STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid
Compound:	Dupilumab (REGN668)
Protocol Number:	R668-BP-1902 Amendment 3
Clinical Phase:	Phase 2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Amendment 1 / July 29, 2024

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAS	ADA analysis set
ABQOL	Autoimmune bullous disease quality of life
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BP	Bullous pemphigoid
BPDAI	Bullous Pemphigoid Disease Area Index
BSA	Body Surface Area
CCL17	Chemokine (C-C motif) ligand 17
CCL18	Chemokine (C-C motif) ligand 18
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMQ	Custom MedDRA® query
CRF/eCRF	Case report form (electronic or paper)
ECG	Electrocardiogram
EDC	Electronic data capture
EDTA	Ethylenediamine tetraacetic acid
EOS	End of study
EQ-5D-3L	European Quality of Life 5-Dimension 3-Level
EQ-VAS	EQ visual analogue scale
ET	Early termination
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLT	High level term
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IVRS	Interactive voice response system
IWRS	Interactive web response system

LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LS	Least squares
MedDRA®	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
MI	Multiple imputation
NAb	Neutralizing antibody
NAS	NAb analysis set
NRS	Numerical rating scale/score
OCS	Oral corticosteroids
PARC	Pulmonary and activation-regulated chemokine
PCSV	Potentially clinically significant value
PGADS	Patient Global Assessment of Disease Severity
PGAT	Patient Global Assessment of Treatment
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PT	Preferred term
Q1	First quartile
q2w	Every 2 weeks
Q3	Third quartile
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SDR	Steroid Dosing Record
SI	Standard international
SMQ	Standardized MedDRA® query
SOC	System organ class
SOE	Schedule of Events
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
WBC	White blood cell
WHO	World Health Organization
WHODD	WHO Drug Dictionary
WOCBP	Women of childbearing potential
WOCF	Worst observation carried forward

1. OVERVIEW

The SAP is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses and analysis presentation to be used for the study specified in protocol R668-BP-1902 Amendment 3 dated Mar 04, 2024.

1.1. Study Description and Objectives

This multicenter, randomized, double-blind, placebo-controlled, parallel-group study is designed to evaluate the efficacy and safety of dupilumab in adult patients with BP. This study will compare the efficacy and safety of dupilumab versus placebo.

1.1.1. Primary Objective

The primary objective of the study is to demonstrate that dupilumab is superior to placebo in achieving sustained remission off OCS in patients with BP.

1.1.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the OCS-sparing effects of dupilumab in patients with BP
- To evaluate the effect of dupilumab on itch in patients with BP
- To evaluate the effects of dupilumab on health-related quality of life measures in patients with BP
- To evaluate the effect of dupilumab in circulating BP180 and BP230 autoantibody titers
- To assess the safety and tolerability of dupilumab administered to patients with BP
- To characterize the trough concentrations of functional dupilumab over time following administration of dupilumab in patients with BP
- To assess the immunogenicity of dupilumab in patients with BP over time

1.1.3. Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate the incidence and time to relapse following control of disease activity
- To evaluate the effect of dupilumab on skin pain in patients with BP
- To evaluate the effect of dupilumab on sleep in patients with BP
- To evaluate the effects of dupilumab on the inflammatory profile in circulation, as measured by serum and plasma chemokines/cytokines, immunoglobulin levels, and gene expression
- To evaluate the effects of dupilumab on inflammatory profiles in the peri-lesional skin of patients with BP as measured by gene expression (may include RNAscope) and immunohistological analysis of skin biopsies

1.2. Statistical Hypothesis

The following null hypothesis and alternative hypothesis of the primary endpoint (see Section 7.1.1) will be tested for the comparison of dupilumab 300 mg q2w against placebo:

- Null hypothesis (H_0): $p_p = p_d$ (ie, the proportion of patients achieving sustained remission at week 36 is the same between the dupilumab group [p_d] and the placebo group [p_p]).
- Alternative hypothesis (H_1): $p_p \neq p_d$ (ie, the proportion of patients achieving sustained remission at week 36 is different between the dupilumab group [p_d] and the placebo group [p_p]).

1.3. Interim Analysis

No interim analysis is planned.

1.4. Timing of Analysis

The primary analysis will be performed once all patients in the study have completed the 36-week treatment period or discontinued from the study. The primary analysis will be considered the final analysis for the primary, secondary, and exploratory week 16 and week 36 efficacy endpoints.

1.5. Modifications from the Statistical Section in the Final Protocol

The parameter of interest for the population-level summary of the primary endpoint of the proportion of patients achieving sustained remission at Week 36 has been changed from the odds ratio to the risk difference. The primary endpoint will now be analyzed using the stratified MH method. The estimate of the MH-weighted risk difference and corresponding 2-sided Wald 95% CI using the Sato variance will be provided. The stratified MH method will also be used for assessing the difference in proportions between treatment groups for other specified binary endpoints.

The primary analysis method for the assessment of the total cumulative dose of OCS will be an ANCOVA model rather than the Wilcoxon rank-sum test, as the Wilcoxon rank-sum test does not quantify the magnitude of the treatment effect. The Wilcoxon rank-sum test will be performed as a supportive analysis.

The definitions of the on-treatment and post-treatment observation periods for AE reporting were modified, as the definitions in the protocol did not adequately handle AE data collected for patients who discontinue from the study drug but continue in the study.

1.6. SAP Revision History

Amendment 1:

SAP Section	Change	Rationale
Section 5.2 Treatment Period Dispositions	Updated the definition of treatment period completers from those who make it to the End of Treatment visit to	Updated to account for patients who may miss the End of Treatment visit but return for a subsequent visit

	those who make it to the End of Treatment visit or the date of the last visit is on or after study day 365	
Section 5.2 Treatment Period Dispositions Section 5.3 Follow-up Period Dispositions	Replaced separate summaries for important protocol deviations during the treatment period and follow-up period with a single summary of all important protocol deviations	To provide a more comprehensive summary of important protocol deviations (ie, all important protocol deviations, regardless of timing, will be summarized)
Section 7.1.2 Key Secondary Efficacy Data	Updated the number of observed daily records of peak pruritus NRS out of 7 days required for calculation of the average weekly score from 3 to 4	Per Health Authority request
Section 7.1.5 Estimand Framework	Updated the parameter of interest for the population-level summary of binary endpoints from the odds ratio to the difference in proportions	Per Health Authority request
Section 7.1.5 Estimand Framework	Updated the text to indicate that WOCF will be applied for non-OCS systemic rescue treatment, and not for topical rescue therapies, for the assessment of the total cumulative dose of OCS from baseline to week 36	For clarity
Section 7.2.1 Analyses of the Primary Endpoint	Updated the primary analysis method for the primary endpoint from the CMH method for odds ratio to the MH method for difference in proportions	Per Health Authority request
Section 7.2.2.2 Continuous Secondary Endpoints at Week 36	Updated the primary analysis approach for the total cumulative dose of OCS from the Wilcoxon rank-sum test to ANCOVA and specified that the Wilcoxon rank-sum test will be performed as a supportive analysis	Per Health Authority request

Section 9.1 Investigational Study Drug Exposure and Compliance	Added description of how compliance will be calculated and summarized	Unintentionally omitted in the original SAP
Section 9.2 Duration of Observation	Replaced all text with a description of how patient time on study will be summarized	Error in original SAP
Section 10.1 Adverse Events	Updated the definitions of the on-treatment and post-treatment observation periods for AE analyses	Previous definitions did not adequately handle AE data collected for patients who discontinue from the study drug but continue in the study
Section 11.4 Assignment of Data to Visit Windows and Unscheduled Assessments	Updated analysis visit windows	To utilize additional available study data in analyses
Throughout	Corrected typographical and grammatical errors; other minor changes made to correct errors or clarify the intended analyses	For clarity

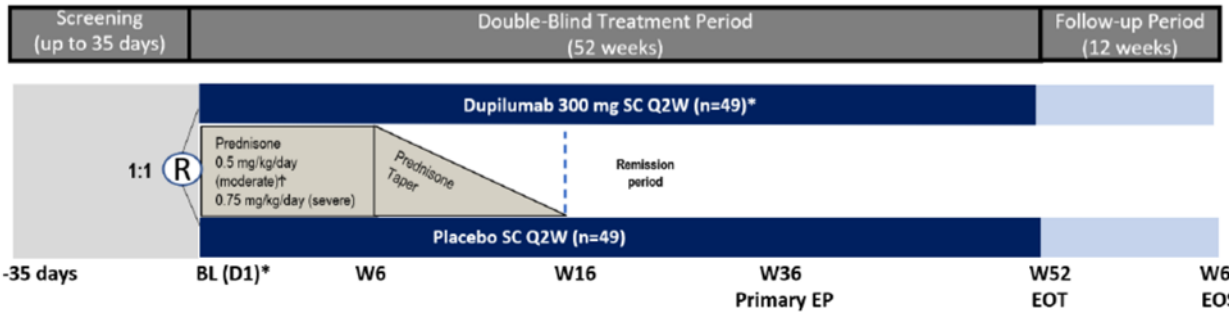
2. INVESTIGATION PLAN

2.1. Study Design

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab versus placebo in patients with BP.

The study consists of the following periods: an up to 35-day screening period, a 52-week double-blind treatment period, and a 12-week safety follow-up period. An overview of the study is provided in Figure 1.

Figure 1: Study Flow Diagram



* Loading 600 mg dose of dupilumab (or equivalent placebo dose) given at day 1
Note: Tapering of prednisone (or prednisolone) should begin no later than week 6
↑ Moderate BP patients may be escalated to 0.75 mg/kg/day if patient is not showing signs of control of disease activity by week 2
Abbreviations: BL, baseline; BP, bullous pemphigoid; EP, endpoint; q2w, every 2 weeks; SC, subcutaneous

Study participants require a confirmed BP diagnosis based on characteristic clinical features, histopathology, immunopathology and serology during screening.

At the baseline visit, approximately 98 eligible patients will be randomized in a 1:1 ratio to receive either a loading dose of 600 mg dupilumab administered SC followed by 300 mg dupilumab administered SC q2w, or a matching placebo loading dose and SC placebo injections q2w, according to a central randomization scheme provided by an IVRS/ IWRS to the designated study pharmacist (or qualified designee). Randomization will be stratified by baseline disease severity (moderate [BPDAI activity score ≥24 and <60] vs. severe [BPDAI activity score ≥60]), region (North America vs. Europe [including Australia, Israel, and Taiwan] vs. Japan) and prior corticosteroid/immunosuppressant use (Yes vs. No). Approximately 10% of the study population is planned to be from Japan. Patients from study sites in Japan will not be stratified.

At the baseline visit, all patients will start a standard regimen of OCS to establish control of disease activity (note: control of disease activity is defined as when new lesions cease to form and existing lesions begin to heal). Specifically, patients with moderate BP (BPDAI activity score ≥24 and <60) will receive 0.5 mg/kg/day of prednisone (or prednisolone) and patients with severe BP (BPDAI activity score ≥60) will receive 0.75 mg/kg/day of prednisone (or prednisolone). Tapering of OCS will begin when there has been 2 weeks of sustained control of disease activity and will follow a protocol-defined schedule as long as control of disease is maintained, which allows patients to get off OCS by week 16 (or sooner). Following the OCS taper period, patients will be monitored for

relapses during a remission period of at least 36 weeks. During the OCS taper period, patients who experience a loss of control of disease activity (ie, new lesions [eg, blisters, urticarial plaques] begin to form and existing lesions do not heal) will be allowed to increase the prednisone (or prednisolone) dose to the dose level where there was control of disease activity before continuing with the predefined OCS tapering regimen. If a patient fails to complete the OCS tapering regimen (to a dose of 0.05 mg/kg/day or less) a second time, they should be considered for rescue treatment (Section 9.3.2). Patients who experience a relapse (defined as the appearance of 3 or more new lesions a month [blisters, eczematous lesions, or urticarial plaques] or at least 1 large [>10 cm diameter] eczematous lesion or urticarial plaque that does not heal within 1 week) after completely tapering off OCS may be rescued, including with re-initiation of OCS.

During the 52-week double-blind treatment period, patients will have study visits every 2 weeks until week 16 (some specified study visits may be conducted as telemedicine visits). After week 4, patients will have the option to self-administer study drug (or have a caregiver/healthcare provider [eg, visiting nurse] administer) during weeks in which no clinic visit is scheduled. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic. After week 16, patients will have in-clinic or phone visits as specified in the Schedule of Events (see Section 14.2.1) during the remainder of the 52-week treatment period. If a BP flare (defined as worsening of disease) is suspected during a phone visit, then the patient should be assessed in person by the investigator at an unscheduled visit for a BP relapse. Study drug will be administered SC q2w through week 50.

Following the 52-week double-blind treatment period, patients will have phone visits as specified in the Schedule of Events (see Section 14.2.2) and then return for an in-person follow-up visit at week 64 (end of study).

2.2. Sample Size and Power Considerations

The sample size calculation of the study is based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the primary endpoint at week 36 for the patients achieving sustained remission as defined in Section 7.1.1. Assuming 35% of the placebo group achieves the primary endpoint, approximately 98 randomized patients (49 per arm) will yield >90% power to detect a 40% difference between groups in the proportion of responders with a 2-sided significance level of α=0.01 using Fisher's exact test. The same sample size will provide >90% power with 2-sided significance level of α=0.05 taking into account a dropout rate of approximately 20%.

The placebo rate of 35% is based on publications (Simon, 2019) (Joly, 2009) and clinical practice. The 40% treatment difference between the dupilumab and placebo groups is based on discussion with experts and corroborated with publications (Abdat, 2020) (Simon, 2019).

3. ANALYSIS SETS

The following defines the sets of subjects whose data will be used for statistical analysis.

3.1. Full Analysis Set

The FAS is defined as all randomized patients analyzed according to the treatment group allocated by randomization (ie, as randomized) regardless of whether the treatment kit is used or not.

All efficacy endpoints will be evaluated on the FAS, which will be considered as the primary analysis set.

3.2. Safety Analysis Set

The SAF includes all randomized patients who have received any study drug; it is based on the treatment received (ie, as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

The actual treatment group as treated is defined by the following rules:

- For patients who received any dose of the active study drug (dupilumab) during the trial, the treatment group allocation for as-treated analysis will be the dupilumab group, regardless of the treatment group that the patient was randomized to.
- For a patient randomized to dupilumab 300 mg q2w, if the patient received all placebo injections, the actual treatment will be assigned as placebo.

3.3. Pharmacokinetic Analysis Set

The PKAS includes all randomized patients who have received any study drug and who had at least 1 non-missing drug concentration result following the first dose of study drug.

3.4. Immunogenicity Analysis Sets

3.4.1. ADA Analysis Set

The AAS includes all patients who have received any amount of study drug (active or placebo) and had at least 1 non-missing ADA result following the first dose of study drug. The AAS is based on the actual treatment received (as treated) rather than as randomized.

3.4.2. Neutralizing Antibody Analysis Set

The NAS includes all patients who are included in the AAS and who tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times and had at least one non-missing post-dose NAb result (either imputed or analysis result). Samples that tested negative for ADA are not assayed in the NAb assay and the corresponding NAb results are imputed as negative and included as such in the NAS. Patients in the NAS with multiple post-dose ADA results which consist of both imputed NAb-negative result(s) for ADA-negative samples and only missing NAb results for all ADA-positive result(s), are set to NAb negative. Patients in the NAS that have at least one post-dose positive NAb analysis result are set to NAb positive even if other NAb results are missing.

4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

Unless otherwise stated, the following conventions will be applied when presenting summary-level statistics.

Continuous variables will be summarized within each treatment group, presenting the following summary statistics: The number of observations with an available value of the variable, mean, standard deviation, median, minimum, maximum, Q1, and Q3.

Categorical data will be summarized within each treatment group by frequency (ie, total number of observations within each level of the categorical variable in a given treatment group). All levels of the categorical variable will be included. If there are observations where the level of the categorical variable is missing, a separate category titled "Missing" will be created. For categorical variables that are ordinal in nature, the order in which the levels of the categories are displayed will be consistent with the natural ordering of the category levels. Percentages will also be calculated for each level of the categorical variables with respect to the total sample size for the respective treatment group.

For the time-to-event data, Kaplan-Meier curves and estimates of the median time-to-event, along with 95% CIs, will be provided.

5. PATIENT DISPOSITION

5.1. Screening Dispositions

The number of screened patients (ie, patients who signed the ICF) who are randomized (ie, assigned a randomization number in the IWRS) and the number of screened patients who are screen-failed will be presented. The number of patients who screen-fail will be broken out by reason for screen failure. If applicable, the number of patients who are improperly randomized (ie, did not meet all inclusion criteria or met one or more exclusion criteria yet were assigned a randomization number in the IWRS) will also be displayed. The corresponding percentages with respect to the total number of screened patients will also be presented.

5.2. Treatment Period Dispositions

The disposition of all randomized patients during the treatment period will be displayed by treatment group and overall using the FAS. A patient is considered to have completed the treatment period if they make it to the End of Treatment visit (Visit 28/Week 52) or the date of the last visit is on or after study day 365.

The following summaries will be provided for each treatment group and overall (unless otherwise specified):

- The total number of patients in each analysis set
- The total number of patients who discontinued the study and the reasons for discontinuation (including COVID-19-related reasons)
- The total number of patients who discontinued the study before week 36 and the reasons for discontinuation (including COVID-19-related reasons)
- The total number of patients who discontinued the study before week 52 and the reasons for discontinuation (including COVID-19-related reasons)
- The total number of patients who discontinued the study treatment and the reasons for discontinuation (including COVID-19-related reasons)
- The total number of patients who discontinued the study treatment before week 36 and the reasons for discontinuation (including COVID-19-related reasons)
- The total number of patients who discontinued the study treatment before week 52 and the reasons for discontinuation (including COVID-19-related reasons)
- The total number of patients who completed week 36 and week 52, respectively

5.3. Follow-up Period Dispositions

For patients who complete the treatment period and proceed into the follow-up period, the number of patients who complete the follow-up period and those who discontinue from the follow-up period will be reported. The patients who discontinue from the follow-up period early will be further summarized by reason for early discontinuation.

Note: In addition to the disposition summaries described above, a summary table of important protocol deviations that occur at any time during the study will be provided.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables will be summarized for the FAS population by treatment group and overall:

- Age at screening (years)
- Age categories (<65 years, ≥65 years, ≥65 to <75 years, ≥75 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Region (North America, Europe, Japan) (IWRS)
  - Note: Taiwan was included in the Europe level of the region stratification factor in the IWRS
- Region (North America, Europe, Asia)
  - Asia will consist of Japan and Taiwan
- Country
- Baseline weight (kg)
- Baseline weight categories (<60 kg, ≥60 to <90 kg, ≥90 kg)
- Height (cm)
- BMI (kg/m^2)
- BMI categories (<15 kg/m^2, ≥15 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2)

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the FAS population by treatment group and overall:

- Duration of BP (years)
- Status of disease at baseline (New onset, Relapsed active disease)
- Age at BP onset (years)
- Prior steroid/immunosuppressant use (Yes, No) (IWRS)
- Baseline BPDAI activity score
- Baseline disease severity (Moderate [BPDAI activity score ≥24 to <60], Severe [BPDAI activity score ≥60]) (IWRS)
- Baseline BPDAI pruritus score

- Baseline peak pruritus NRS score
- Baseline skin pain NRS score
- Baseline sleep quality NRS score
- Baseline BSA affected by BP
- Baseline ABQOL score
- Baseline EQ-5D-3L utility index
- Baseline EQ-5D-3L VAS score
- Baseline PGADS (No symptoms, Mild symptoms, Moderate symptoms, Severe symptoms, Very severe symptoms)
- Baseline eosinophil count (10^9/L)
- Baseline total IgE concentration in serum (kU/L)
- Baseline BP180 IgG concentration in serum (U/mL)
- Baseline BP230 IgG concentration in serum (U/mL)
- Baseline PB180 IgE concentration in serum (U/mL)
- Baseline BP230 IgE concentration in serum (U/mL)
- Baseline BP180 IgG4 concentration in serum (U/mL)
- Baseline BP230 IgG4 concentration in serum (U/mL)
- Baseline serum CCL17 (pg/mL)
- Baseline serum CCL18 (pg/mL)
- [redacted]
- [redacted]
- Baseline erosions/blisters count category
- Baseline urticarial, eczematous or erythematous plaques count category
- Baseline Karnofsky Performance Status Scale score

6.3. Medical History

Patient medical histories will be coded using MedDRA®. The frequency and percentage of each medical history event will be summarized by SOC and PT for each treatment group, and overall based on the FAS.

7. EFFICACY/PHARMACODYNAMIC DATA

7.1. Description of Efficacy/Pharmacodynamic Data

The efficacy data include measurements or scores for individual patients for the following: BP clinical assessment (includes disease control, complete remission, disease relapses), total cumulative dose of OCS, peak pruritus NRS, skin pain NRS, sleep quality NRS, BPDAI activity score, BPDAI pruritus score, EQ-5D-3L, BSA, blister and urticaria/eczematous plaque count, ABQOL, PGADS, PGAT, and BP180 and BP230 autoantibody concentrations. Although "titer" is used in the objectives and endpoints, the concentration will be used in the analysis instead.

7.1.1. Primary Efficacy Data

The primary endpoint is the proportion of patients achieving sustained remission at week 36, defined as:

- Achievement of complete remission and off OCS no later than week 16 after randomization (Note: complete remission is defined as absence of new lesions and epithelialization of old lesions), and
- Absence of disease relapse from the time the patient has completed the OCS taper (no later than week 16 after randomization) to week 36 (Note: relapse is defined as the appearance of 3 or more new lesions a month (blisters, eczematous lesions, or urticarial plaques) or at least 1 large [>10 cm diameter] eczematous lesion or urticarial plaque that does not heal within 1 week), and
- Absence of need for rescue therapy during the 36-week double-blind treatment period (Note: rescue therapy includes increase of OCS dose during the taper, re-initiation of OCS after completion of the OCS taper, or initiation of any BP-directed therapy).

Patients will undergo this assessment at time points according to the Schedule of Events specified in Section 14.2. Sustained remission will be derived based on these criteria.

Patients who do not have a week 36 BP assessment but meet non-responder criteria based on observed data or who cannot achieve sustained remission by definition will be considered as non-responders (ie, 1) cannot achieve complete remission and off OCS no later than week 16 after randomization, which is only applicable to those who have already completed the week 16 visit; 2) relapse from the time the patient has completed the OCS taper to week 36; 3) use rescue therapy during the 36-week double-blind treatment period; 4) Loss of disease control (ie, new lesions [eg, blisters, urticarial plaques] begin to form and existing lesions do not heal) during the OCS taper period will be considered treatment failures; 5) Patients requiring doses greater than 0.75 mg/kg/day of prednisone (or prednisolone) and those who do not achieve control of disease activity by week 4 will be considered treatment failures).

7.1.2. Key Secondary Efficacy Data

The key secondary efficacy endpoints are:

- Total cumulative dose of OCS from baseline to week 36

- Percent change in weekly average of daily peak pruritus NRS from baseline to week 36
- Proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline to week 36
- Percent change in BPDAI activity score from baseline to week 36
- Time to first use of rescue medication (up to week 36)

Total Cumulative Dose of OCS

The OCS doses are collected in the SDR form. Each entry in the SDR form includes the daily dose, dose start date and dose end date. The steroid dosing will be converted to prednisone equivalent as specified in Table 15.

For each patient, the total cumulative dose of OCS will be calculated as follows (after applying the intercurrent events and missing data handling strategies as outlined in Table 4) for the primary analysis:

1. Period (from baseline to week 36/week 52) is defined by Period start date and Period end date:
   a. Period start date = date of first dose of study drug
   b. Period end date = Target date of period end (ie, week 36 or week 52). [Target date of period end is calculated as: date of first dose of study drug + 36×7 for week 36 or date of first dose of study drug + 52×7 for week 52]
2. For each day within that period, a patient's total daily OCS dose can be obtained from the SDR form and imputed data (ie, data that follows the intercurrent events and missing data handling rules in Table 4) by comparing the date with dose start date and dose end date. For example, the 08Sep2023 total daily OCS dose of the patient will be calculated as the sum of all the daily OCS doses (collected in the SDR form or imputed) with dose start date≤08Sep2023≤dose end date.
3. Average daily dose of OCS within the specific period (from baseline to week 36/week 52) = sum of total daily OCS doses taken each day within the period ÷ (period end date - period start date + 1)
4. Total cumulative dose of OCS from baseline to week 36 = (Average daily dose of OCS within week 36) × 36 × 7; Total cumulative dose of OCS from baseline to week 52 = (Average daily dose of OCS within week 52) × 52 × 7

These derivations will be modified as needed to conduct the sensitivity analyses described in Section 7.2.2.2.

Peak Pruritus Numerical Rating Scale

The peak pruritus NRS is a simple assessment tool that patients will use to report the maximum intensity of their pruritus (itch) during a 24-hour recall period. Patients will complete the rating scale throughout the study.

The peak pruritus NRS score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum itch intensity (the daily score ranges from 0 to 10 with higher

score indicating higher itch intensity) during the 7 days immediately preceding the first dose or the corresponding target visit date. In addition, the daily score entered on the first dose day but prior to the injection will be included in the baseline weekly average. Details are provided in Section 11.4. A minimum of 4 daily scores out of the 7 days is required to calculate the average score. If there are less than 4 diary entries for the 7-day period, the peak pruritus NRS score is considered as missing for that period.

Bullous Pemphigoid Disease Area Index Activity Score

The BPDAI activity score is a validated instrument in BP patients (wijayanti, 2017). The total BPDAI activity score is the arithmetic sum of 3 subcomponents: cutaneous blisters/erosions, cutaneous urticaria/erythema, and mucosal blisters/erosions. Scores can range from 0 to 360 for BPDAI total activity (maximum 240 for total skin activity and 120 for mucosal activity), with higher scores indicating greater disease activity. This questionnaire will be collected at screening, baseline, in-clinic visits, the ET visit and unscheduled visits.

Time to First Use of Rescue Medication

This is calculated from the date of randomization to the date of the first use of rescue medication (Section 9.3.2).

7.1.3. Other Secondary Efficacy Data

Other secondary efficacy endpoints are:

- Duration of complete remission while not requiring OCS (up to week 36)
- Proportion of patients who do not achieve control of disease activity, who relapse after achieving control of disease activity, or do not achieve complete remission (up to week 36) (Note: control of disease activity is defined when new lesions cease to form and existing lesions begin to heal)
- Proportion of patients who achieve a reduction in BPDAI activity score of at least 50%, 75%, and 90% from baseline to week 36
- Change in ABQOL from baseline to week 36
- Change from baseline to week 36 in percent BSA of BP involvement
- Change in BP180 and BP230 autoantibody (IgG) titers from baseline to week 36
- Proportion of patients with sustained remission at week 52
- Total cumulative dose of OCS from baseline to week 52
- Duration of complete remission while not requiring OCS (up to week 52)
- Proportion of patients who do not achieve control of disease activity, who relapse after achieving control of disease activity, or do not achieve complete remission (up to week 52)
- Percent change in weekly average of daily peak pruritus NRS from baseline to week 52

- Proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline to week 52
- Percent change in BPDAI activity score from baseline to week 52
- Proportion of patients who achieve a reduction in BPDAI activity score of at least 50%, 75%, and 90% from baseline to week 52
- Change in ABQOL from baseline to week 52
- Change from baseline to week 52 in percent BSA of BP involvement
- Change in BP180 and BP230 autoantibody (IgG) titers from baseline to week 52
- Proportion of patients in complete remission and off OCS at week 16
- Percent change in BPDAI activity score from baseline to week 16
- Proportion of patients who achieve a reduction in BPDAI activity score of at least 50%, 75%, and 90% from baseline to week 16
- Percent change in weekly average of daily peak pruritus NRS from baseline to week 16
- Proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline to week 16

Duration of Complete Remission While Not Requiring OCS

Achievement of complete remission (defined in Section 7.1.1) is one of the components of Bullous Pemphigoid Clinical Assessment completed by investigators. Duration of complete remission while not requiring OCS will be derived as the sum of the durations of each complete remission without OCS period between the date of first dose of study drug and week 36 (study day 253) or week 52 (study day 365). A complete remission without OCS period is defined as the interval between the date of the visit when the complete remission was achieved without OCS and the date of the next closest visit that complete remission was not achieved or the date OCS was reinitiated, whichever was earlier. There is no overlap between any complete remissions for each patient. If a complete remission without OCS period does not end before week 36 or week 52, the duration after that will not be counted towards the corresponding duration of complete remission. If a patient has a rescue therapy, the date of the rescue defines the end of remission, and any subsequent remission in any subsequent time period will not be included in the calculation of duration of complete remission. Missing assessment at a visit will be considered as not complete remission. For patients who cannot get off OCS, the duration of complete remission while not requiring OCS is 0.

Control of Disease Activity

Control of disease activity is defined as when new lesions (eg, blisters, urticarial plaques) cease to form and existing lesions begin to heal (eg, show signs of epithelialization). Initial control of disease is obtained when there have been no new lesions and lesions have begun to heal for at least 24 hours.

Autoimmune Bullous Disease Quality of Life

ABQOL has been shown to have good validity and reliability (Sebaratnam, 2013). This questionnaire consists of 17 items, which encompass physical burden of the disease, psychiatric effects, and effects on daily life functioning. Each question ranges from 0 to 3 points, with higher scores indicating poorer quality of life. The ABQOL score is the sum of the scores from the 17 questions. The maximum ABQOL score is 51.

Body Surface Area

BSA affected by BP will be assessed for each major section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined.

7.1.4. Exploratory Efficacy/Biomarker Data

The exploratory endpoints are;

- Time to first relapse after achieving control of disease activity (up to week 52)
- Percentage reduction of OCS dose at week 36 compared with the dose needed to control disease activity
- Percentage reduction of OCS dose at week 52 compared with the dose needed to control disease activity
- Percentage reduction of OCS dose at week 16 compared with the dose needed to control disease activity
- Change (absolute and percent) in weekly average of daily sleep quality NRS from baseline to week 36
- Change (absolute and percent) in weekly average of daily sleep quality NRS from baseline to week 52
- Change (absolute and percent) in weekly average of daily skin pain NRS from baseline to week 36
- Change (absolute and percent) in weekly average of daily skin pain NRS from baseline to week 52
- Change in circulating concentrations of total IgE, CCL17, CCL18 at each scheduled sampling time point compared to baseline
- Change in serum BP180 and BP230 autoantibody titers (both IgG4 and IgE subclasses) at each scheduled sampling time point compared to baseline
- Percentage of patients who respond “no symptoms/mild symptoms” in the PGADS at week 36
- Percentage of patients who respond “much better/a little better” to the PGAT question at week 36
- Change from baseline to week 36 in EQ-5D-3L
- Change from baseline to week 52 in EQ-5D-3L

- Change from baseline to week 36 in BPDAI pruritus
- Change from baseline to week 52 in BPDAI pruritus

Sleep Quality Numerical Rating Scale

Sleep quality is measured using a validated sleep quality NRS. This is an 11-point scale (0 to 10) in which 0 indicates worst possible sleep while 10 indicates best possible sleep. The patients are asked to select the number that best describes the quality of their sleep during the previous night. The sleep quality NRS score is determined based on the average of daily NRS scores during the 7 days immediately preceding the first dose or the corresponding target visit date (see Section 11.4 for additional details).

Skin Pain Numerical Rating Scale

Skin pain is measured using a validated skin pain NRS. This is an 11-point scale (0 to 10) in which 0 indicates no pain while 10 indicates worst pain possible. The patients are asked to select the number that best describes their skin pain during a 24-hour recall period. The skin pain NRS score is determined based on the average of daily NRS scores during the 7 days immediately preceding the first dose or the corresponding target visit date (see Section 11.4 for additional details).

Patient Global Assessment of Disease Severity

Patients rate their overall wellbeing based on a 5-point scale. Patients are asked: “Overall, how would you rate your bullous pemphigoid symptoms right now?”. Response choices are: “No Symptoms”, “Mild Symptoms”, “Moderate Symptoms”, “Severe Symptoms”, “Very Severe Symptoms”.

Patient Global Assessment of Treatment

Patients rate their satisfaction with the study treatment based on a 5-point scale. Patients are asked: “Compared to before you started the study, how would you rate your bullous pemphigoid symptoms now?”. Response choices are: “Much Better”, “A Little Better”, “No Difference”, “A Little Worse”, “Much Worse”.

Patient-Assessed EQ-5D-3L

The EQ-5D-3L is a standardized 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-3L consists of 2 parts: the descriptive system and the EQ-VAS.

The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: “no problem” (level 1), “some problems” (level 2), “extreme problems” (level 3). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement (ie, no problems, some problems, or severe problems) 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, visual analogue scale 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.

The questionnaire is administered only to the subset of patients who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries).

Change from baseline by visit in the EQ-5D-3L EQ-VAS and utility index scores will be provided. The EQ-5D-3L utility index will be calculated using the UK time-trade-off value set which maps each health state to an index score that quantifies health status.

Bullous Pemphigoid Disease Area Index Pruritus

A separate subjective component of the BPDAI, BPDAI Pruritus, is used to assess pruritus. The intensity of pruritus is subjectively graded using a visual analogue scale where 0 represents no itch and 10 represents maximal itching. Patient marks an "x" to indicate severity of itching in the past 24 hours, in the past week, and in the past month, producing a total score out of 30. In cases where the patient was unable to reliably complete the grading (due to impaired mental functioning), pruritus was inferred from the degree of excoriations, also scored out of 30. However, for this study, patients should be the only ones completing this assessment.

Percentage Reduction of OCS Dose at Weeks 16, 36, and 52 Compared with the Dose Needed to Control Disease Activity

The initial per-protocol OCS daily dose, 0.5 mg/kg/day of prednisone (or prednisolone) for moderate BP (BPDAI activity score ≥24 and <60) or 0.75 mg/kg/day of prednisone (or prednisolone) for severe BP (BPDAI activity score ≥60) will be used as the denominator to calculate the percentage reduction.

Percentage reduction of OCS dose at week 16, 36, 52 = (Total cumulative dose of OCS from baseline to week *z* / (week *z* days) - initial OCS daily dose) / initial OCS daily dose × 100%, where z =16, 36, 52.

7.1.5. Estimand Framework

The intercurrent events, strategies for the primary estimand of interest for the primary endpoint, key secondary endpoints, and other select secondary endpoints and missing data handling methods are provided in Table 1, Table 2, Table 3, Table 4, and Table 5. Week 16, week 36 and week 52 endpoints will be handled in the same manner.

Table 1: Summary of Primary Estimand for Primary Endpoint (Binary)

Endpoint Category	Estimand				
	Population	**Treatment**	**Endpoint**	**Intercurrent Events and Missing Data Handling**	**Population-Level Summary**
Primary Endpoint - Binary	Patients with BP	• Dupilumab • Placebo	Achievement of sustained remission at Week 36.	Intercurrent Events: • Rescue treatment: Patients will be considered as non-responders after such events (Composite Strategy). • Treatment discontinuation: Data collected after the patient discontinued treatment will be included in the analysis (Treatment Policy Strategy). Missing data: Applying the above two rules for intercurrent events, if there are still missing data and the observed data cannot determine that the patient is a non-responder, the handling methods are as follows: • Patient will be considered as a non-responder if the patient's data are missing at week 36 due to discontinuation from the study caused by lack of efficacy, treatment-related AEs or death. • For any other missing data, including missing data due to COVID-19, MI approach will be used.	Difference in the proportion of patients with sustained remission at Week 36 between treatment groups.

Table 2: Summary of Primary Estimand for Key Secondary Endpoint (Binary)

Endpoint Category	Estimand				
	Population	**Treatment**	**Endpoint**	**Intercurrent Events and Missing Data Handling**	**Population-Level Summary**
Key Secondary Endpoint - Binary	Patients with BP	• Dupilumab • Placebo	Achievement of improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline to week 36.	Intercurrent Events: • Rescue treatment: Patients will be considered as non-responders after such events (Composite Strategy). • Treatment discontinuation: Data collected after the patient discontinued treatment will be included in the analysis (Treatment Policy Strategy). Missing data: Applying the above two rules for intercurrent events, if there are still missing data, the handling methods are as follows: • Patient will be considered as a non-responder if the patient's data are missing at week 36 due to discontinuation from the study caused by lack of efficacy, treatment-related AEs, or death. • For any other missing data, including missing data due to COVID-19, MI approach will be used. MI will be based on the continuous variable, weekly average of daily peak pruritus NRS.	Difference in the proportion of patients with improvement (reduction) of weekly average of daily peak pruritis NRS ≥4 from baseline to week 36 between treatment groups.

Table 3: Summary of Primary Estimand for Other Secondary Endpoints in the Hierarchical Testing Order List (Binary)

Endpoint Category	Estimand				
	Population	**Treatment**	**Endpoint**	**Intercurrent Events and Missing Data Handling**	**Population-Level Summary**
Other Secondary Endpoints - Binary	Patients with BP	• Dupilumab • Placebo	Achievement of a reduction in BPDAI activity score of at least 90% from baseline to week 36.	Intercurrent Events: • Rescue treatment: Patients will be considered as non-responders after such events (Composite Strategy). • Treatment discontinuation: Data collected after the patient discontinued treatment will be included in the analysis (Treatment Policy Strategy). Missing data: Same as for the primary endpoint. (MI will be based on the continuous variable, BPDAI activity score.)	Difference in the proportion of patients with a reduction in BPDAI activity score of at least 90% from baseline to week 36.

Table 4: Summary of Primary Estimand for Secondary Endpoints in the Hierarchical Testing Order List (Continuous)

Endpoint Category	Estimand				
	Population	**Treatment**	**Endpoint**	**Intercurrent Events and Missing Data Handling**	**Population-Level Summary**
Secondary Endpoints - Continuous	Patients with BP	• Dupilumab • Placebo	• Total cumulative dose of OCS from baseline to week 36.	Intercurrent Events: • Non-OCS systemic rescue treatment: Days after non-OCS systemic rescue treatment will be imputed using WOCF including baseline (Composite Strategy). • Treatment discontinuation: Data collected after the patient discontinued treatment will be included in the analysis (Treatment Policy Strategy). Missing data: • Missing values subsequent to discontinuation from the study until week 36 (day 36×7+1) will be imputed with the daily average OCS dose of the other patients who have completed the week 36 visit in the same treatment arm; the daily average will be computed using the daily records from the day after a given patient discontinues from the study through study day 36×7+1.	• Difference in mean in total cumulative dose of OCS between treatment groups.
			• Percent change in weekly average of daily peak pruritus NRS from baseline to week 36.	Intercurrent Events: • Rescue treatment: data after rescue treatment will be imputed using the worst value* (Composite Strategy). • Treatment discontinuation: Data collected after the patient discontinued treatment will be	• Difference in mean percent change from baseline to week 36 in weekly average of daily peak

Endpoint Category	Estimand				
	Population	**Treatment**	**Endpoint**	**Intercurrent Events and Missing Data Handling**	**Population-Level Summary**
			• Percent change in BPDAI activity score from baseline to week 36. • Change from baseline to week 36 in percent body surface area (BSA) of BP involvement.	included in the analysis (Treatment Policy Strategy). Missing data: • WOCF (including baseline) approach will be used for the missing data from study discontinuation due to death, treatment-related AEs, or lack of efficacy. • An MI approach will be used to impute all week 36 missing values due to other reasons, including COVID-19.	pruritus NRS score between treatment groups. • Difference in mean percent change from baseline to week 36 in BPDAI activity score between treatment groups. • Difference in mean change from baseline to week 36 in percent BSA between treatment groups.
			• Change in autoimmune bullous disease quality of life (ABQOL) from baseline to week 36. • Change in BP180 autoantibody (Immunoglobulin G [IgG]) titers	Intercurrent Events: • Rescue treatment: data after rescue treatment will be imputed using the worst value* (Composite Strategy). • Treatment discontinuation: Data collected after the patient discontinued treatment will be included in the analysis (Treatment Policy Strategy).	• Difference in mean change from baseline to week 36 in ABQOL score between treatment groups. • Difference in mean change from baseline

Endpoint Category	Estimand				
	Population	**Treatment**	**Endpoint**	**Intercurrent Events and Missing Data Handling**	**Population-Level Summary**
			from baseline to week 36.	Missing data: • WOCF (including baseline) approach will be used for the missing data from study discontinuation due to death, treatment-related AEs, or lack of efficacy. • An MI approach will be used to impute all week 36 missing values due to other reasons, including COVID-19.	to week 36 in BP180 titer between treatment groups.
			• Duration of complete remission while not requiring OCS (up to week 36).	Intercurrent Events: • Rescue treatment: After rescue treatment, patients will be considered as not achieving complete remission (Composite Strategy). • Treatment discontinuation: Data collected after the patient discontinued treatment will be included in the analysis (Treatment Policy Strategy). Missing data: • After discontinuation from the study due to lack of efficacy, treatment-related AEs, or death, patients will be considered as not achieving complete remission. • MI approach will be used for missing data due to other reasons, including COVID-19.	• Difference in mean in duration of complete remission while not requiring OCS between treatment groups.

* Worst value from the closest visit immediately prior to rescue medication use (scheduled visit including baseline or unscheduled visit), on the visit of initiation of rescue treatment or afterwards up to and including week 36. Data are captured at visits; therefore, the worst value around and after the time of rescue treatment will be carried forward from one of the following until week 36 (whichever value is worst): the visit immediately prior to starting rescue treatment; or the visit when rescue treatment was started; or the visits after rescue treatment was started.

Table 5: Summary of Primary Estimand for Key Secondary Endpoints (Time-to-Event)

Endpoint Category	Estimand				
	Population	**Treatment**	**Endpoint**	**Intercurrent Events and Missing Data Handling**	**Population-Level Summary**
Key Secondary Endpoint – Time-to-Event	Patients with BP	• Dupilumab • Placebo	• Time to first use of rescue medication (up to week 36)	Intercurrent Events: • Treatment discontinuation: Data collected after the patient discontinued treatment will be included in the analysis (Treatment Policy Strategy). Missing data: • Study discontinuation due to lack of efficacy, treatment-related AEs, or death will be considered as having used rescue medication at the time of study discontinuation. • Study discontinuation due to any other reasons will be censored at the date of study discontinuation.	• Hazard ratio between treatment groups for time to first use of rescue medication

7.2. Analysis of Efficacy/Pharmacodynamic Data

The analyses of efficacy variables are described in the subsections below and summarized in Section 14.1.

7.2.1. Analyses of the Primary Endpoint

The primary analysis of the proportion of patients achieving sustained remission at week 36 will be performed using the stratified MH method, adjusting for baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), and prior corticosteroid/immunosuppressant use (Yes versus No). The estimate of the MH-weighted risk difference and corresponding 2-sided Wald 95% CI using the Sato variance will be presented along with the p-value. An exact method such as Barnard's exact test for p-value and 2-sided Miettinen and Nurminen 95% CI (based on the method of Lu and Guo, 2021) for the risk difference will be used if the expected frequencies in all cells are not at least 5.

The primary estimand for the primary endpoint is summarized in Table 1.

- For missing data, MI will be used with a seed number of 51468 to generate 50 complete datasets based on patients who have non-missing sustained remission outcome at week 36. The MI will utilize the logistic regression method with treatment group as an independent variable, baseline disease severity, region, and prior corticosteroid/immunosuppressant use as covariates, and status of achieving sustained remission at week 36 as the response variable in the logistic regression model.

Each of the imputed complete datasets will be analyzed by the MH test, and Rubin's rules will be applied to combine the estimates and perform statistical inference across imputations.

7.2.1.1. Sensitivity and Additional Analyses

Sensitivity analyses of the primary endpoint will assess alternative methods to impute missing data and include the following:

Tipping point analysis approach:

If the primary analysis is significant, tipping point analysis will be conducted to assess the robustness of the analysis result. The impact from missing data due to study discontinuation or other reasons on the comparison of the proportions of patients achieving sustained remission between the dupilumab and placebo groups will be examined.

- A series of analyses will be performed by varying the number of responders for the patients with missing data within each treatment group. For example, if there are 5 patients with missing data for each treatment group, then vary the number of responders from 0 to 5 for these patients for each treatment group.
- For each combination, the proportions of patients achieving sustained remission will be analyzed using the MH test.
- A "tipping point" will be identified when the result is no longer statistically significant (ie, p-value >0.05).

Other sensitivity analyses

The primary analysis will be repeated with the following modifications, respectively. The analysis method and data handling will be the same as the primary analysis unless otherwise specified.

1. Patient will be considered as a non-responder if the patient's data are missing at week 36, regardless of reason.
2. Patient will be considered as a non-responder if the patient discontinues from treatment before week 36, regardless of the reason for discontinuation (composite strategy).

Additional analyses

Each component of the primary endpoint (Section 7.1.1) will be analyzed using the same strategy and data handling method as the primary analysis.

3. Achievement of complete remission and off OCS no later than week 16 after randomization,
4. Absence of disease relapse from the time the patient has completed the OCS taper to week 36, and
5. Absence of need for rescue therapy during the 36-week double-blind treatment period.

7.2.1.2. Subgroup Analyses

Subgroups are defined by key baseline factors recorded on the eCRF (unless otherwise specified) and listed as follows.

Subgroups to be considered for both primary efficacy and safety analyses:

- Age group (<65 years, ≥65 years, ≥65 to <75 years, ≥75 years)
- Sex (Male, Female)
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, Other)
- Race (White, Non-white)
- Baseline weight group (<60 kg, ≥60 to <90 kg, ≥90 kg)
- Region (North America, Europe, Asia)

Subgroups to be considered for primary efficacy analyses only:

- Baseline disease severity (moderate BP, severe BP) (IWRS)
- Prior corticosteroid/immunosuppressant use (Yes, No) (IWRS)
- BP status at screening (New onset, Relapsed active disease)

Subgroups described above will be summarized for the primary efficacy endpoint. Treatment difference and its 95% confidence interval in subgroups of patients will be presented in forest plots.

Note: The subgroup analysis may not be performed if the number of patients within the subgroup is <10% of overall sample size. The baseline disease severity, region, and prior corticosteroid/immunosuppressant use factors will not be included in the subgroup analysis when performing the MH test.

Subgroups to be considered for primary efficacy, key secondary efficacy and important safety analyses (which are for China and/or Japan submission and may be performed outside of the Clinical Study Report):

- Asia
- Japan, Non-Japan

7.2.2. Analyses of Secondary Endpoints

7.2.2.1. Binary Secondary Endpoints at Week 36

Secondary efficacy endpoints that measure binary responses at week 36 will be analyzed in the same fashion as the primary endpoint, including the method to handle missing data. The estimand for the binary key secondary endpoint is summarized in Table 2. The estimand for the other binary secondary endpoints that are listed in the hierarchical testing order (Table 6) is summarized in Table 3. Other binary secondary endpoints at week 36 that are not in the hierarchical testing order list will also be analyzed using the same method.

7.2.2.2. Continuous Secondary Endpoints at Week 36

The endpoint of total cumulative dose of OCS from baseline to week 36 will be summarized by treatment group and analyzed using an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes versus No), and baseline OCS dose included in the model as covariates. The treatment group difference will be tested at the 2-sided 5% significance level. The endpoint calculation is described in Section 7.1.2. A supportive analysis will be performed using the non-parametric Wilcoxon rank-sum test.

For the days after a non-OCS systemic rescue medication is taken, the WOCF (using highest dose of OCS before the non-OCS systemic rescue medication use, including baseline) method will be used to impute each day, regardless of whether any OCS is also taken on the same day. In addition, the following sensitivity analyses will be performed separately:

- If a patient had non-OCS systemic rescue treatment, the days after will be excluded from the calculation of the total cumulative dose.
- Ignoring the impact of non-OCS systemic rescue medication and no data imputation in the calculation.
- For patients discontinuing the study due to lack of efficacy, treatment-related AEs, or death, the WOCF method will be used to impute each day until week 36.

Other continuous secondary efficacy endpoints at week 36 will be analyzed using an ANCOVA model for the FAS with treatment group, baseline disease severity (moderate versus severe BP),

region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes versus No), and relevant baseline measurement included in the model as covariates.

The estimand for the continuous secondary endpoints that are listed in the hierarchical testing order (Table 6) is summarized in Table 4.

- The MI approach will follow the steps below using a seed number of 6681902 to generate 50 complete datasets in the first 2 steps:
  - Step 1: Use the Markov Chain Monte Carlo method to fill in the intermittent missing values so that a monotone missing pattern will be formed.
  - Step 2: For each of the imputed datasets with monotone missing pattern in Step 1, the remaining missing data will be imputed using the regression method with treatment group, baseline disease severity, region, prior corticosteroid/immunosuppressant use, and the relevant baseline measurement as covariates and the post-baseline measurements up to week 36 as response variable.
  - Step 3: Each of the 50 imputed datasets will be updated to account for any single imputation methods (eg, worst value, WOCF, and/or mean value imputation per Table 4) and then analyzed using ANCOVA.
  - Step 4: The results from the 50 analyses on the complete datasets will be combined to generate a valid overall statistical inference using Rubin's formula (Ratitch, 2013). The LS means and difference in LS means between the dupilumab and placebo groups will be presented.

7.2.2.3. Time-to-event Secondary Endpoints at Week 36

Time to first use of rescue medication will be analyzed by a cox proportional hazards model including treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), and prior corticosteroid/immunosuppressant use (Yes versus No) in the model as covariates. Patients who do not use rescue medication up to week 36 (Day 253, inclusive) will be censored at Day 253. The hazard ratio between the two treatment groups will be reported with the 95% confidence interval and p-value. The estimand for the time-to-event secondary endpoint in the hierarchical testing order is summarized in Table 5.

7.2.2.4. Secondary Endpoints at Weeks 16 and 52

Secondary endpoints at weeks 16 and 52 will be analyzed in the same manner as for the corresponding endpoints at week 36.

7.2.3. Analyses of Exploratory Endpoints

The exploratory efficacy endpoints, unless specified otherwise, will be analyzed descriptively. No formal statistical hypothesis testing will be performed.

All observed values, regardless of whether rescue treatment is used or discontinuation from study treatment, will be used for analysis. No missing values will be imputed.

For the endpoint “time to first relapse after achieving control of disease activity (up to week 52)”, Kaplan-Meier curves and estimates of the median time-to-event along with 95% CIs, will be provided.

8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

8.1. Hypotheses Testing Methods

The statistical hypothesis specified in Section 1.2 will be tested for the primary endpoint at a 2-sided 5% significance level.

8.2. Multiplicity Control

A hierarchical procedure will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and specified secondary endpoints comparing the dupilumab group and the placebo group. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in Table 6.

Table 6: Hierarchical Order

	Endpoints	Testing Order
Primary Endpoint	Proportion of patients achieving sustained remission at week 36	1
Key Secondary Endpoints	Percent change in BPDAI activity score from baseline to week 36	2
	Time to first use of rescue medication (up to week 36)	3
	Proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline to week 36	4
	Percent change in weekly average of daily peak pruritus NRS from baseline to week 36	5
	Total cumulative dose of OCS from baseline to week 36	6
Other Secondary Endpoints	Duration of complete remission while not requiring OCS (up to week 36)	7
	Proportion of patients who achieve a reduction in BPDAI activity score of at least 90% from baseline to week 36	8
	Change from baseline to week 36 in percent BSA of BP involvement	9
	Change in BP180 autoantibody (IgG) titers from baseline to week 36	10
	Change in ABQOL from baseline to week 36	11

9. SUMMARY OF EXPOSURE DATA

9.1. Investigational Study Drug Exposure and Compliance

The duration of exposure to study drug is calculated as follows:

(Date of last study drug injection - date of first study drug injection) + 14

NOTE: exposure will be calculated based on the last study drug injection date and first study drug injection date regardless of temporary dosing interruption or dosing extension due to COVID-19.

Summary of exposure to study drug up to week 36 and week 52 will include the number of study drug doses administered and the duration of exposure. Duration of exposure will be summarized for each treatment group using the number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

In addition, the duration of exposure will be summarized categorically by counts (n) and percentages (%) for each of the following categories and cumulatively by these categories as well:

- Treatment duration: 1 - 14 Days, 15 - 28 Days, 29 - 42 Days, 43 - 56 Days, 57 - 70 Days, 71 - 84 Days,…, 323 - 336 Days, 337 - 350 Days, 351 - 364 Days, ≥365 Days, with an increment of 2 weeks for each successive category.
- Cumulative treatment duration: ≥14 Days, ≥28 Days, ≥42 Days, ≥56 Days, ≥70 Days,…, ≥336 Days, ≥350 Days, ≥364 Days, with an increment of 2 weeks for each successive category.

Summary of compliance with study drug through week 36 and week 52 will be presented by treatment group. Compliance with study drug will be calculated as follows:

(Number of study drug injections during the exposure period)/(Number of planned study drug injections during the exposure period) × 100%

Treatment compliance will be summarized for each treatment group using the number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. Treatment compliance will also be presented by the following ranges: <80% and ≥80%.

9.2. Duration of Observation

The duration of observation during the study (in days) will be calculated for each individual patient as:

(Date of last visit – date of first study drug administration) + 1 day

The duration of observation will be summarized for each treatment group using the number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. In addition, the duration of observation will be summarized categorically by counts (n) and percentages (%) by the following cumulative categories: ≥1 Day, ≥15 Days, ≥29 Days, ≥43 Days, etc, with a 14-day increment added for each successive category.

9.3. Prior and Concomitant Medications

Any treatment administered from the time of informed consent to the end of study participation will be recorded. This includes medications that were started before the study and are ongoing during the study. Medications will be coded using the WHO Drug Dictionary (WHODRUG).

Prior medications: medications taken prior to administration of the first dose of study drug.

Concomitant medications: medications taken following the first dose of study drug through the EOS visit. This includes medications that were started before the study and are ongoing during the study.

9.3.1. Prohibited Medications

Treatment with prohibited medications during the study is defined in protocol section 8.10.1.

9.3.2. Rescue Medication

Rescue medication during the study is defined in protocol section 8.3.

The following medications used for BP are considered rescue medications:

- Super high potency topical corticosteroids (anytime during the study)
- Systemic non-steroidal immunosuppressive drugs or immunomodulating biologics for BP (including but not limited to omalizumab, rituximab, mycophenolate-mofetil, azathioprine, methotrexate) (anytime during the study)
- Second increase in OCS dose during the OCS taper period (until week 16)
- Re-initiation of OCS post-taper (ie, after being completely off OCS)
- Use of OCS after week 16

The number and percentage of patients taking prior/concomitant medications, prohibited medications, and rescue medications will be summarized for each treatment group and overall, based on the study period-specific FAS, by ATC Level 2 and ATC Level 4, sorted by decreasing frequency of ATC Level 2 and ATC Level 4 in the overall group. Patients will be counted only once in each medication and therapeutic class linked to the medication.

9.4. Prior and Concomitant Procedures

Procedures are recorded from the day of informed consent until the EOS visit and all procedures are coded to a PT and associated primary SOC according to MedDRA®. Prior and concomitant procedures are defined as below:

Prior procedures: procedures performed prior to administration of the first dose of study drug.

Concomitant procedures: procedures performed following the first dose of study drug through the EOS visit.

The following concomitant procedures are prohibited during the study treatment:

- Major elective surgical procedures

The number and percentage of patients undergoing prior/concomitant procedures will be summarized for each treatment group and overall, based on the study period-specific FAS, by SOC and PT, and sorted by decreasing frequency of SOC and PT in the overall group.

10. ANALYSIS OF SAFETY DATA

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs, physical examination and 12-lead electrocardiogram (ECG)).

Thresholds for PCSVs in laboratory variables, vital signs and ECG are defined in Section 14.3. A treatment-emergent PCSV is any PCSV that developed or worsened in severity compared to baseline during the on-treatment or follow-up periods. The baseline when determining treatment-emergent PCSV refers to the baseline value of the study.

The time interval to detect any event or abnormality is from the time of signing the ICF to the end of the study.

The summary of safety results will be presented for each treatment group. For safety variables/summaries involving baseline values, eg, absolute change from baseline or shift table, the study baseline will be utilized.

10.1. Adverse Events

Treatment-emergent adverse events are AEs that developed or worsened in severity compared to baseline during the treatment or follow-up periods. As only the worsening pre-existing AEs and new AEs reported during the treatment and follow-up periods will be collected in the study, all AEs collected during the treatment and follow-up periods are considered as TEAEs.

Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment.

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period through Week 36 is defined as the time from the administration of the first dose of study drug to minimum(date of last dose of study drug + 14, relative day 36×7+1).
- The on-treatment period through Week 52 is defined as the time from the administration of the first dose of study drug to the date of the last dose of study drug + 14 days. TEAEs that have an onset during the on- treatment period and continue afterwards into the follow-up period will be counted only once as TEAEs during the on-treatment period.
- The post-treatment period (follow-up period) is defined as the time from the day after the end of the on-treatment period to the end of study date

For details on handling missing data and partial dates, see Section 11.3.

TEAE summaries will present the number (n) and percentage (%) of patients experiencing a TEAE by SOC and PT, sorted by decreasing frequency of SOC and PT in the dupilumab 300 mg q2w group. Multiple occurrences of AEs of the same PT (or SOC) in the same patient will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event. The denominator for computation

of percentage is the number of patients in each treatment group for the corresponding analysis period.

An overall summary of TEAEs will be provided with number (n) and percentages (%) of patients with any:

- TEAE
- Serious TEAE
- TEAE of special interest (AESI) (see Section 10.1.1)
- TEAE with fatal outcome
- TEAE leading to permanent treatment discontinuation

Detailed summaries of all TEAEs in each treatment group will include:

- TEAEs
  - TEAEs by primary SOC/PT
  - TEAEs by primary SOC/HLT/PT
  - TEAEs by primary SOC/PT with incidence of PT ≥5% in any treatment group
  - TEAEs by primary SOC/PT/Severity
  - TEAEs related to study drug by primary SOC/PT
  - TEAEs of special interest by AESI category (see Section 10.1.1) and primary SOC/PT
- Serious TEAEs by primary SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by primary SOC/PT
- TEAEs with fatal outcome by primary SOC/PT

The number and percentage of patients with injection site reactions by PT will be summarized.

10.1.1. Adverse Events of Special Interest

An AESI, serious or non-serious, is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

AESIs for this study include the following:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis

- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)

The summaries for AESIs are specified in Section 10.1. Search algorithms are in Table 13.

10.1.2. Other Adverse Events of Interest

Other adverse events of interest such as conjunctivitis CMQ (broad or narrow), conjunctivitis cluster, keratitis cluster, and COVID-19 SMQ will be summarized by PT.

The search algorithms for these AEs are listed in Table 14.

10.2. Laboratory Parameters

Laboratory measurements will be converted to values in standard international (SI) units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs. Patient laboratory parameter measurements will be evaluated by PCSV criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSV criteria (Section 14.3). Patients meeting the PCSV criteria will be summarized by patient count (and percent) for a post-baseline PCSV measurement by treatment group, regardless of baseline PCSV status. When the PCSV definition involves a change from baseline value, patients must have a baseline value to be included in the summary. All measurements collected during the study, including values from unscheduled visits, will be used in the PCSV analyses.

10.3. Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV.

10.4. Electrocardiography (ECG)

The following ECG parameters will be summarized descriptively:

- Heart Rate
- PR Interval
- QRS Duration
- QT Interval
- QTcB Interval
- QTcF Interval
- RR Interval

- Interpretation

Specifically, the interpretation parameter categorizes ECG status as Normal or Abnormal. Consequently, a shift table will be created to illustrate patients' transition in ECG status from baseline to post-baseline time points by treatment group.

10.5. Immunogenicity Data

10.5.1. Immunogenicity Variables

The immunogenicity variables include:

- ADA status (positive or negative), titer and time point/visit
- NAb status (positive or negative) and time point/visit

Serum samples in this study will be collected at the clinic visits specified in Section 14.2. Samples positive in the ADA assay will be analyzed for the presence of neutralizing antibody in the NAb assay.

Analysis of immunogenicity data will be performed by the Clinical Pharmacology function.

10.5.2. Analysis of Immunogenicity Data

10.5.2.1. Analysis of ADA Data

The immunogenicity variables described in Section 10.6.1 will be summarized by ADA status, ADA category and maximum titer category observed in patients in the ADA analysis set. For samples confirmed as drug-specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post-baseline ADA titers are reported as less than 4-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post-baseline titer result ≥4-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post-baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post-baseline samples separated by at least a 12-week post-baseline period (based on nominal sampling time), with no ADA-negative results in-between, regardless of any missing samples

- Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
- Transient - Not persistent or indeterminate, regardless of any missing samples

The maximum titer category of each patient is classified as:

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

The following listings will be provided by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of patients with pre-existing immunoreactivity
- Number (n) and percent (%) of treatment-emergent ADA-positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA-positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA-positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA-positive patients
- Number (n) and percent (%) of treatment-boosted ADA-positive patients

10.5.2.2. Analysis of Neutralizing Antibody (NAb) Data

The absolute occurrence (n) and percent of patients (%) by NAb status will be provided for patients in the NAb analysis set by treatment group.

- Negative: Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay.
- Positive: Samples tested positive in the NAb assay.

10.5.3. Association of Immunogenicity with Exposure, Safety and Efficacy

The analyses in this section will only be performed if the incidence of treatment-emergent ADA positive is sufficient to make meaningful conclusions (ie, more than 5% in any treatment group).

10.5.3.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to dupilumab will be explored by treatment group. Plots of dupilumab concentration may be provided for analyzing the potential impact of ADA category, maximum titer category, and NAb status on individual patient drug concentration profiles.

10.5.3.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (HLT="Injection site reactions")
- Hypersensitivity (AESI category "Hypersensitivity")
- Anaphylaxis (SMQ: Anaphylactic reaction [Narrow])

Potential association between immunogenicity variables and efficacy endpoint profiles may be explored (eg, scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following ADA response categories:

- ADA Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category
- NAb positive

10.6. Pharmacokinetic Data

10.6.1. Pharmacokinetic Variables

The pharmacokinetic variable is the concentration of functional dupilumab and time. Samples in this study will be collected using a sparse sampling schedule. The sampling time points are specified in Section 14.2.

10.6.2. Analysis of Pharmacokinetic Data

No formal statistical analysis will be performed. Functional dupilumab concentration in serum (C_{trough} time point) will be summarized at each time point using descriptive statistics. Plots of mean concentration versus nominal time may be presented. Analysis of pharmacokinetic data will be performed by the Clinical Pharmacology function.

11. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

11.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline value is defined as the latest available valid value before the first dose of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization.

The following rules specify the determination by both date/time information:

- The date and time of first injection will be used to determine the baseline for the AE, vital sign, lab (including biomarker), PK, and ADA data.
- Only the date of first injection will be used to determine the baseline for all other data.

For re-screened patients, all data from the same patient will be used to derive baseline regardless of whether the data are from the screen failure patient ID or enrolled patient ID.

11.2. Laboratory and Biomarker Data Conventions

For the laboratory safety variables and biomarker data, if the data are below the LLOQ/limit of linearity, half of the lower limit value (ie, LLOQ/2) will be used for quantitative analyses. For data above the ULOQ/limit of linearity, the upper limit value (ie, ULOQ) will be used for quantitative analyses.

11.3. Data for Non-Efficacy Endpoints

Rules for handling missing data for efficacy variables are described in Section 7.2.1 and Section 7.2.2.

For non-efficacy endpoints, missing data will not be imputed in listings.

Adverse event

If the severity of a TEAE is missing, it will be classified as “severe” in the frequency tables by severity of TEAEs. If the assessment of relationship of a TEAE to the study drug is missing, it will be classified as “related” in the frequency tables of TEAEs related to study drug.

Adverse event start date

The AE start date will be used for AE classification. If the AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed, and an imputation flag will indicate which date component is missing.

If the AE start day is missing and the AE start month and year are not missing: If the AE start year is the same as the first dose year and the AE start month is the same as the first dose month, then impute the AE start day using the day of first dose. If this leads to a date after the AE end date, use the AE end date instead. Otherwise, impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. The imputation flag is ‘D’.

If the AE start month is missing and the AE start year is not missing: If the AE start year is less than the first dose year, use the informed consent day and month. If the AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use the AE end date instead. If the AE start year is after the first dose year, use 01 January. The imputation flag is 'M'.

If the AE start year is missing: Impute the AE start date using the day of first dose. If this leads to a date after the AE end date, use the AE end date instead. The imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since the AE end date will be used for the imputation of the AE start date, in order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in the CRF will be kept in the final analysis dataset.

If the AE end day is missing and the AE end month and year are not missing: Impute the AE end date using the last day of the month. If this leads to a date after the end of study follow-up date, use the end of study date instead.

If the AE end month is missing and the AE end year is not missing: Impute the AE end date using 31 December as the day and month. If this leads to a date after the end of study date, use the end of study date instead.

If the AE end year is missing: Impute the AE end date using the end of study date.

Medication missing/partial dates

To determine whether a medication is a prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to the randomization date, and the missing medication end date is estimated as late as possible.

Prior medication start date

If the start day is missing and the start month and year are not missing: Impute the start day using the first day of the month. The imputation flag is 'D'.

If the start month is missing and the start year is not missing: Impute the day and month using 01 January. The imputation flag is 'M'.

If the start year is missing: Impute the start date using 2 years before the informed consent date. Imputation flag is 'Y'.

Prior medication end date

If the end day is missing and the end month and year are not missing: Impute the end date using the last day of the month. If this leads to a date on or after the first dose date, use first dose date -1 instead. The imputation flag is 'D'.

If the end month is missing and the end year is not missing: Impute the end date using 31 December as the day and month. If this leads to a date on or after the first dose date, use first dose date -1 instead. The imputation flag is 'M'.

If the end year is missing: Impute the end date using the first dose date -1. The imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start dates is the same as that for prior medication start dates.

Concomitant medication end date

If the end day is missing and the end month and year are not missing: Impute the end date using the last day of the month. If this leads to a date after the end of study date, use the last study visit date instead. The imputation flag is 'D'.

If the end month is missing and the end year is not missing: Impute the end date using 31 December as the day and month. If this leads to a date after the end of study date, use the last study visit date instead. The imputation flag is 'M'.

If the end year is missing: Impute the end date using the last study visit date. The imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records need to be confirmed with the study data manager and study medical director.

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Data analyzed using by-visit analysis (efficacy [excluding daily diary data], laboratory data, ECG, vital signs, ADA) will be summarized by the study scheduled visits described in the study protocol and SAP (Section 14.2).

Analysis visit windows will be created per the study Schedule of Events table for each parameter and will be applied if the data from the study scheduled visits are unavailable. The following general rules will be applied to the unscheduled visit and/or ET visit mapping for each parameter. For imputations using methods like worst case or WOCF, all visit data will be taken into account, including those not mapped as analysis visits.

1. If the ET visit falls in an analysis window which has no missing value of the parameter, the ET visit will be mapped to the next scheduled visit.
2. If both the ET visit and an unscheduled visit of the same parameter are available in the same analysis visit window, only the ET visit will be mapped.
3. If multiple unscheduled visits of the same parameter are available in the same analysis visit window, the unscheduled visits will be mapped using the following rules:
    a. The closest unscheduled visit to the target day will be selected.
    b. If the distance is a tie, the unscheduled visit after the target day of the scheduled visit will be used.
    c. If multiple unscheduled visits occur on the same day, the first unscheduled visit will be utilized.
4. If an unscheduled visit is greater than 4 weeks apart from the target day of the scheduled visit, the unscheduled visit will not be mapped.

Unscheduled and ET visits will be mapped per the analysis visit windows based on the study day and scheduled visit of each parameter, respectively (see Table 7, Table 8, and Table 9).

Table 7: Analysis Visit Windows for Efficacy Endpoints

Visit from SOE	Target Study Day	Analysis Visit Window Based on Study Day[a]			
		BPDAI Activity Score, BSA, Blister and Urticaria/Eczematous Plaque Count, BP Clinical Assessment	PGADS, EQ-5D-3L, ABQOL	PGAT	BPDAI Pruritus
Baseline	1	≤1	≤1		≤1
Week 2	15	[2, 22]			
Week 4	29	[23, 36]			
Week 6	43	[37, 50]			
Week 8	57	[51, 64]			
Week 10	71	[65, 78]			
Week 12	85	[79, 92]			
Week 14	99	[93, 106]			
Week 16	113	[107, 120]	[2, 120]	[2, 120]	[2, 120]
Week 24	169	[121, 176]			
Week 32	225	[177, 232]			
Week 36	253	[233, 260]	[121, 260]	[121, 260]	[121, 260]
Week 44	309	[261, 316]			[261, 316]
Week 52	365	[317, 372]	[261, 372]	[261, 372]	[317, 372]

a Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 1st injection date; otherwise, study day = date of assessment – 1st injection date. If a patient never received any dose of study drug, the randomization date will be used in place of the 1st injection date.

Table 8: Analysis Visit Windows for Safety and Biomarker Endpoints

Visit from SOE	Target Study Day	Analysis Visit Window Based on Study Day			
		Vital Signs	Physical Exam, ECG, ADA, Weight	Height	Laboratory, PK, Biomarkers
Baseline	1	≤1	≤1	≤1	≤1
Week 2	15	[2, 22]			
Week 4	29	[23, 36]			[2, 36]
Week 6	43	[37, 50]			
Week 8	57	[51, 64]			
Week 10	71	[65, 78]			
Week 12	85	[79, 92]			
Week 14	99	[93, 106]			
Week 16	113	[107, 120]	[2, 120]		[37, 120]
Week 24	169	[121, 176]			
Week 32	225	[177, 232]			
Week 36	253	[233, 260]	[121, 260]	[2, 260]	[121, 260]
Week 44	309	[261, 316]			
Week 52	365	[317, 372]	[261, 372]	[261, 372]	[261, 372]

a Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 1st injection date; otherwise, study day = date of assessment – 1st injection date. If a patient never received any dose of study drug, the randomization date will be used in place of the 1st injection date.

Table 9: Analysis Visit Windows for the 12-week Follow-up Period

Visit from SOE	Target Study Day	Analysis Visit Window Based on Study Day after End of Treatment
Week 64 EOS Visit (Patient discontinued from the treatment period)	85 (relative to the early termination visit)	≥2
Week 64 EOS Visit (Patient completed the treatment period)	85 (relative to the week 52 visit)	≥2

a Study days are calculated from the day of the early termination visit for patients not completing the treatment period or the day of the week 52 visit for patients completing the treatment period. Study day = (date of assessment – ET visit/week 52 visit date +1) when date of assessment is on or after the ET visit/week 52 visit date. If a patient does not complete the week 52 visit or ET visit, the week 64 visit will be not applicable for the patient.

For the analyses of the primary efficacy endpoint (proportion of patients achieving sustained remission at week 36) as well as for any analyses of BPDAI, the following modifications will be made to the visit mapping rules:

- For the primary efficacy endpoint, all available information from both scheduled and unscheduled/ET visits will be used to determine whether the patient was a responder or non-responder
- For analyses of BPDAI, if both a scheduled visit value and one or more unscheduled/ET visit values are available within the same analysis window, the worst value among these available measurements will be used for the analysis

11.4.1. Analysis Visit Windows for E-Diary Data

For peak pruritus, skin pain, and sleep quality NRS data (collected daily through an e-Diary), the analysis visit windows will be implemented following the procedure below:

Step 1: Diary study day derivation

- If diary date ≥ 1st injection date, diary study day = diary date – 1st injection date + 1
- If diary date < 1st injection date, diary study day = diary date – 1st injection date.

Step 2: Analysis visit windows are defined as follows:

- If there is an available measurement on Day 1 prior to the time of administration of the first dose of study drug, the baseline window is defined as Day -6 to Day 1; otherwise, the baseline window is defined as Day -7 to Day -1
- Day 1 to Day 7 after 1st injection = Week 1, Day 8 to Day 14 = Week 2, etc, with 7-day intervals between visit windows, through Day 358 to Day 364 = Week 52.

Note: Day 1 is the day of the first study drug injection, Day -1 is the day before, and there is no Day 0.

11.5. Pooling of Categorical Variables for Statistical Analyses

None.

12. TECHNICAL DETAILS PERTAINING TO INTERIM ANALYSIS

No interim analysis is planned.

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14. APPENDIX

14.1. Summary of Statistical Analyses

Efficacy Analyses:

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Proportion of patients achieving sustained remission at week 36	FAS	Proportion of responders at week 36 with 95% confidence interval	Mantel-Haenszel method for difference in proportions	See Section 7.2.1.1	Yes [1]	Histogram
Secondary Endpoints						
Secondary binary data (proportion of patients with improvement [reduction] of weekly average of daily peak pruritus NRS ≥4 from baseline to week 36)	FAS	Proportion of improvers at week 36 with 95% confidence interval	Mantel-Haenszel test	NA	No	Histogram
Secondary continuous variables (except the total cumulative dose of OCS)	FAS	Mean, change, and percent change from baseline to post-baseline visits	ANCOVA with WOCF-MI approach (See Section 7.2.2.2)	NA	No	Line plot
Total cumulative dose of OCS from baseline to week 36	FAS	Mean at week 36	ANCOVA	Non-parametric Wilcoxon rank-sum test Different non-OCS rescue treatment and missing data handling methods in Section 7.2.2.2	No	NA

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Time to first use of rescue medication (up to week 36)	FAS	Hazard ratio between treatment groups for time to first use of rescue medication	Cox proportional hazards model	NA	No	Kaplan-Meier curves

[1] Note: The subgroup analysis may not be performed if the number of patients within the subgroup is <10% of the overall sample size. The baseline disease severity, region, and prior corticosteroid/immunosuppressant use factors will not be included in the subgroup analysis when performing the MH test.

Safety Analyses:

Endpoint	Analysis Population	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	Yes	No
Laboratory Measures	SAF	Descriptive statistics	No	No	No
Vital Signs	SAF	Descriptive statistics	No	No	No
Physical Exams	SAF	Descriptive statistics	No	No	No
ECG	SAF	Descriptive statistics	No	No	No

14.2. Schedule of Time and Events

14.2.1. Schedule of Events (Screening, Baseline, and Double-Blind Treatment Period)

Table 10: Schedule of Events (Screening, Baseline, and Double-Blind Treatment Period)

Study Period	**Screening[3,4]**	**Double-Blind Treatment Period**																		
Study Milestone		**BL**																		
In-Clinic Visit (V)[1] or Phone Visit (PV)[2]	V1	V2	V3	V4	V5[1a]	V6[1a]	V7[1a]	V8[1a]	V9[1a]	V10	PV11	PV12	PV13	V14	PV15	PV16	PV17	V18	PV19	V20
Week (W)	-	-	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36
Study Day (D)	D-35 to D-1	D1	D15	D29	D43	D57	D71	D85	D99	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253
Visit Window in Days	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Screening/ Baseline																				
Inclusion/ Exclusion	X	X																		
Informed Consent	X																			
Medical History/Demographics	X																			
Karnofsky Performance Status	X																			
Patient e-Diary Training (Pruritus, Pain, and Sleep Quality NRS Assessments)[5]	X																			
Randomization		X																		
Treatment																				
Review Patient e-Diary Data[6]		X	X	X	X	X	X	X	X	X				X				X		X
Study Drug and/or Background Treatment (OCS) Administration/ Dispensing[7,8,9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Accountability[10]			X	X	X	X	X	X	X	X				X				X		X
Injection Training/Observation[11]			X	X																
Administer Patient Dosing Diary (ies)[7]		X	X	X	X	X	X	X	X	X				X				X		X

Study Period	**Screening[3,4]**	**Double-Blind Treatment Period**																		
Study Milestone		**BL**																		
In-Clinic Visit (V)[1] or Phone Visit (PV)[2]	V1	V2	V3	V4	V5[1a]	V6[1a]	V7[1a]	V8[1a]	V9[1a]	V10	PV11	PV12	PV13	V14	PV15	PV16	PV17	V18	PV19	V20
Week (W)	-	-	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36
Study Day (D)	D-35 to D-1	D1	D15	D29	D43	D57	D71	D85	D99	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253
Visit Window in Days	**-**	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Collect Patient Dosing Diary (ies)[12]			X	X	X	X	X	X	X	X				X				X		X
Concomitant Meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Screening[3,4]**	**Double-Blind Treatment Period**																		
Study Milestone		**BL**																		
In-Clinic Visit (V)[1] or Phone Visit (PV)[2]	V1	V2	V3	V4	V5[1a]	V6[1a]	V7[1a]	V8[1a]	V9[1a]	V10	PV11	PV12	PV13	V14	PV15	PV16	PV17	V18	PV19	V20
Week (W)	-	-	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36
Study Day (D)	D-35 to D-1	D1	D15	D29	D43	D57	D71	D85	D99	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253
Visit Window in Days	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Efficacy[13,14]																				
Pruritus, Pain, and Sleep Quality NRS (daily)[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Global Assessment of Disease Severity (PGADS)		X								X										X
Patient Global Assessment of Treatment (PGAT)										X										X
BPDAI Pruritus	X	X								X										X
EQ-5D-3L		X								X										X
ABQOL		X								X										X
BPDAI Activity Score, BSA, Blister and Urticaria/Eczematous Plaque Count, BP Clinical Assessment (includes disease relapses)	X	X	X	X	X	X	X	X	X	X				X				X		X
Photograph BP Area (select sites)[16]		X								X										X
Assessment of BP Flare[29]											X	X	X		X	X	X		X	
Safety																				
Vital Signs[17]	X	X	X	X	X	X	X	X	X	X				X				X		X
Physical Exam	X									X										X
ECG	X									X										X
Weight	X	X								X										X

Study Period	**Screening[3,4]**	**Double-Blind Treatment Period**																		
Study Milestone		**BL**																		
In-Clinic Visit (V)[1] or Phone Visit (PV)[2]	V1	V2	V3	V4	V5[1a]	V6[1a]	V7[1a]	V8[1a]	V9[1a]	V10	PV11	PV12	PV13	V14	PV15	PV16	PV17	V18	PV19	V20
Week (W)	-	-	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36
Study Day (D)	D-35 to D-1	D1	D15	D29	D43	D57	D71	D85	D99	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253
Visit Window in Days	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Height	X																			X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory testing																				
Hematology, Chemistry	X	X		X						X										X
Skin Biopsies for BP Diagnosis (Histology, Immunofluorescence)[18]	X																			
Serologies (HIV Ab, HBsAg, HBsAb, HBcAb[19], HCV Ab[20], HBV DNA[21], HCV RNA[22], TB test[23])	X																			
Serum FSH (if needed to confirm menopausal status)	X																			
Pregnancy Test (WOCBP only)[24]	Serum	Urine		Urine		Urine		Urine		Urine		Urine		Urine		Urine		Urine		Urine
Urinalysis	X	X		X						X										X
PK and Immunogenicity Samples[25]																				
Functional Dupilumab PK Sample		X		X						X										X
Anti-dupilumab Antibody Sample		X								X										X
Biomarker Samples																				
Skin Biopsy (IHC, RNA) (select sites)[26]		X																		X
Serum Total IgE, TARC		X		X						X										X

Study Period	**Screening[3,4]**	**Double-Blind Treatment Period**																		
Study Milestone		**BL**																		
In-Clinic Visit (V)[1] or Phone Visit (PV)[2]	V1	V2	V3	V4	V5[1a]	V6[1a]	V7[1a]	V8[1a]	V9[1a]	V10	PV11	PV12	PV13	V14	PV15	PV16	PV17	V18	PV19	V20
Week (W)	-	-	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36
Study Day (D)	D-35 to D-1	D1	D15	D29	D43	D57	D71	D85	D99	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253
Visit Window in Days	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
PARC, [redacted]		X		X						X										X
[redacted]																				
BP180, BP230 Autoantibodies	X[27]	X		X						X										X
Optional FBR Samples																				
Serum		X								X										X
Plasma		X								X										X
Optional Genomics Sub-study[28]																				
Whole Blood DNA		X																		
Whole Blood RNA		X								X										X

Study Period	**Double-Blind Treatment Period**							
Study Milestone								**EOT**
In-Clinic Visit (V) [1] or Phone Visit (PV) [2]	PV21	PV22	PV23	V24	PV25	PV26	PV27	V28
Week (W)	W38	W40	W42	W44	W46	W48	W50	W52
Study Day (D)	D267	D281	D295	D309	D323	D337	D351	D365
Visit Window in Days	±3	±3	±3	±3	±3	±3	±3	±3
Treatment								
Review Patient e-Diary Data[6]				X				X
Study Drug and/or Background Treatment	X	X	X	X	X	X	X	

Study Period	**Double-Blind Treatment Period**							
Study Milestone								**EOT**
In-Clinic Visit (V) [1] or Phone Visit (PV) [2]	PV21	PV22	PV23	V24	PV25	PV26	PV27	V28
Week (W)	W38	W40	W42	W44	W46	W48	W50	W52
Study Day (D)	D267	D281	D295	D309	D323	D337	D351	D365
Visit Window in Days	±3	±3	±3	±3	±3	±3	±3	±3
(OCS) Administration/ Dispensing[7,8,9]								
Accountability[10]				X				X
Administer Patient Dosing Diary (ies)[7]				X				
Collect Patient Dosing Diary (ies)[12]				X				X
Concomitant Meds/Procedures	X	X	X	X	X	X	X	X
Efficacy[13,14]								
Pruritus, Pain, and Sleep Quality NRS (daily)[15]	X	X	X	X	X	X	X	X
Patient Global Assessment of Disease Severity (PGADS)								X
Patient Global Assessment of Treatment (PGAT)								X
BPDAI Pruritus				X				X
EQ-5D-3L								X
ABQOL								X
BPDAI Activity Score, BSA, Blister and Urticaria/Eczematous Plaque Count, BP Clinical Assessment (includes disease relapses)				X				X
Photograph BP Area (select sites)[16]								X
Assessment of BP Flare[29]	X	X	X		X	X	X	

Study Period	**Double-Blind Treatment Period**							
Study Milestone								**EOT**
In-Clinic Visit (V) [1] or Phone Visit (PV) [2]	PV21	PV22	PV23	V24	PV25	PV26	PV27	V28
Week (W)	W38	W40	W42	W44	W46	W48	W50	W52
Study Day (D)	D267	D281	D295	D309	D323	D337	D351	D365
Visit Window in Days	±3	±3	±3	±3	±3	±3	±3	±3
Safety								
Vital Signs[17]				X				X
Physical Exam								X
ECG								X
Weight								X
Height								X
Adverse Events	X	X	X	X	X	X	X	X
Laboratory testing								
Hematology, Chemistry								X
Pregnancy Test (WOCBP only)[24]		Urine		Urine		Urine		Urine
Urinalysis								X
PK and Immunogenicity Samples[25]								
Functional Dupilumab PK Sample								X
Anti-Dupilumab Antibody Sample								X
Biomarker Samples								
Skin Biopsy (IHC, RNA) (select sites)[26]								X
Serum Total IgE, TARC								X
PARC[redacted]								X
[redacted]								
BP180, BP230 Autoantibodies								X

Study Period	**Double-Blind Treatment Period**							
Study Milestone								**EOT**
In-Clinic Visit (V) [1] or Phone Visit (PV) [2]	PV21	PV22	PV23	V24	PV25	PV26	PV27	V28
Week (W)	W38	W40	W42	W44	W46	W48	W50	W52
Study Day (D)	D267	D281	D295	D309	D323	D337	D351	D365
Visit Window in Days	±3	±3	±3	±3	±3	±3	±3	±3
Optional FBR Samples								
Serum								X
Plasma								X
Optional Genomics Sub-study[28]								
Whole Blood RNA								X

ABQOL: Autoimmune bullous disease quality of life; BP: Bullous pemphigoid; BPDAI: Bullous Pemphigoid Disease Area Index; BSA: Body surface area; EQ-5D-3L: European Quality of Life 5-Dimension 3-Level; FBR: Future biomedical research; FSH: Follicle-stimulating hormone; HBV: Hepatitis B virus; HBcAb: Hepatitis B core antibody; HBsAb: Hepatitis B surface antibody; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; ICH: immunohistochemistry; NRS: Numerical rating score; OCS: oral corticosteroids; PARC: Pulmonary and activation-regulated chemokine; PGADS: Patient Global Assessment of Disease Severity; PGAT: Patient Global Assessment of Treatment; PK: Pharmacokinetic; TARC: Thymus and activation-regulated chemokine; TB: Tuberculosis; WOCBP: women of childbearing potential.

14.2.2. Schedule of Events (Follow-up Period, Unscheduled Visit, Unscheduled Visit for BP Relapse, and Early Termination Visit)

Table 11: Schedule of Events (Follow-up Period, Unscheduled Visit, Unscheduled Visit for BP Relapse, and Early Termination Visit)

Study period	**Follow-up Period**			**Unscheduled Visit (if applicable)[3]**	**Unscheduled Visit for BP Relapse (if applicable)[3]**	**Early Termination Visit (if applicable)[4]**
Study milestone			**EOS**			
In-Clinic Visit (V)[1] or Phone Visit (PV)[2]	PV29	PV30	V31			
Week (W)	W56	W60	W64			
Study Day (D)	D393	D421	D449			
Visit window in days	±3	±3	±3			
Treatment						

Study period	**Follow-up Period**			**Unscheduled Visit (if applicable)[3]**	**Unscheduled Visit for BP Relapse (if applicable)[3]**	**Early Termination Visit (if applicable)[4]**
Study milestone			**EOS**			
In-Clinic Visit (V)[1] or Phone Visit (PV)[2]	PV29	PV30	V31			
Week (W)	W56	W60	W64			
Study Day (D)	D393	D421	D449			
Visit window in days	±3	±3	±3			
Review Patient e-Diary Data[5]			X	X	X	X
Study Drug and/or Background Treatment (OCS) Administration/Dispensing[7]				X	X (only if needed)	
Accountability[8]				X	X	X
Administer Patient Dosing Diary (ies)[6]				X	X	
Collect Patient Dosing Diary (ies)[9]				X	X	X
Concomitant Meds/Procedures	X	X	X	X	X	X
Efficacy[10,11]						
Pruritus, Pain, and Sleep Quality NRS (daily)[12]	X	X	X	X	X	X
Patient Global Assessment of Disease Severity (PGADS)			X			X
Patient Global Assessment of Treatment (PGAT)			X			X
BPDAI Pruritus			X	X	X	X
EQ-5D-3L			X			X
ABQOL			X	X		X
BPDAI Activity Score, BSA, Blister and Urticaria/Eczematous Plaque Count, BP Clinical Assessment (includes disease relapses)			X	X	X	X
Photograph BP Area (select sites)[13]			X		X	X
Assessment of BP Flare[18]	X	X				
Safety						
Vital Signs[14]			X	X	X	X
Physical Exam			X	X		X
ECG			X	X		X

Study period	**Follow-up Period**			**Unscheduled Visit (if applicable)[3]**	**Unscheduled Visit for BP Relapse (if applicable)[3]**	**Early Termination Visit (if applicable)[4]**
Study milestone			**EOS**			
In-Clinic Visit (V)[1] or Phone Visit (PV)[2]	PV29	PV30	V31			
Week (W)	W56	W60	W64			
Study Day (D)	D393	D421	D449			
Visit window in days	±3	±3	±3			
Weight			X	X		X
Adverse Events	X	X	X	X	X	X
Laboratory testing						
Hematology, Chemistry			X	X		X
Pregnancy Test (WOCBP only)[15]			Urine	Urine		Urine
Urinalysis			X	X		X
PK and Immunogenicity Samples[16]						
Functional Dupilumab PK Sample			X	X	X	X
Anti-dupilumab Antibody Sample			X	X	X	X
Biomarker Samples						
Skin Biopsy (IHC, RNA) (select sites)[17]				X		X
Serum Total IgE, TARC			X		X	X
PARC, [redacted]			X		X	X
[redacted]						
BP180, BP230 Autoantibodies			X	X	X	X
Optional FBR Samples						
Serum			X			
Plasma			X			
Optional Genomics Sub-study						
Whole Blood RNA			X			

ABQOL: Autoimmune bullous disease quality of life; BP: Bullous pemphigoid; BPDAI: Bullous Pemphigoid Disease Area Index; BSA: Body surface area; EQ-5D-3L: European Quality of Life 5-Dimension 3-Level; FBR: Future biomedical research; IHC: Immunohistochemistry; NRS: Numerical rating score; OCS: oral corticosteroids; PARC: Pulmonary and activation-regulated chemokine; PGADS: Patient Global Assessment of Disease Severity; PGAT: Patient Global Assessment of Treatment; PK: Pharmacokinetic; TARC: Thymus and activation-regulated chemokine; WOCBP: women of childbearing potential.

14.2.3. Footnotes for the Schedule of Events Tables

Footnotes for Table 10:

1. Assessments/procedures should be conducted in the following order: patient-reported outcomes, investigator assessments, safety and laboratory assessments (including sample collection for ADA, pharmacokinetics [PK], biomarkers [including skin biopsy at select study sites only], DNA, and RNA), and then administration of study drug.
    a. Visits 5 through 9 may be conducted as in-clinic or telemedicine visits. All telemedicine visits must include the BPDAI Activity Score, BSA, Blister and Urticaria/Eczematous Plaque Count, and BP Clinical Assessment (including disease relapses as assessed by the investigator) performed via video during the visit for a virtual assessment by the investigator with support from a healthcare provider (eg, visiting nurse) present with the patient. If a telemedicine visit is conducted, Accountability and Collecting Dosing Diaries are to be performed at the next in-clinic visit. Study drug and background treatment (OCS) dispensation should occur, if necessary, at these visits.
2. The site will contact the patient by telephone to conduct these visits. The patient, caregiver, or healthcare provider (eg, visiting nurse) may administer study drug on these days. Patients who receive study drug outside the study center will complete a dosing diary to document compliance with study drug administration and to document any related issues.
3. Patients may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions (eg, medication use, concomitant illness, medical condition), unless the reason for the screen failure is related to failing the disease diagnostic criteria.
4. During the screening period, treatments for BP will be washed out, as applicable, according to eligibility requirements (see Section 7.2.2 of the protocol).
5. Patients will receive training on completion of e-diary to record completion of assessment of Pruritus, Pain, and Sleep Quality NRS scales.
6. Study site staff will check patient data collected on the e-diary.
7. Study site staff will counsel patients on completing the dosing diary(ies) at each visit.
8. Starting at baseline visit, prednisone (or prednisolone) tablets will be dispensed to the patient in sufficient quantities until their next clinic visit. Patients will be counseled on documenting their daily prednisone (or prednisolone) dose in their dosing diary. Patients will return the remaining dispensed medication at each clinic visit. Refer to Section 8.2 (Background Treatments) of the protocol for OCS dosing.

9. Starting at week 6, for patients who choose to self-administer study drug, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic. Study drug (s) will be administered biweekly, either in the clinic or outside the clinic (self-administration or administration by a caregiver or healthcare provider [eg, visiting nurse]). An unscheduled visit may be used for in-clinic injections. Study drug will be administered through week 50.
10. Patients will return the original kit box for the prefilled syringe at each clinic visit.
11. Patients or caregivers will be trained on how to administer study drug under the observation of site staff to ensure correct administration technique is used. This will enable administration at home in between clinic visits.
12. Study site staff will review and check compliance each time the patient dosing diary(ies) are collected.
13. Questionnaires will be completed before any other assessments or invasive procedures (blood draws, study drug injection, etc.).
14. The questionnaires will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).
15. Pruritus, Pain, and Sleep Quality NRS will be completed daily via electronic questionnaire (e-diary). Reporting of these data begins on visit 1 (screening).
16. Select sites only - photograph BP area.
17. Vital signs (heart rate, blood pressure, respiration rate, and body temperature) should be taken pre-dose.
18. Biopsy for histology and direct immunofluorescence to be performed during screening unless a ≤6-month-old biopsy report (from the screening visit) for histology and direct immunofluorescence is available. Histopathology, immunopathology, and serological confirmation of BP performed at a local laboratory with results available within 6 months of the screening visit is acceptable.
19. In case of results showing HBsAg negative, HBsAb negative, and HBcAb positive, HBV DNA testing will be performed prior to randomization to rule out a false positivity and to confirm current infection.
20. In case of results showing positive Hep C Ab, HCV RNA testing will be performed to rule out a false positivity and to confirm current infection.
21. Will only be performed in patients whose serology results show HBsAg negative, HBsAb negative and HBcAb positive.
22. Will only be performed in patients whose serology results show positive Hep C Ab.
23. Tuberculosis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.

24. Not required if postmenopausal status confirmed at screening. After visit 1, monthly urine pregnancy tests are required for WOCBP.
25. Blood samples for both PK and ADA will be collected before the administration of study drug. Pharmacokinetic samples will be collected for the determination of dupilumab concentration and ADA samples for the immunogenicity assessment of dupilumab. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, unscheduled additional PK and ADA samples may be collected at or near the event.
26. Select study sites only - Skin biopsies will be collected at baseline and week 36. Additional peri-lesional skin biopsy for immunohistochemistry (IHC) and RNA analysis (includes RNAscope) to be collected during a relapse from patients who provide consent. At week 52, the skin biopsy will be collected only if active lesions are still present.
27. Serological confirmation of BP for diagnostic criteria performed through a local laboratory within 6 months of the screening visit is acceptable (see inclusion criterion #2 in Section 7.2.1 of the protocol).
28. A blood sample for genomic DNA (optional) will be collected pre-dose at baseline (day 1). If the sample collection is missed at that time point, the sample can be collected at any other study visit. Whole blood samples for RNA (optional) will be collected according to time points in Table 1 of the protocol.
29. If a BP flare (defined as worsening of disease) is suspected during a phone visit, then the patient should be assessed in person by the investigator at an unscheduled visit for a BP relapse (Table 2 of the protocol).

Footnotes for Table 11:

1. Assessments/procedures should be conducted in the following order: patient-reported outcomes, investigator assessments, safety and laboratory assessments (including sample collection for ADA, pharmacokinetics [PK], biomarkers [including skin biopsy at select study sites only], DNA, and RNA), and then administration of study drug.
2. The site will contact the patient by telephone to conduct these visits.
3. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for other reason (eg, before a rescue medication/procedure is used), as warranted. The assessments and procedures performed during an unscheduled visit will depend upon the reason for the visit. During an unscheduled visit, any of the study procedures noted may be performed, but not all are required. If the unscheduled visit is due to an AE, collect samples for PK and ADA analysis. An unscheduled visit may also be used for those patients who choose in-clinic administration of study drug. If a BP flare is suspected during a phone visit, then the patient is to return for assessments and procedures specified in Table 2 of the protocol for an unscheduled visit for BP relapse.

4. Patients who are withdrawn from the study will be asked to return to the clinic for early termination assessments.
5. Study site staff will check patient data collected on the e-diary.
6. Study site staff will counsel patients on completing the dosing diary(ies) at each visit.
7. If applicable, prednisone (or prednisolone) tablets will be dispensed to the patient in sufficient quantities until their next clinic visit. Patients will return the remaining dispensed medication at each clinic visit.
8. Patients will return the original kit box for the prefilled syringe at each clinic visit.
9. Study site staff will review and check compliance each time the patient dosing diary (ies) are collected.
10. Questionnaires will be completed before any other assessments or invasive procedures (blood draws, study drug injection, etc.).
11. The questionnaires will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).
12. Pruritus, Pain, and Sleep Quality NRS will be completed daily via electronic questionnaire (e-diary).
13. Select sites only - photograph BP area.
14. Vital signs (heart rate, blood pressure, respiration rate, and body temperature) should be taken pre-dose.
15. Not required if postmenopausal status confirmed at screening.
16. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional PK and ADA samples may be collected at or near the event.
17. Select sites only: skin biopsies for IHC and RNA analysis (includes RNAscope) to be performed on patients that relapse.
18. If a BP flare (defined as worsening of disease) is suspected during a phone visit, then the patient should be assessed in person by the investigator at a scheduled visit or at an unscheduled visit for BP relapse.

14.3. Criteria for Potentially Clinically Significant Values (PCSV)

Table 12: Criteria for Potentially Clinically Significant Values

Parameter	Treatment-Emergent PCSV	Comments
Clinical chemistry		
ALT/SGPT	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post-baseline may be provided
AST/SGOT	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post-baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	
Total Bilirubin	>1.5 and ≤ 2.0 ULN and baseline ≤ 1.5 ULN* >2.0 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post-baseline may be provided
Conjugated Bilirubin[a]	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin ≤35% Total Bilirubin or Total Bilirubin ≤1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis

Parameter	Treatment-Emergent PCSV	Comments
ALT or AST and Total Bilirubin	((ALT>3 ULN or AST>3 ULN) and TBILI>2 ULN) and baseline ((ALT ≤3 ULN and AST≤3 ULN) **or** TBILI ≤2 ULN)	
CPK	>3 and ≤ 10 ULN and baseline ≤ 3ULN >10 ULN and baseline ≤ 10ULN	
Creatinine	≥150 µmol/L (Adults) and baseline <150 µmol/L ≥30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994.
Albumin	≤25 g/L and >25 g/L at baseline	
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	
Blood Urea Nitrogen (BUN)	≥17 mmol/L and <17 mmol/L at baseline	
Chloride Hypochloremia Hyperchloremia	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	
Sodium Hyponatremia Hypernatremia	≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention

Parameter	Treatment-Emergent PCSV	Comments
Glucose Hypoglycaemia Hyperglycaemia	Hypoglycaemia: (≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or ≥LLN) at baseline Hyperglycaemia: >=7 mmol/L (fasted) and <7 mmol/L at baseline (fasted); >=11.1 mmol/L (unfasted) and <11.1 mmol/L at baseline (unfasted)	
HbA1c	>8% and <= 8% at baseline	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and ≤2 ULN or ≤10 mg/L (if ULN not provided) at baseline	
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	
Lymphocytes	>4.0 Giga/L and ≤4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and ≥1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and ≥1.0 Giga/L at baseline (Black)	
Eosinophils	(>0.5 Giga/L and >ULN) and (≤0.5 Giga/L or ≤ ULN at baseline)	
Monocytes	>0.7 Giga/L and ≤ 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L and ≤ 0.1 Giga/L at baseline	
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).

Parameter	Treatment-Emergent PCSV	Comments
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male; ≤0.32 v/v and > 0.32 v/v at baseline for Female ≥0.55 v/v and < 0.55 v/v at baseline for Male; ≥0.5 v/v and < 0.5 v/v at baseline for Female	
RBC	<4 Tera/L and baseline ≥4 Tera/L For Male; <3 Tera/L and baseline ≥3 Tera/L for Female ≥7 Tera/L and baseline < 7 Tera/L for Male; ≥6 Tera/L and baseline < 6 Tera/L for Female	
Platelets	<100 Giga/L and ≥100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Temperature	Rectal, ear: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary or skin infrared (temporal): >99 °F/37.2 °C	

Parameter	Treatment-Emergent PCSV	Comments
Respiratory rate	<12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG parameters		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms and < 120 ms at baseline	
QTc Borderline Prolonged Additional	Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and ≤ 450 ms at baseline for Male; >470 to <500 ms and ≤ 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline Increase from baseline: Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and QTc>60 ms are the PCSV to be identified in individual subjects/patients listings. 5 independent criteria

The ULN is based upon central lab reference ranges. The reference range might be different for different age-groups. For the purpose of this study in a particular patient the reference range based upon age at baseline will be used as reference throughout the study for determining PCSVs.
[a] Lab parameters not collected in this study.

14.4. Search Algorithms for AESIs and Other Adverse Events of Interest

The search algorithm is meant to assist the process of identification of TEAEs of interest. However, since the algorithm might not be specific in some cases, an additional blinded review may be performed by the medical monitor, based on medical judgement, to identify any TEAE that may have been inaccurately assigned as an AESI by the algorithmic search. The blinded adjudication and approval of the listing of TEAEs of special interest/TEAE syndrome will be done prior to the database lock and post database lock. Signature approval by the medical director will be filed to the Trial Master File for each adjudication. Any changes between the pre-DB lock listing and the post-DB lock final listing will be reviewed and documented.

Table 13: Search Algorithm for Adverse Events of Special Interest

AESI Category	Search Algorithm
Anaphylactic reactions	SMQ (Narrow) Anaphylactic reaction
Systemic hypersensitivity reactions (excluding events already included under anaphylactic reaction)	SMQ (Narrow) Hypersensitivity minus SMQ (Narrow) Anaphylactic reaction Note: Adjudication of relevant PTs will be required by the study medical monitor, before database lock
Helminthic infections	HLT Cestode infections <OR> HLT Helminthic infections NEC <OR> HLT Nematode infections <OR> HLT Trematode infections
Any severe type of conjunctivitis or blepharitis	(CMQ (Broad) Conjunctivitis or any PT containing “blepharitis”) and Severity= “severe”
Keratitis	SMQ (Narrow) Corneal disorders
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	(HLT Eosinophilic disorders <OR> PT Eosinophil count increased) Note: Adjudication of relevant PTs will be required by the study medical monitor, before database lock

Table 14: Search Algorithms for Other Adverse Events of Interest

AE Category	Search Algorithm
Conjunctivitis CMQ (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]
Conjunctivitis CMQ (Narrow)	CMQ10644 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, and Atopic keratoconjunctivitis]
Conjunctivitis Cluster	CMQ10643 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye inflammation, Eye irritation, Giant papillary conjunctivitis]
Keratitis Cluster	CMQ30102 based on the following PTs [Keratitis, Allergic keratitis, Atopic keratoconjunctivitis, Ulcerative keratitis, Ophthalmic herpes simplex]
Covid-19	SMQ (Narrow) COVID-19

14.5. Converting Systemic Corticosteroid Doses to Prednisone Equivalents

If systemic corticosteroids other than prednisone are used for BP, then the following table (Boutry, et al., 2008) will be used to convert other OCS/systemic corticosteroids to an equivalent dose of prednisone.

Table 15: Converting Systemic Glucocorticoid Doses to Prednisone Equivalents

Glucocorticoid	Prednisone equivalent (mg)
Prednisone	1
Prednisolone	1
Hydrocortisone	0.25
Methylprednisolone	1.25
Dexamethasone	6.67

Note: If any other systemic corticosteroids are used, they will be converted to the closest prednisone equivalent dose using a standard conversion, as applicable.

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