To remove the sentence "A key secondary endpoint will be the responder analyses of itch improvement of at least 4 points at Week 24." as it is now the primary endpoint, and to provide rationale for choosing the primary endpoint timepoint at Week 24 with the following language: "The timing of the primary assessment, ie, at Week 24, was based on the results of the primary analysis of EFC16460, showing that the effect of dupilumab over time showed continuous improvement after Week 12 across all endpoints, with a similar time course of improvement in both itch and lesion endpoints through at least Week 24. Since improvement of itch and lesions may occur prior to Week 24, responder analyses assessments will be performed at earlier time points as well, starting at Week 2 for itch, and Week 4 for lesions."	To provide rationale and maintain consistency in language with the change in the primary endpoint.

Amendment Number	Approval Date	Changes	Rationale
		To specify that the rationale for a 24-week duration of the trial is an appropriate duration based on data observed from EFC16460 and to remove references to atopic dermatitis trials.	To reflect that data from EFC16460 has informed our understanding of the dupilumab treatment effect continuing to improve itch through Week 24. The Week 24 timepoint most accurately represents the overall treatment effect and synchronizes the primary itch assessment with the primary lesion assessment.
		To reflect that the primary endpoint timepoint is Week 24.	To maintain consistency in language with the change in the primary endpoint.
		To update Table 6 to reflect that the primary endpoint is assessed at Week 24.	To maintain consistency in language with the change in the primary endpoint.
		To remove the possibility of re-evaluating the timing of the primary database lock of EFC16459 based on the observed treatment effect size in EFC16460, that was added per Amendment 02. And to consequently remove the 2 populations (ITT-Week 12 and ITT-Week 24) that were added per Amendment 02.	Amended protocol 02 was submitted in few countries but was withdrawn following a Health Authority feedback and was not implemented in any country.
		Subsection 10.12.2 was added and the overall rationale and table with summary of changes for Amended protocol 02 were moved from the cover page to this section.	This is aligned with Sanofi procedures.

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

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: 18-<40, 40–<65, 65-<75, and ≥75 years),
- Gender (Male, Female),
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, unknown),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown),
- Region (Asia: Japan, China, South Korea; East Europe: Russia; Latin America: Argentina, Mexico; Western Countries: USA, France),

- Territory (North America: USA; European Union: France; Rest of World: Russia, Japan, China, South Korea, Argentina, Mexico),
- Weight in kg (quantitative and qualitative variable: (<60, ≥60- <90, ≥90 kg),
- BMI in kg/m^2 (quantitative and qualitative variable: (<25, ≥25- <30, ≥30 kg/m^2).

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

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

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.

- Prurigo nodularis (Yes, Ongoing condition)
- Atopic dermatitis (Yes, Ongoing condition)
- Allergic rhinitis history (Yes, Ongoing condition)
- Allergic rhinoconjunctitvitis (Yes, Ongoing condition)
- Asthma history (Yes, Ongoing condition)
- Food allergy history (Yes, Ongoing condition)
- Eosinophilic esophagitis history (Yes, Ongoing condition).

Disease characteristics at baseline

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

- Duration of PN and grouping (years; <3 and ≥3) to be derived as
  - (Year of randomization – Year of first diagnosis of PN) + (month of randomization - month of first diagnosis of PN)/12
- Age of onset of PN (years)
- History of atopy (atopic or non-atopic)
  - Number of mild AD participants under atopic
- Stable use of TCS/TCI (yes or no)
- Baseline WI-NRS score
- Baseline IGA PN-S score (summary and frequency by each score level)
- Baseline IGA PN-A score (summary and frequency by each score level)

- Baseline skin Pain-NRS score
- Baseline Sleep-NRS score
- Baseline PGIS score
- PAS (number of prurigo lesions in a total and in representative area, and healed prurigo lesions) at baseline
- Baseline Hospital Anxiety and Depression Scale (HADS) total score
  - Baseline Hospital Anxiety score
  - Baseline Depression Scale score
- Baseline Dermatology Life Quality Index (DLQI) score
- Baseline EuroQol five dimensions questionnaire (ED-5D-5L) (single index score and VAS)
- 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)
- Antidepressant use (yes or no) at baseline
- HIV (positive versus negative).

Prior or concomitant medications and procedure

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

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

- Prior medications/procedures are those the participant used prior to first investigational medicinal product (IMP) injection. Prior medications/procedures can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications/procedures 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/procedures 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/procedure can be classified as a prior medication/procedure and/or as a concomitant medication/procedure and/or as post-treatment medication/procedure. If it cannot be determined whether a given medication/procedure was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication/procedure.

The prior and concomitant medications/procedure 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 time for the same medication.

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

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

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

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

Background intervention

Participants will be required to apply moisturizers (emollients) once or twice daily for at least the 7 consecutive days immediately before baseline (Day 1) and continue until Week 36.

The compliance of moisturizers (emollients) used from 7 days before the baseline visit to Week 36 (or end of study), which is defined as the (number of days moisturizers used during the period)/(number of days within the period) x 100%, will be summarized by intervention group.

Similarly, the compliance of moisturizers (emollients) used from the baseline visit to Week 12 and Week 24 will be summarized by intervention group respectively.

In addition, the compliance of use of TCS/TCI from the baseline visit to Week 12 and Week 24 for participants with the stratification of stable use of TCS/TCI (yes) will be summarized by intervention group respectively.

Prohibited medications/procedures

The concomitant use of the following therapies is prohibited during the entire study. Study treatment will need to be discontinued in participants receiving these treatments:

- Systemic immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, hydroxychloroquine, dapsone, sulfasalazine, colchine, etc)
- Other monoclonal antibodies (which are biological modifiers)
- Phototherapy, including tanning beds
- Naltrexone or other opioid antagonist
- Gabapentin, pregabalin, and thalidomide

The concomitant use of the following therapies is prohibited except if the dose has been stable for at least 3 months prior to screening, but study treatment will not need to be discontinued in participants receiving the treatments listed below. The dose should also remain stable (can be reduced or discontinued if medically indicated) and should not be increased during the study.

- Paroxetine, fluvoxamine, or other SSRIs
- SNRIs
- Amitriptyline or other tricyclic or tetracyclic antidepressants

The concomitant use of the following therapies is also prohibited during the entire study, but study treatment will not need to be discontinued in participants receiving the treatments listed below:

- Intralesional corticosteroid injections and cryotherapy
- Sedating antihistamine
- Non-sedating antihistamine if used specifically for the treatment of itch secondary to AD or PN.

The number and percentage of participants who take the prohibited medications/procedures will be provided. In addition, the time (week) of first prohibited medication/procedure taken will also be analyzed using Kaplan-Meier method.

Rescue medications

The following rescue medications may be used:

- Dermatological preparations of high potency or superpotent TCS and TCI.

If medically necessary (ie, to control intolerable PN symptoms), rescue treatment for PN may be provided to study participants at the discretion of the Investigator.

Although the use of rescue medications is allowed at any time during the study, the use of rescue medications should be delayed, if possible, for at least 14 days following the initiation of the investigational treatment. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eCRF.

- For the purpose of the efficacy responder analysis, a pre-specified algorithm will be used to classify rescue. In addition, a blinded review of all post-baseline medications to adjudicate rescue treatment, based on medical judgment, will be performed to adjudicate rescue. Participants who receive rescue treatment as per this adjudication during the study will be considered treatment failures.

The rescue medications will be analyzed by the same method as that used for prohibited medications/procedures.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Demographic formulas

Age of onset of PN is calculated as:

Year of PN 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) $\times$ weight (kg) $\times$ (1 - 0.15 $\times$ sex (0-M, 1-F))/ (0.814 $\times$ creatinine (μmol/l))

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

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

Analysis windows for time points

Efficacy assessment

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the randomization day. If a participant receives IMP prior to the randomization by mistake, the reference date of efficacy assessment will be the date of the first IMP administration for that participant.

For daily eDiary data (WI-NRS, skin Pain-NRS, Sleep-NRS), all available values of daily measurements will be assigned to each week window according to Table 10, and then weekly average score will be calculated. Randomization day is used as the reference day (Day 1).

Table 10 - Time window for eDiary efficacy variables

Time	Target day	Day range for calculating weekly score
Baseline (Week 0)	1	-7- <1
Week 1	8	1-11
Week 2	15	12-18
Week 3	22	19-25
Week 4	29	26-32
Week 5	36	33-39
Week 6	43	40-46
Week 7	50	47-53
Week 8	57	54-60
Week 9	64	61-67
Week 10	71	68-74
Week 11	78	75-81
Week 12	85	82-88
Week 13	92	89-95
Week 14	99	96-102
Week 15	106	103-109
Week 16	113	110-116
Week 17	120	117-123
Week 18	127	124-130
Week 19	134	131-137
Week 20	141	138-144
Week 21	148	145-151
Week 22	155	152-158
Week 23	162	159-165
Week 24	169	166-172
Week 25	176	173-179
Week 26	183	180-186
Week 27	190	187-193
Week 28	197	194-200
Week 29	204	201-207
Week 30	211	208-214
Week 31	218	215-221
Week 32	225	222-228
Week 33	232	229-235

Time	Target day	Day range for calculating weekly score
Week 34	239	236-242
Week 35	246	243-249
Week 36	253	250-256

For other efficacy variables, 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

		Time windows for				
Visit	**Target Day**	**DLQI, IGA PN-A/PN-S**	**HADS, EQ-5D-5L, Missed school/work days**	**PGIS**	**PGIC**	**PAS**
Visit 1 (Week -4 to -2)	<1			<-14		<-14
Visit 2 (Week 0)	1	1^-	1^-	-14-1^-		-14-1^-
Visit 3 (Week 4)	29	1^+-42		1^+-42	1^+-42	1^+-42
Visit 4 (Week 8)	57	43-70		43-70	43-70	43-70
Visit 5 (Week 12)	85	71-126	1^+-126	71-126	71-126	71-126
Visit 6 (Week 24)	169	127-210	127-210	>126	>126	127-210
Visit 7 (Week 36)	253	>210	>210			>210

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

Safety assessment

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP administration. Selected safety variables will be summarized by the analysis window define 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

		Time windows for							
Visit	**Target Day**	**Vital signs**	**Hematology, biochemistry**	**Urinalysis**	**CD4 T cell count and HIV test**	**Serum Pregnancy test**	**Urine Pregnancy test**	**Physical examination**	**ECG**
Visit 1 (Week -4 to -2)	<1	<-14	<-14	<-14	1-	<-14		<-14	1-
Visit 2 (Week 0)	1	-14-1-	-14-1-	-14-1-			-14-1-	-14-1-	
Visit 3 (Week 4)	29	1+-42	1+-42	1+-42			1+-42		
Visit 4 (Week 8)	57	43-70	43-70	43-70			43-70		
Visit 5 (Week 12)	85	71-126	71-126	71-126			71-126		
Visit 6 (Week 24)	169	127-210	127-210	>126	1+		127-210	1+-210	1+
Visit 7(Week 36)	253	>210	>210				>210	>210	

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

Pharmacokinetics/pharmacodynamics assessment

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 treatment, 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 distance to 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	Time windows for		
		Serum dupilumab concentration	Anti-drug antibodies	Total IgE
Visit 1 (Week -4)	<1			
Visit 2 (Week 0)	1	1^-	1^-	1^-
Visit 3 (Week 4)	29	1^+-42		1^+-42
Visit 4 (Week 8)	57	43-70		43-70
Visit 5 (Week 12)	85	71-126	1^+-126	71-126
Visit 6 (Week 24)	169	127-210	127-210	127-210
Visit 7(Week 36)	253	>210	>210	>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.

5.5 APPENDIX 5 SAMPLE SAS CODE

The multiple imputation and analysis model for the primary analysis of change from baseline in WI-NRS at Week 24 will be built with the following sample SAS code.

1. 40 datasets with a monotone missing pattern will be obtained, induced by Markov Chain Monte Carlo (MCMC) method on participants who have not taken the prohibited medications and/or rescue medications or have discontinued study treatment due to lack of efficacy prior to Week 24.

```
proc mi data=dat_etd seed=16460 nimpute=40 out=dat_mc;
    mcmc impute=monotone;
    var atopicyn stableyn region antidblyn trt01p winrsbl chg1winrs …
    chg24winrs;
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, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, baseline anti-depressant use (yes or no), and baseline value of the response variable.

```
proc mi data=dat_mc nimpute=1 seed=16461 out=dat_mi;
    by _imputation_;
    class atopicyn stableyn region antidblyn trt01p;
    monotone method=reg;
    var atopicyn stableyn region antidblyn trt01p winrsbl chg1winrs …
    chg24winrs;
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 atopicyn stableyn region antidblyn trt01p;
```

```
      model  chg24winrs = atopicyn stableyn region antidblyn
               trt01p winrsbl;
      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

Grouping	Preferred Term/Medication Code	Preferred Term/Medication
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

5.7 APPENDIX 7 MEDICATION/PROCEDURE ADJUDICATION ALGORITHM

Algorithm for determining whether treatment with following medications or procedures constitutes treatment failure resulting in setting data as non-responder after taking medication or undergoing procedure in the main statistical analysis

1. Not required to adjudicate post-baseline medications (WHODD-coded) or procedures (CMQ-coded) as these will be considered treatment failures if used at any time[1].
   a) Always considered treatment failure
      - ATC2 = CORTICOSTEROIDS FOR SYSTEMIC USE
      - ATC2=IMMUNOSUPPRESSANTS (systemic, eg, oral or parenteral route)
      - Preferred Drug Name = Ciclosporin
      - Preferred Drug Name = Methotrexate
      - Preferred Drug Name = Mycophenolate sodium
      - Preferred Drug Name = Mycophenolic acid
      - Preferred Drug Name = Azathioprine
      - Preferred Drug Name = Gabapentin
      - Preferred Drug Name = Pregabalin
      - Preferred Drug Name = Thalidomide
      - Preferred Drug Name = Lenalidomide
      - Preferred Drug Name = Baricitinib
      - Preferred Drug Name = Ruxolitinib
      - Preferred Drug Name = Tofacitinib
      - Preferred Drug Name = AbrocitinibPreferred Drug Name = Delgocitinib
      - Preferred Drug Name = Nalbuphine
      - Preferred Drug Name = Naltrexone
      - Preferred Drug Name = Naloxone
      - Preferred Drug Name = Vixarelimab
      - Preferred Drug Name = Nemolizumab
      - Preferred Drug Name = Serlopitant
      - Preferred Drug Name = Aprepitant
      - CMQb HLT Phototherapies
      - CMQ Tanning_single PT
   b) Never considered treatment failure:
      - ATC2 = EMOLLIENTS AND PROTECTIVES

- ATC2 = GENERAL NUTRIENTS
- ATC2 = VITAMINS
- ATC2 = ANTIVIRALS FOR SYSTEMIC USE
- ATC2 = ANTIFUNGALS FOR DERMATOLOGICAL USE
- ATC2 = ANTISEPTICS AND DISINFECTANTS
- ATC2 = ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
- ATC2 = ANTI-ACNE PREPARATIONS, excluding D10AA Corticosteroids, combinations for treatment of acne
- ATC2 = OPHTHALMOLOGICALS
- ATC1 = ANTIINFECTIVES FOR SYSTEMIC USE, excluding D07C Corticosteroids, combinations with antibiotics
- ATC1 = BLOOD AND BLOOD FORMING ORGANS
- ATC1 = ALIMENTARY TRACT AND METABOLISM
- ATC1 = MUSCULO-SKELETAL SYSTEM, excluding M01BA Antiinflammatory/antirheumatic agents in combination with corticosteroids
- ATC2 = COUGH AND COLD PREPARATIONS
- ATC2= PSYCHOLEPTICS, excluding N05BB Diphenylmethane derivatives and N05C HYPNOTICS AND SEDATIVES

1 A blinded review of all post-baseline medications or procedures to adjudicate whether treatment constitutes treatment failure, based on medical judgment, may be performed in addition. A listing of treatments or procedures classified as treatment failure in a manner inconsistent with the classification under #1 will be provided, along with supporting rationale.

2. Require to adjudicate medications or procedures that may constitute treatment failure

- All other medications and procedures listed in the protocol and Table 5 of the SAP (not noted in 1. above) given for indications consistent with PN[2]
- Considerations in determining treatment failure include the criteria already set forth in Table 5 of the SAP in addition to the type of medication or procedure, indication, dose, route of administration, timing, frequency and the potential impact of the use of the prohibited medications/procedures and rescue medications on the primary and key secondary efficacy endpoints.

2 Below is a list of indications consistent with PN based on PT level from concomitant medication/procedure data using MedDRA dictionary

System Organ Class	High Level Term	Preferred Term	Preferred Term Code
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Neurodermatitis	10029263
Infections and infestations	Bacterial infections NEC	Eczema impetiginous	10051890
Infections and infestations	Skin structures and soft tissue infections	Dermatitis infected	10012470
Infections and infestations	Skin structures and soft tissue infections	Eczema infected	10014199
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis	10012431
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Dermatitis atopic	10012438
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Eczema	10014184

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Approve & eSign	[redacted]

Approve & eSign	[redacted]