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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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
Study Name:	LIBERTY-BP ADEPT
Clinical Phase:	2/3
Protocol Number:	R668-BP-1902
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Amendment 3 Date of Issue:	*See appended electronic signature page*
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AMENDMENT HISTORY

Amendment 3

The purpose of this amendment is to [redacted]. None of the changes in this amendment will affect study conduct. The following table outlines the changes made to the protocol along with the corresponding rationale.

Description of Change	Brief Rationale	Section Number and Name
[redacted]		
"Time to first use of rescue medication (up to week 36)" has been added as a new key secondary endpoint for efficacy.	Assessing the time to first use of rescue medication is clinically important, as it permits evaluation of efficacy in delaying the need for use of rescue medications (eg, oral corticosteroids/ other immunosuppressive medications). Participants are permitted to use rescue medications during the study to manage disease worsening (eg, loss of control or relapses).	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Key Secondary Efficacy Endpoints
Two secondary endpoints for efficacy have been clarified as follows (amended text is underlined): • "Proportion of patients who do not achieve control of disease activity, who relapse after achieving control of disease activity, <u>or do not achieve complete remission</u> (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 do not achieve control of disease activity, who relapse after achieving control of disease activity, <u>or do not achieve</u>	Disease control, complete remission, and relapses are assessed during the study as measures of disease activity. The endpoints have been clarified to include complete remission to provide a comprehensive view of disease activity.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.3 Other Secondary Endpoints

Description of Change	Brief Rationale	Section Number and Name
complete remission (up to week 52)"		
Missing data handling methods have been further clarified for the primary and secondary efficacy analyses.	Missing data handling methods are clarified [redacted]	Clinical Protocol Synopsis: Statistical Plan Section 6.2 Planned Interim Analysis Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Table 3 Summary of Primary Estimand for Primary Endpoint Table 4 Summary of Primary Estimand for Key Secondary Endpoint (Binary) Table 5 Summary of Primary Estimand for Key Secondary Endpoint (Continuous)
In the case of use of rescue treatment as an intercurrent event for continuous endpoints, the imputation strategy is further elaborated. [redacted]	The purpose of this strategy is to try to accurately capture disease worsening at week 36 as possible. Bullous pemphigoid is known to flare. All patients will have received steroids at the beginning of the study with the intended effect of disease improvement. If a patient has a flare of disease requiring rescue medications, the intent is to accurately capture it.	Clinical Protocol Synopsis: Statistical Plan Section 11.4.3.2 Secondary Efficacy Analysis Table 5 Summary of Primary Estimand for Key Secondary Endpoint (Continuous)
Administrative change to the Medical/Study Director name	To accurately reflect the name and title of the current Medical/Study Director	Title Page
Minor editorial corrections and clarifications.	For clarification.	Throughout the protocol.

Amendment 2

Overall Rationale for Amendment 2: The primary purpose of this protocol amendment is to reduce study burden for patients from protocol-required invasive procedures and to provide flexibility for the visit options (eg, telemedicine) in view of the COVID-19 pandemic; to update patient eligibility requirements; and to add estimand for the statistical analyses of primary and key secondary efficacy endpoints. The following table outlines the changes made to the protocol and the rationale.

Description of Change	Brief Rationale	Section Number and Name
Clarified inclusion criterion for the serological evidence necessary for a diagnosis of bullous pemphigoid (BP) to allow for either a positive BP180 or BP230 serology result, or a positive indirect immunofluorescence (utilizing a peripheral blood specimen) result, and to expand the window for use of results from a historical biopsy from 3 months to 6 months.	To provide flexibility for eligibility criteria while ensuring appropriate patients qualify for the study.	Clinical Study Protocol Synopsis: Target Population Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, criterion #2 Section 9.1.1.1 Table 1 Schedule of Events Footnotes, footnotes #18 and 27 (previously #19 and 29) Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit
Updated exclusion criteria: • The washout period for systemic corticosteroids (prednisone or prednisolone equivalent) was changed from 2 weeks to at least 7 days • To clarify reference to systemic antihistamine use to require a stable dose of antihistamine use for at least 7 days prior to the baseline visit. Patients on a stable dose of systemic antihistamine for at least 7 days prior to baseline may enter study; however, the dose of these medications should remain unchanged for the duration of the study. Exclusion criterion related to use of topical antihistamines was removed. • The washout period for antibiotics directed at the treatment of BP was changed from 2 weeks to at least 7 days. • The washout period for nicotinamide directed at the treatment of BP was changed from 2 weeks to at least 7 days. • Patients previously treated with an IL-5 inhibitor such as benralizumab or mepolizumab may be entered after a washout period of 5 half-lives (if	To clarify eligibility requirements while ensuring appropriately symptomatic patients are eligible.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration Section 7.2.2 Exclusion Criteria, criteria #4, 5, 6, 7, 8, and 10 Section 8.10.1 Prohibited Medications and Procedures

Description of Change	Brief Rationale	Section Number and Name
known) or 16 weeks prior to the baseline visit, whichever is longer.		
The following changes were made: • Changed the required biomarker and exploratory [redacted] sample collection timing and removed the requirement for [redacted]. Updated exploratory objectives to remove/revise objectives related to [redacted] samples. • Changed the requirement for skin biopsies after visit 1 (screening visit) to select study sites only.	To minimize study burden for patients of invasive procedures.	Clinical Study Protocol Synopsis: Objectives Section 2.3 Exploratory Objectives Table 1: Schedule of Events (Screening, Baseline, and Double-Blind Treatment Period) Table 2: Schedule of Events (Follow-up Period, Unscheduled Visit, Unscheduled Visit for BP Relapse, and Early Termination Visit) Section 9.1.1.1 Table 1 Schedule of Events Footnotes, footnotes #1 and 26 (previously #27), previous footnote #28 deleted Section 9.1.1.2 Table 2 Schedule of Events Footnotes, footnotes #1 and 17 (previously #18), previous footnote #19 deleted) Section 9.2.6.1 Exploratory Research
Updated Schedule of Events: • To allow telemedicine visits for study visits 5 through 9. • Changed visits 12 and 16 from in-person visits to phone visits. • Added row for Karnofsky performance status at visit 1 • Patients may self-administer study drug beginning at week 6. • Added that a healthcare provider (eg, visiting nurse) could perform the injection of study medication if patient (or caregiver) did not wish to self-administer. • Removed PK and biomarker blood draws at weeks 24 and 44. • Removed monitoring of patients at study site for 30 minutes post-study drug administration. • Updated footnotes and cross-references to footnotes accordingly.	To minimize study burden for patients and to provide study visit options (eg, telemedicine visits) in view of the COVID-19 pandemic.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration Table 1: Schedule of Events (Screening, Baseline, and Double-Blind Treatment Period) Table 2: Schedule of Events (Follow-up Period, Unscheduled Visit, Unscheduled Visit for BP Relapse, and Early Termination Visit) Section 9.1.1.1 Table 1 Schedule of Events Footnotes, footnotes #1a, 2, 9, and 17 (previously #18); deleted prior footnote #7 Section 9.1.1.2 Table 2 Schedule of Events Footnotes, footnote #14 (previously #15), deleted prior footnote #6 Section 9.2.3.1 Vital Signs
Added assessment for BP flare during phone visits and added unscheduled visits for BP relapse.	To evaluate potential disease worsening.	Table 1: Schedule of Events (Screening, Baseline, and Double-Blind Treatment Period) Table 2: Schedule of Events (Follow-up Period, Unscheduled Visit, Unscheduled

Description of Change	Brief Rationale	Section Number and Name
		Visit for BP Relapse, and Early Termination Visit) Section 9.1.1.1 Table 1 Schedule of Events Footnotes, footnote #29 (new footnote) Section 9.1.1.2 Table 2 Schedule of Events Footnotes, footnotes #3 and 18 (new footnote) Section 9.1.3.1 Unscheduled Visit for BP Relapse (new section) Section 9.2.2.14 Assessment of Bullous Pemphigoid Flare (new section)
Increased number of study sites from approximately 30 to approximately 40 sites.	To ensure the targeted number of patients is enrolled.	Clinical Study Protocol Synopsis: Site Location(s), Sample Size Section 7.1 Number of Patients Planned
Updated prohibited medications: • Clarified prohibited medications that may be used as rescue treatment and whether or not use results in discontinuation of study drug. • Clarified that initiation, discontinuation, or change in dosing regimen of systemic antihistamines after the baseline visit is prohibited. • Added that changes to treatments known to cause or exacerbate BP should be made in consultation with the medical monitor.	To ensure the use of rescue medications are appropriately accounted for in the endpoint analysis.	Section 8.10.1 Prohibited Medications and Procedures Section 7.2.2 Exclusion Criteria, criteria #5 and 6
Updated the risks-benefits associated with dupilumab and removed the 30-minute post-dose monitoring for hypersensitivity reactions	To provide more current information.	Section 3.3.1 Risk-Benefit of Dupilumab for Patients with Bullous Pemphigoid
Added that [redacted] may be used for exploratory biomarker research.	To allow for exploratory research.	Section 9.2.6.1 Exploratory Research
Patients from study sites in Japan will not be stratified.	Approximately 10% (~10 patients) will be randomized from Japan. Given the small number of patients from Japan, using [redacted] strata may result in an imbalance of patients across strata.	Clinical Study Protocol Synopsis, Study Design Section 6.1 Study Description and Duration Section 8.6 Method of Treatment Assignment
Added primary estimand of interest and intercurrent event(s) strategy, and added missing data-handling methods for primary and key secondary efficacy endpoints. [redacted]. Removed	To implement a concept estimand in the primary analysis approaches for the primary and key secondary efficacy	Clinical Study Protocol Synopsis, Statistical Plan Section 11 Statistical Plan Section 11.3.1 Efficacy Analysis Sets Section 11.4 Statistical Methods

Description of Change	Brief Rationale	Section Number and Name
per-protocol set (PPS) from protocol. Removed statements regarding updating the statistical analysis plan (SAP). Updated summaries of patient disposition and adverse events (AEs).	endpoints based on International Council for Harmonisation (ICH) E9 (R1). For clarification, consistency, and completeness.	Section 11.4.1 Patient Disposition Section 11.4.3.1 Primary Efficacy Analysis Table 3: Summary of Primary Estimand for Primary Endpoint (new table) Section 11.4.3.2 Secondary Efficacy Analysis Table 4: Summary of Primary Estimand for Key Secondary Endpoint (Binary) (new table) Table 5: Summary of Primary Estimand for Key Secondary Endpoint (Continuous) (new table) Section 11.4.3.3 Subgroup Analysis Section 11.4.5.1 Adverse Events
Minor editorial corrections and clarification.	For clarification.	Throughout the protocol.

Amendment 1

The purpose of this protocol amendment is to address regulatory authority feedback regarding study design. The number of patients to be enrolled in the study has been increased. The duration of the double-blind treatment period has been extended. Additional exclusion criteria have been incorporated. Other minor changes were made for clarification and to protect patient safety and data integrity during the COVID-19 pandemic. The following table outlines the changes made to the protocol and the rationale.

Description of Change	Rationale	Section Changed
Increased the duration of the double-blind treatment period from 36 weeks to 52 weeks and added visits/procedures at weeks 38 (phone visit), 40 (phone visit), 42 (phone visit), 44, 46 (phone visit), 48 (phone visit), 50 (phone visit), and 52.	To comply with the request of a regulatory authority.	Clinical Study Protocol Synopsis: Study Design, Study Duration, Endpoints Section 3.2.1 Rationale for Study Design Section 4.1.3 Other Secondary Endpoints Section 4.1.4 Exploratory Endpoints Section 6.1 Study Description and Duration Figure 1: Study Flow Diagram Table 1: Schedule of Events (Screening, Baseline, and Double-Blind Treatment Period) Table 2: Schedule of Events (Follow-up Period, Unscheduled Visits, and Early Termination Visit) Section 9.1.1.1 Table 1 Schedule of Events Footnotes, #10, #25, #27 Section 11.4.3.2 Secondary Efficacy Analysis

Description of Change	Rationale	Section Changed
		Section 11.4.5.1 Adverse Events
New secondary endpoints were added at week 52.	These new secondary endpoints correspond to the new double-blind treatment period, which was increased from 36 weeks to 52 weeks.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.3 Other Secondary Endpoints
[redacted]	To comply with the request of a regulatory authority.	Clinical Study Protocol Synopsis: Site Location(s), Population, Statistical Plan Section 7.1 Number of Patients Planned Section 8.6 Method of Treatment Assignment Section 11.2 Justification of Sample Size Section 11.4 Statistical Methods Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity
Increased the screening period from 14 days to 35 days.	To ensure inclusion is documented for histological and serological confirmation of bullous pemphigoid (BP) prior to randomization and to ensure appropriate medication washout for exclusion criteria.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration Figure 1: Study Flow Diagram Table 1: Schedule of Events (Screening, Baseline, and Double-Blind Treatment Period)
Added new exclusion criteria and clarified existing criteria.	To comply with the request of a regulatory authority and for clarification.	Section 7.2.2 Exclusion Criteria, #8 , #23 , #24
Added an additional prohibited medication to the prohibited medication list and clarified restrictions regarding receiving live virus vaccines during the study.	To comply with the request of a regulatory authority	Section 8.10.1 Prohibited Medications and Procedures
Added [redacted] for early termination (ET) visits, where these assessments were previously inadvertently omitted.	For clarification.	Table 2: Schedule of Events (Follow-up Period, Unscheduled Visits, and Early Termination Visit)
Provided updated clinical evidence to support investigating dupilumab as a possible efficacious and well-tolerated treatment for BP.	To align with updated clinical data.	Section 1 Introduction Section 3.2.1 Rationale for Study Design

Description of Change	Rationale	Section Changed
		Section 3.3.1 Risk-Benefit of Dupilumab for Patients with Bullous Pemphigoid Section 19 References
Added language to clarify general changes in study conduct in the context of the COVID-19 pandemic.	To address guidance from the US and EU regarding the conduct of clinical trials during the COVID-19 pandemic.	Section 3.3 Risk-Benefit Section 9.1 Schedule of Events Section 11 Statistical Plan
Minor clarifications and editorial corrections.	For clarification and consistency.	Throughout the protocol.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABQOL	Autoimmune bullous disease quality of life
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Bullous pemphigoid
BPDAI	Bullous Pemphigoid Disease Area Index
BSA	Body Surface Area
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence interval
[redacted]	[redacted]
CRF/eCRF	Case report form (electronic or paper)
CRO	Contract research organization
CRSwNP	Chronic rhinosinusitis with nasal polyposis
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EDTA	Ethylenediamine tetraacetic acid
EoE	Eosinophilic esophagitis
[redacted]	[redacted]
EQVAS	EQ visual analogue scale
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
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
ICF	Informed consent form
ICH	International Council for Harmonisation
[redacted]	[redacted]
IgG	Immunoglobulin G
[redacted]	[redacted]
IL-4	Interleukin 4
IL-13	Interleukin 13
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenous immunoglobulin
IVRS	Interactive voice response system
IWRS	Interactive web response system
MI	Multiple imputation
NAb	Neutralizing antibody
NRS	Numerical rating score
OCS	Oral corticosteroids
[redacted]	[redacted]
[redacted]	[redacted]
PCSV	Potentially clinically significant value
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic
PT	Preferred term
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SC	Subcutaneous
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

WBC	White blood cell
WOCBP	Women of childbearing potential
WOCF	Worst observation carried forward

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CLINICAL STUDY PROTOCOL SYNOPSIS

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
Site Location(s)	Approximately 40 sites globally
Objective(s)	Primary objective: • To demonstrate that dupilumab is superior to placebo in achieving sustained remission off oral corticosteroids (OCS) in patients with bullous pemphigoid (BP) Secondary objectives: • 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 on 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 [redacted] • [redacted]

- [redacted]

Study Design

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

The study consists of a 35-day screening period, a 52-week double-blind treatment period, and a 12-week follow-up period. After patients provide informed consent, patients will be assessed for study eligibility at the screening visit.

During the screening period, treatments for BP will be washed out, as applicable, according to eligibility requirements.

At the baseline visit, eligible patients will be randomized to receive dupilumab or matching placebo. [redacted] In addition, all patients will start a standard regimen of OCS beginning at the baseline visit to obtain control of disease activity (note: control of disease activity is defined as when new lesions cease to form and existing lesions begin to heal). [redacted]

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 during the remainder of the 52-week treatment period. Study drug will be administered subcutaneously (SC) q2w through week 50.

	Following the 52-week double-blind treatment period, patients will have phone visits as specified and then return for an in-person follow-up visit at week 64 (end of study).
Study Duration	The duration of the study for a patient is approximately 64 weeks, excluding the screening period.
End of Study Definition	The end of study is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Sample Size:	Approximately 98 patients will be enrolled at approximately 40 study sites.
Target Population:	The proposed study population is patients with BP. All patients must have documented clinical features of BP at the screening visit and confirmed diagnosis of BP based on histopathology, immunopathology, and serology by the baseline visit. Diagnosis of BP based upon histopathology, immunopathology, and serologic testing performed at a local laboratory with results available within 6 months of the screening visit is acceptable to fulfill the criteria for diagnostic confirmation of BP. Bullous pemphigoid patients must also have moderate-to-severe disease at the screening and baseline visits defined by a BPDAI activity score ≥24; and a peak pruritus numerical rating score (NRS) for maximum itch intensity ≥4 at baseline. Patients are also required to have a minimum Karnofsky Performance Status Scale score of 50% at the screening visit.
Treatment(s)	
Study Drug **Dose/Route/Schedule:**	Dupilumab: (loading) dose of [redacted] administered SC, followed by [redacted] administered SC q2w.
Placebo **Route/Schedule:**	Dupilumab-matching placebo (containing same formulation as dupilumab without active substance): loading dose administered SC, followed by SC q2w dosing.
Background Treatment	Prednisone/prednisolone
Dose/Route/Schedule:	In addition to dupilumab (or matching placebo), all patients will start on a standard regimen of OCS (prednisone or prednisolone) to obtain control of disease activity. [redacted]. Control of disease activity is expected to occur by 2 weeks after randomization with the starting doses of OCS, but some patients may take longer; usually no longer than 4

weeks. For moderate BP patients who are not showing signs of disease control (eg, continued blister or urticarial plaque formation) 2 weeks after randomization (week 2), [redacted]. Tapering of OCS will begin when there has been 2 weeks of sustained control of disease activity. [redacted]. These patients should receive rescue treatment per investigator's discretion.

Patients will undergo a protocol-defined OCS tapering regimen as long as they maintain control of disease activity. The OCS taper employed in this study uses a schedule typical for this disease which is as follows:

[redacted]

- [redacted]

[redacted]

- [redacted]

Endpoints

Primary:

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).

Secondary:

Key secondary efficacy endpoints:

- 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)

Other secondary efficacy endpoints:

- 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 autoimmune bullous disease quality of life (ABQOL) from baseline to week 36
- Change from baseline to week 36 in percent body surface area (BSA) of BP involvement
- Change in BP180 and BP230 autoantibody (Immunoglobulin G [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

Secondary endpoints for safety:

- Incidence of treatment-emergent adverse events (TEAEs) from baseline through end of treatment (up to week 52)
- Incidence of treatment-emergent serious adverse events (SAEs) from baseline through the end of treatment (up to week 52)
- Incidence of adverse events of special interest (AESIs) from baseline through the end of treatment (up to week 52)
- Incidence of TEAEs from baseline through end of study (up to week 64)
- Incidence of treatment-emergent SAEs from baseline through the end of study (up to week 64)
- Incidence of AESIs from baseline through the end of study (up to week 64)

	Secondary endpoints for clinical pharmacology and immunogenicity: • Concentrations of functional dupilumab in serum at each scheduled sampling timepoint from baseline to end of study (up to week 64) • Incidence of treatment-emergent anti-drug antibody (ADA) responses and titer over time (up to week 64) Note: The safety, clinical pharmacology and immunogenicity endpoints will not be included in the testing hierarchy.
Procedures and Assessments	Efficacy will be assessed during the study at specified clinic visits using patient-reported assessments (including Pruritus, Pain, and Sleep Quality NRS [daily], [redacted], [redacted], BPDAI Pruritus, [redacted], ABQOL, BPDAI activity score, BSA, blister and urticaria/eczematous plaque count, and BP clinical assessment [includes disease relapses]). Photography will also be done at select sites. Safety will be assessed by vital signs, physical examinations, 12-lead electrocardiograms (ECG), and height and weight measurements. Patients will report all adverse events experienced from the time of signed informed consent until their last study visit.
Statistical Plan	The sample size calculation of the study is based on a comparison between dupilumab [redacted] q2w versus placebo with regard to the primary endpoint. [redacted] The full analysis set (FAS) is defined as all randomized patients analyzed according to the treatment group allocated by randomization regardless of whether the treatment kit is used or not. All efficacy endpoints will be evaluated on the FAS, which will be considered to be the primary analysis set. The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF. For the time-to-event data, Kaplan-Meier curves and estimates, and median time along with 95% confidence interval (CI), will be provided. 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.

All statistical tests will be performed 2-sided with a type I error rate of 5% unless otherwise stated.

Primary Efficacy Analysis:

[redacted]

Secondary Efficacy Analysis:

[redacted]

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

1. INTRODUCTION

Bullous pemphigoid (BP) is a rare, autoimmune subepidermal blistering disease with a clinical course that may last from months to years. The disease characteristically presents in the elderly (mean onset age of 80) with a prodromal, non-bullous phase which may progress over weeks to years to a generalized, pruritic bullous eruption. In the bullous phase, BP is characterized by large, tense, serous, or hemorrhagic bullae arising on erythematous, urticarial, or eczematous skin. Because of the intractable pruritus and the presence of bullous, eroded or impetiginized lesions, the disease often has a profound, negative impact on the quality of life (Kouris, 2016). The estimated mortality rate during the first year in the bullous phase of disease varies between 10% and 40%, depending on the series (Bystryn, 2005) (Joly, 2005).

Clinical findings and histological features suggest that a type 2 or T-helper type 2 (Th2) cell-mediated immune response plays a central role in the pathogenesis of BP. In support of the type 2-mediated response, elevated blood eosinophils, increased total serum [redacted] concentrations, and elevated serum and blister-fluid levels of different soluble, inflammatory Th2 cell-response mediators have been described in large cohorts of patients with BP (Cozzani, 2018).

Currently, there are no approved pharmacologic treatments for BP in the United States. Systemic corticosteroids are approved for BP in some countries in the European Union. In Japan, human immunoglobulin is approved for the treatment of BP inadequately controlled by corticosteroids. While high doses of oral corticosteroids (OCS) (eg, doses of prednisone [redacted]) have been considered the mainstay of treatment for many years, it has been clearly demonstrated that the prolonged use of high OCS doses are deleterious and directly responsible for a high rate of treatment side effects and contribute to the high mortality rate associated with this disease (Joly, 2002) (Joly, 2005) (Roujeau, 1998). Due to the toxicity of OCS in this elderly population, it is recommended that the cumulative dose of OCS be limited, and the high doses of OCS tapered expeditiously (eg, initial reduction of the OCS dose by one-third steps every 2 weeks) to the minimal effective dose of OCS that can control the disease (Venning, 2012). Moreover, to compensate for the high disease relapse rate (up to 80%) which occurs during OCS tapering, OCS-sparing immunosuppressive agents (eg, mycophenolate mofetil, methotrexate, rituximab) are frequently added (Joly, 2002) (Simon, 2019) (Venning, 2012) (Lamberts, 2018). However, these treatments have additional undesirable side effects, such as increased risk of infections and others (eg, myelosuppression and gastrointestinal toxicity for mycophenolate mofetil, myelosuppression and hepatotoxicity for methotrexate, and potentially fatal infusion-related reactions and severe mucocutaneous reactions for rituximab) (Joly, 2002) (Simon, 2019) (Venning, 2012).

Highly potent topical corticosteroids (eg, clobetasol propionate 0.05% cream) have been demonstrated to be effective for BP and may be safer than high doses of OCS (Joly, 2009) (Joly, 2002). Despite their efficacy, highly potent topical corticosteroids can result in cutaneous atrophy, striae, and folliculitis. Long-term application of highly potent topical corticosteroids is also not recommended for sensitive skin areas (eg, face, groin, axillae) or for application over a large body surface area, which may result in substantial systemic absorption with a resultant side effect profile similar to that of systemic corticosteroids. Therefore, there exists a significant unmet medical need for an effective treatment that has a favorable safety profile for long-term use for the treatment of BP.

Dupilumab is a targeted immunomodulatory agent selectively inhibiting the type 2 inflammatory pathway, and therefore may potentially provide therapeutic benefit as an OCS-sparing agent in patients with BP. Dupilumab may also avoid the significant side effects typically associated with the use of broad immunosuppressants and may even be more preferable in many patients than the prolonged use of highly potent topical corticosteroids. Blocking interleukin 4 (IL-4) receptor alpha (IL-4Rα) with dupilumab inhibits IL-4 and interleukin 13 (IL-13) type-2 cellular and cytokine-induced responses, including release of pro-inflammatory cytokines, chemokines, [redacted], and infiltration by mast cells and eosinophils responsible for tissue damage. In clinical studies, a significant decrease in IgE, eotaxin-3, and [redacted] in circulation and/or tissue RNA expression has been demonstrated after dupilumab treatment across several clinical indications (atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis [CRSwNP], and eosinophilic esophagitis [EoE]).

Bullous pemphigoid shares pathophysiological pathways with these type 2 inflammatory diseases mediated by key type 2 cytokines, IL-4 and IL-13; therefore, dupilumab has the potential to be an effective treatment with a favorable safety profile for long-term use for BP. The preliminary clinical evidence to support the hypothesis for efficacy of dupilumab in the treatment of BP is derived from a case series of clinically significant improvement in the majority of patients (Abdat, 2020). In a retrospective case series study conducted at 5 centers, 13 patients with a confirmed diagnosis of BP were treated with dupilumab 300 mg (after an initial loading dose of 600 mg) SC. In this study, 92.3% (12/13) patients achieved either disease clearance or a clinical improvement after treatment with dupilumab. Additionally, 76.9% (10/13) patients experienced resolution of their bullae and residual pruritis. Dupilumab was well tolerated with no dupilumab-related adverse events. This case series provides further clinical support for dupilumab as a possible efficacious and well tolerated treatment for BP (Abdat, 2020).

The current multicenter, randomized, double-blind, placebo-controlled, parallel-group study is designed to investigate the efficacy and safety of dupilumab in patients with BP. It is anticipated that patients with BP treated with dupilumab may achieve sustained clinical remission while being able to taper expeditiously off their background OCS, thus potentially curtailing the side effects of chronic OCS use in this vulnerable elderly population.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. 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.

2.2. 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

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- [redacted]

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Dupilumab is efficacious in the treatment of patients with moderate-to-severe BP.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is designed to investigate the efficacy and safety of dupilumab in patients with moderate-to-severe BP. A double-blinded, randomized, placebo-controlled design is chosen to minimize bias in data collection and interpretation. The presence of a placebo arm is appropriate for the objectives of this study since it will provide the most robust assessment of the efficacy and safety of dupilumab. There will be a 52-week, double-blind treatment period and a 12-week follow-up period.

All patients will start on day 1/baseline dupilumab (or matched placebo) and receive a standard regimen of OCS (prednisone or prednisolone) to obtain control of disease activity (Joly 2002) (Murrell, 2012) (Venning, 2012). [redacted] (Joly, 2002).

Per the "Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts," control of disease activity occurs when new lesions (eg, blisters, urticarial plaques) cease to form and existing lesions begin to heal (eg, show signs of epithelialization) (Murrell, 2012). Patients will therefore be maintained on their assigned treatment level of OCS until they have achieved control of disease activity. Control of disease activity is expected to occur by 2 weeks after randomization with the aforementioned background doses of OCS, but some patients may take longer, usually no longer than 4 weeks (Joly, 2002) (Simon, 2019).

Although the majority (~95%) of moderate BP patients achieve control of disease activity on 0.5 mg/kg/day of prednisone (or prednisolone), a few may require higher doses (Joly, 2002). For moderate BP patients who are not showing signs of disease control (eg, continued blister or urticarial plaque formation) 2 weeks after randomization (week 2), the dose of OCS may be increased to [redacted] of prednisone (or prednisolone). Doses higher than [redacted] of prednisone have not been shown to be more effective in BP in achieving control of disease and have been associated with increased mortality and side effects (Kirtschig, 2010). Patients requiring doses greater than [redacted] of prednisone (or prednisolone) in achieving control of disease activity, [redacted], will be considered treatment failures. These patients should receive rescue treatment per investigator's discretion and will be requested to complete the study visits and per-protocol assessments for the duration of the study. If patients are rescued with a systemic immunosuppressive/immunomodulating agent (including but not limited to omalizumab,

rituximab, mycophenolate-mofetil, azathioprine, and methotrexate), they will be discontinued from study drug.

It is recommended that tapering of OCS should begin when there has been 2 weeks of sustained control of disease activity. This coincides with the "end of the consolidation phase" which is defined as the time at which there has been control of disease activity for a minimum of 2 weeks and when tapering of OCS should begin (Murrell, 2012). Oral corticosteroid tapering may therefore start at week 4 or up to week 6 depending on when initial control of disease activity was achieved (eg, if initial control of disease activity occurred at week 4, OCS tapering should begin at week 6).

Patients will undergo a protocol-defined OCS tapering regimen as long as they maintain control of disease activity. The OCS taper employed in this study uses a schedule typical for this disease which allows for patients to be off OCS by week 16 (or sooner), as described in Section 8.2. Following the period in which OCS are completely tapered off, there will be a remission period of at least 36 weeks where patients will be assessed for relapses off OCS. This study provides the opportunity to investigate long-term efficacy/effectiveness and safety over the 52-week treatment period. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab.

3.2.2. Rationale for Dose Selection

The dose regimen of dupilumab selected for this study is an initial (loading) dose of [redacted] administered subcutaneously (SC), followed by [redacted] administered SC q2w. Dupilumab [redacted] q2w has proven to be effective and has shown to have a favorable safety profile in adult patients with moderate-to-severe atopic dermatitis (AD, another skin disease), moderate-to-severe asthma, and in CRSwNP. In addition, dupilumab [redacted] q2w was demonstrated to have a significant steroid-sparing effect while significantly reducing exacerbations and improving lung function in a population of severe corticosteroid-dependent asthmatic patients. Based on the case studies and the demonstrated efficacy of dupilumab at this dose in other type 2 inflammatory diseases, the selected dose is considered appropriate for investigation in patients with BP. Furthermore, the selected dosing regimen is [redacted].

Furthermore, for AD, a loading dose was administered to more rapidly achieve effective drug concentrations, thereby allowing a rapid PD response as demonstrated by improvement in pruritus, a hallmark of AD. Similarly, as pruritus is a core symptom of BP, and to achieve effective drug concentrations more rapidly, a loading dose is selected for this study.

3.3. Risk-Benefit

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interferes with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the

sponsor plans to obtain approvals from health authorities/ethics committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

3.3.1. Risk-Benefit of Dupilumab for Patients with Bullous Pemphigoid

Benefits

The underlying role of type 2 inflammation in BP bears striking similarities to the role of type 2 inflammation in AD, asthma, EoE, and CRSwNP, conditions in which dupilumab has been demonstrated to have significant efficacy, leading to approved indications for AD, asthma, and CRSwNP. Specifically, similar to BP, the skin lesions of AD are characterized by increased expression of proinflammatory type 2 cytokines, such as IL-4, [redacted], and by skin infiltration of Th2 cells. Bullous pemphigoid also bears similarities to EoE, which is characterized by eosinophil, mast cell, and Th2 cell infiltration and an increase in expression of type 2 cytokines and chemokines (eg, IL-4, IL-13, eotaxin-3).

Current standard of care in BP includes the use of topical and systemic corticosteroids, and other immunosuppressant therapies; however, these are associated with significant risks, particularly in an elderly population, and a more targeted therapy with an improved benefit/risk profile would be highly beneficial. Chronic use of broad immunosuppressants (eg, OCS) contributes to the high morbidity and mortality in patients with BP.

The goals of a new therapy for BP are to suppress new lesion and blister development, to encourage lesion healing, and to achieve sustained disease remission with no disease flares. There is preliminary clinical evidence for the efficacy of dupilumab in the treatment of BP derived from a case series in which clinically significant improvement in disease activity was observed in patients who would otherwise have been very unlikely to improve (see Section 1). Given the biologic rationale and preliminary clinical evidence, it is anticipated that patients with BP treated with dupilumab may achieve sustained clinical remission while being able to taper expeditiously off their background OCS, thus potentially curtailing the side effects of chronic OCS use in this vulnerable elderly population.

Risks

Dupilumab has an extensive safety database. As of 28 March 2020, 10191 subjects were enrolled into the development program for dupilumab and are included in the safety population: 382 as healthy volunteers, 4405 from AD studies, 3614 from asthma studies, 782 from CRSwNP studies, 232 from EoE studies, 103 from the grass allergy study, 145 from peanut allergy studies, 511 from the chronic obstructive pulmonary disease study, 5 from prurigo nodularis studies, and 12 from the chronic spontaneous urticaria study. The number of subjects exposed to dupilumab in clinical studies was 8720 (356 in healthy volunteer studies, 4052 in AD studies, 3263 in asthma studies, 470 in CRSwNP studies, 166 in EoE studies, 52 in the grass allergy study, 96 in peanut allergy studies, 256 in the chronic obstructive pulmonary disease study, 3 in prurigo nodularis studies, and 6 in the chronic spontaneous urticaria study).

The identified adverse drug reactions are injection site reactions, serum sickness-like reaction/serum sickness, anaphylactic reaction, conjunctivitis, conjunctivitis allergic,

conjunctivitis bacterial, blepharitis, dry eyes, eye pruritus, herpes simplex (primarily mucocutaneous in nature), and oral herpes.

Overall, systemic hypersensitivity has been established as an important identified risk with dupilumab. As protein therapeutics, all monoclonal antibodies are potentially immunogenic. Rare, serious and systemic hypersensitivity reactions have been observed in the dupilumab program including serum sickness/serum sickness-like reaction in the adult AD clinical trials and anaphylaxis related to dupilumab in the adult asthma clinical trials. If a clinically significant systemic hypersensitivity event occurs, appropriate therapeutic intervention will be administered, and the patient will be discontinued from treatment.

An important potential risk, eosinophilia associated with clinical symptoms, has been observed in the asthma clinical trials (a few cases of eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia) but not in AD clinical studies.

Risk/Benefit Conclusion

Long-term treatment with OCS and other immunosuppressives have a less favorable safety and tolerability profile than what has been observed with dupilumab. The safety data available to date, in conjunction with the risk monitoring and mitigation strategies in the study protocol, and the clinical benefit of dupilumab demonstrated in multiple type 2 indications (AD, asthma, CRSwNP) and case reports and series in BP so far, support a favorable benefit-risk profile for dupilumab.

A risk-benefit statement with respect to the overall clinical development program is provided in the investigator brochure.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

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).

4.1.2. Key Secondary Efficacy Endpoints

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 numerical rating score (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)

4.1.3. Other Secondary Endpoints

Other secondary endpoints for efficacy:

- 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; see Section 9.2.2.12 for complete definitions)
- 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 autoimmune bullous disease quality of life (ABQOL) from baseline to week 36
- Change from baseline to week 36 in percent body surface area (BSA) of BP involvement
- Change in BP180 and BP230 autoantibody (Immunoglobulin G [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

Other secondary endpoints for safety:

- Incidence of treatment-emergent adverse events (TEAEs) from baseline through end of treatment (up to week 52)
- Incidence of treatment-emergent serious adverse events (SAEs) from baseline through the end of treatment (up to week 52)

- Incidence of adverse events of special interest (AESIs) from baseline through the end of treatment (up to week 52)
- Incidence of TEAEs from baseline through end of study (up to week 64)
- Incidence of treatment-emergent SAEs from baseline through the end of study (up to week 64)
- Incidence of AESIs from baseline through the end of study (up to week 64)

Other secondary endpoints for clinical pharmacology and immunogenicity:

- Concentrations of functional dupilumab in serum at each scheduled sampling time point from baseline to end of study (up to week 64)
- Incidence of treatment-emergent anti-drug antibody (ADA) responses and titer over time (up to week 64)

Note: The safety, clinical pharmacology and immunogenicity endpoints will not be included in the testing hierarchy.

4.1.4. Exploratory Endpoints

The exploratory endpoints are:

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc.), disease characteristics including medical history, and medication history for each patient.

5.2. Efficacy Variables

The efficacy variables include measurements or scores for individual patients for the following: BP clinical assessment (includes disease relapses), total cumulative dose of OCS, peak pruritus NRS, skin pain NRS, sleep quality NRS, BPDAI activity score, BPDAI pruritus, [redacted], BSA, blister and urticaria/eczematous plaque count, ABQOL, [redacted], [redacted] and BP180 and BP230 autoantibody titers.

5.3. Safety Variables

The safety variables include recordings, measurements or laboratory test results for individual patients for the following: Adverse events, concentrations of functional dupilumab in serum, vital signs, physical examinations, electrocardiogram (ECG), hematology, blood chemistry, and urinalysis.

5.4. Pharmacokinetic Variables

The pharmacokinetic variable is the concentration of functional dupilumab at each time point. Samples in this study will be collected using a sparse sampling schedule. The sampling time points are specified in Table 1.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 1.

5.6. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic and biomarker variables include biopsy and laboratory test results for individual patients for the following:

[redacted]

[redacted]

[redacted]

Serum anti-BP180 and anti-BP230 autoantibodies of the IgG subclass concentration: A serologic characteristic of BP is the presence of circulating autoantibodies in patient serum, which are mostly against BP180 (collagen XVII) and BP230 (hemidesmosomal proteins). NC16A, a non-collagenous stretch of the BP180 ectodomain, is the primary target of the pathogenic IgG antibodies. Autoantibodies from BP patients react with BP180, which leads to the degradation of the basement membrane, and this has been regarded as a central event in BP pathogenesis. IgG autoantibodies against BP180 are the ones first to be detected, followed by IgG autoantibodies against BP230. Concentrations of anti-BP180 and anti-BP230 are elevated during active disease and decrease with resolution of BP.

[redacted]

6. STUDY DESIGN

6.1. Study Description and Duration

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

The study consists of a 35-day screening period, a 52-week double-blind treatment period, and a 12-week follow-up period. After patients provide informed consent, they will be assessed for study eligibility at the screening visit.

Study participants are required to have characteristic clinical features of BP present at the screening visit (eg, urticarial, eczematous or erythematous plaques, bullae, pruritus). Patients are also required to have a minimum Karnofsky Performance Status Scale score of 50% at the screening visit. Patients with severe concomitant illness(es) at the screening visit that, in the investigator's judgment, would adversely affect the patient's participation in the study will be excluded.

Study participants are required to have a confirmed diagnosis of BP based on histopathology, immunopathology, and serology at the baseline visit as described in Section 7.2.1.

Patients must also have moderate-to-severe BP at the screening and baseline visits, as determined by a BPDAI activity score ≥24. Patients are also required to have a peak pruritus NRS for maximum itch intensity ≥4 at the baseline visit.

During the screening period, treatments for BP will be washed out, as applicable, according to eligibility requirements (see Section 7.2.2).

At the baseline visit, eligible patients will be randomized to receive dupilumab or matching placebo. Randomization will be stratified by [redacted]. In addition, all patients will receive a standard regimen of OCS (prednisone or prednisolone) beginning at the baseline visit to obtain control of disease activity (Joly, 2002) (Murrell, 2012) (Venning, 2012). [redacted] (Joly, 2002).

Per the publication of "Definitions and Outcome Measures for Bullous Pemphigoid: Recommendations by an International Panel of Experts (Murrell, 2012)," control of disease activity occurs when new lesions (eg, blisters, urticarial plaques) cease to form and existing lesions begin to heal (eg, show signs of epithelialization) (Murrell, 2012). Patients will therefore be maintained on their assigned treatment level of OCS until they have achieved control of disease activity. Control of disease activity is expected to occur by 2 weeks after randomization with the aforementioned doses of OCS, but some patients may take longer, usually no longer than 4 weeks (Joly, 2002) (Simon, 2019).

Although the majority (~95%) of moderate BP patients achieve control of disease activity on [redacted] of prednisone (or prednisolone), a few may require higher doses (Joly, 2002). For

moderate BP patients who are not showing signs of disease control (eg, continued blister or urticarial plaque formation) 2 weeks after randomization (week 2), the dose of OCS may be increased [redacted] of prednisone (or prednisolone). Doses higher than [redacted] of prednisone have not been shown to be more effective in BP and have been associated with increased mortality and side effects (Kirtschig, 2010). Patients requiring doses greater than [redacted] will be considered treatment failures. These patients should receive rescue treatment per investigator's discretion and will be requested to complete the study visits and per-protocol assessments for the duration of the study.

After achieving sustained control of disease activity, patients will follow a protocol-defined OCS tapering regimen as long as they maintain control of disease activity. Tapering of OCS starts after 2 weeks of sustained control of disease activity. This signifies the "end of the consolidation phase" which is defined as the time at which there has been sustained control of disease activity for a minimum of 2 weeks and when tapering of OCS should begin (Murrell, 2012). Oral corticosteroid tapering may therefore start at week 4 or up to week 6 depending on when initial control of disease activity is achieved (eg, if initial control of disease activity occurs at week 4, OCS tapering should begin at week 6).

The OCS taper employed in this study uses a schedule typical for this disease (as described in Section 8.2) which allows for patients to be off OCS by week 16 (or sooner). [redacted]

Following this OCS taper period, there will be a remission period of at least 36 weeks where patients will be observed for relapses off OCS. A 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 (Murrell, 2012). Patients who experience a relapse after completely tapering off OCS may be rescued, including with re-initiation of OCS.

Unless permanently discontinued from the study, all patients will be requested to complete the scheduled study visits and assessments whether or not they complete study drug treatment, and whether or not they receive rescue treatment.

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 [see Table 1]). After week 4, patients will have the option to self-administer study drug (or have a caregiver/healthcare provider [eg, visiting nurse] administer study drug) 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 during the remainder of the 52-week treatment period. 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 and then return for an in-person follow-up visit at week 64 (end of study).

Efficacy, safety, and laboratory assessments will be performed as specified in Table 1. Samples to measure dupilumab concentrations, assess immunogenicity, and for research purposes will be collected at specified time points throughout the study, as noted in Table 1.

An overview of the study is provided in Figure 1.

Figure 1: Study Flow Diagram

6.1.1. End of Study Definition

The end of study is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

No interim analysis is planned. An unblinded primary analysis may be performed once all patients in the study have completed the 36-week treatment period or discontinued from the study. If performed, the primary analysis will be considered the final analysis for the primary and secondary efficacy endpoints for week 36; safety and PK analyses up to week 36 will also be performed. No changes in the conduct of the study will be made and no need for alpha adjustment based on the primary analysis.

A description of the statistical methods to be employed is in Section 11.4, and blinding implications are discussed in Section 8.7.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

Although the safety of dupilumab has been well established in a large number of clinical trials across multiple indications, this study represents the first study primarily conducted in elderly patients with a severe, potentially life-threatening disease. Therefore, an independent data monitoring committee (DMC), composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the DMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The DMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study.

All activities and responsibilities of the DMC are described in the DMC charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 98 patients (49 patients per arm) will be enrolled at approximately 40 global sites.

7.2. Study Population

The proposed study population is patients with BP. All patients must have documented clinical features of BP at the screening visit and histological and serological confirmation of BP by the baseline visit. Bullous pemphigoid patients must also have moderate-to-severe disease at the screening and baseline visits defined by a BPDAI activity score ≥24; and a peak pruritus NRS for maximum itch intensity ≥4 at baseline. Patients are also required to have a minimum Karnofsky Performance Status Scale score of 50% at the screening visit.

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Patients must have characteristic clinical features of BP (eg, urticarial or eczematous or erythematous plaques, bullae, pruritus) at the screening and baseline visits.
2. Study participants are required to have a confirmed diagnosis of BP based on histopathology, immunopathology, and serology at the baseline visit. Required for inclusion:
   a. Compatible histopathologic findings on a skin biopsy specimen supporting a diagnosis of BP (eg, a subepidermal blister with eosinophils within the cleft, a mixed cellular inflammatory infiltrate that includes eosinophils) AND
   b. Characteristic direct immunofluorescence findings on a skin biopsy specimen demonstrating linear IgG and/or C3 at the basement membrane zone AND
   c. At least 1 of the following serologic assessments (utilizing a peripheral blood specimen):
      i. Positive indirect immunofluorescence demonstrating IgG antibodies localizing to the roof (epidermal side) of split-skin substrate
      ii. Increased IgG serum antibody levels by immunoassay to BP antigens, BPAG1 (230-kd, also known as BP230) and/or BPAG2 (180-kd, also known as BP180)

   NOTE: Histopathology, immunopathology, and serologic testing performed at a local laboratory with results available within 6 months of the screening visit that confirm the diagnosis of BP are acceptable to fulfill the above criteria for diagnostic confirmation of BP.
3. BPDAI activity score ≥24 at baseline and screening visits.
4. Baseline peak pruritus NRS score for maximum itch intensity ≥4.

   NOTE: Baseline 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) during the 7 days immediately preceding randomization. A minimum of 3 daily scores out of the 7 days is required to calculate the baseline average score.

5. Male or female, age 18 to 90 at the screening visit (age 20 to 90 for sites in Japan)
6. Karnofsky performance status score ≥50% at the screening visit.
7. Willing and able to comply with clinic visits and study-related procedures.
8. Willing and able to understand and complete study-related questionnaires.
9. Willing and able to provide voluntary signed informed consent.

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Forms of pemphigoid other than classic BP (eg, Brunsting-Perry cicatricial pemphigoid, anti-p200 pemphigoid, epidermolysis bullosa acquisita, or BP with concomitant pemphigus vulgaris).
2. Patients who are receiving treatments known to cause or exacerbate BP (eg, angiotensin converting enzyme inhibitors, penicillamine, furosemide, phenacetin, dipeptidyl peptidase 4 inhibitor) who have not been on a stable dose of these medications for at least 4 weeks prior to the screening visit.
3. Have ever received treatment with an IL-4 or IL-13 antagonist such as dupilumab, tralokinumab, or lebrikizumab.
4. Treatment with systemic corticosteroids within 7 days before the baseline visit.
5. Treatment with topical corticosteroids of medium potency or higher, topical calcineurin inhibitor, or topical crisaborole within 7 days before the baseline visit.
6. Initiation, discontinuation, or change in the dosage regimen of systemic antihistamines within 7 days before the baseline visit. Patients on a stable dose of systemic antihistamines for at least 7 days prior to the baseline visit may be included in the study; however, the dose of these medications should remain unchanged for the duration of the study.
7. Treatment with an antibiotic (such as doxycycline or dapsone) directed at the treatment of BP within 7 days before the baseline visit.
8. Treatment with nicotinamide directed at the treatment of BP within 7 days prior to the baseline visit (note: use of multivitamins containing nicotinamide is allowed).
9. Treatment with non-steroidal immunosuppressive/immunomodulating drug(s) (eg, mycophenolate mofetil, azathioprine, or methotrexate) within 4 weeks before the baseline visit.
10. Treatment with BP-directed biologics as follows:
    a. Any cell-depleting agents including but not limited to rituximab: within 12 months before the baseline visit, or until lymphocyte and CD 19+ lymphocyte count returns to normal, whichever is longer

b. Other biologics (such as IL-5 inhibitors benralizumab or mepolizumab): within 5 half-lives (if known) or 16 weeks prior to the baseline visit, whichever is longer
c. Intravenous immunoglobulin within 16 weeks prior to the baseline visit.

11. Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit.
12. Planned or anticipated use of any prohibited medications or procedures during study treatment.
13. Any active infection requiring systemic treatment; patients with such infection must have their infection resolved at least 1 week before baseline to be eligible to enroll in the study.
14. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
15. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per investigator's judgment.
16. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
17. With a current diagnosis of hepatitis B viral infection at the time of screening as evidenced by
    a. Positive hepatitis B surface antigen (HBsAg) or
    b. Positive total hepatitis B core antibody (HBcAb) confirmed by positive hepatitis B virus (HBV) DNA.

NOTE: Patients who have gained immunity for hepatitis B virus infection after vaccination (patients who are HBsAg negative, hepatitis B surface antibody [HBsAb] positive, and HBcAb negative) or after natural infection (patients who are HBsAg negative, hepatitis B surface antibody [HBsAb] positive, and HBcAb positive) are eligible for the study. These patients will be allowed to enroll into the study, but will be followed using routine clinical and liver function tests.

In case of results showing HBsAg negative, HBsAb negative, and HBcAb positive, an HBV DNA testing will be performed prior to randomization to rule out a false positivity and to confirm current infection.

18. With a current diagnosis of hepatitis C viral infection at the time of screening as evidence by
    a. Positive hepatitis C virus (HCV) Ab AND
    b. Positive HCV RNA.
19. On current treatment for hepatic disease including, but not limited to, acute or chronic hepatitis, cirrhosis, or hepatic failure, or has evidence of liver disease as indicated by persistent (confirmed by repeated tests ≥2 weeks apart) elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal (ULN) during the screening period.

20. Presence of any 1 or more of the following abnormalities in laboratory test results at screening:
    a. Platelet count $\leq 100 \times 10^3/\mu L$
    b. Neutrophil count $\leq 1.5 \times 10^3/\mu L$.
21. Presence of skin comorbidities that may interfere with study assessments.
22. History of malignancy within 5 years before the baseline visit, except completely treated in situ carcinoma of the cervix, or completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.
23. Known systemic hypersensitivity to dupilumab or the excipients of the drug product.
24. Patients having a contraindication to systemic corticosteroids (eg, severe osteoporosis, adrenal insufficiency, Cushing's disease) that, in the investigator's judgment, would adversely affect the patient's participation in the study.
25. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to, patients with short life expectancy, patients with uncontrolled diabetes (HbA1c ≥9%), patients with cardiovascular conditions (eg, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), debilitating neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, hepatobiliary, metabolic, pulmonary, or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents.
26. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents.
27. History of alcohol or drug abuse within 2 years before the screening visit.
28. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
29. Pregnant or breastfeeding women or planning to become pregnant or breastfeed during the patient's participation in this study.
30. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral,

injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
b. intrauterine device; intrauterine hormone-releasing system
c. bilateral tubal ligation
d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure).
e. and/or sexual abstinence †, ‡.

*Women of childbearing potential are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

31. Patient is a member of the investigational team or his/her immediate family.

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor has the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.4.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study/study drug will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Dupilumab: (loading) dose of [redacted] administered SC, followed by [redacted] administered SC q2w.

Dupilumab-matching placebo (containing same formulation as dupilumab without active substance): loading dose administered SC, followed by SC q2w dosing.

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Background Treatment

All patients will receive a standard regimen of OCS (prednisone or prednisolone) on day 1/baseline visit to obtain control of disease (Joly, 2002) (Murrell, 2012) (Venning, 2012). Specifically, [redacted] (Joly, 2002).

Per the "Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts" (Murrell, 2012), control of disease activity occurs when new lesions (eg, blisters, urticarial plaques) cease to form and existing lesions begin to heal (eg, show signs of epithelialization). Patients will therefore be maintained on their assigned treatment level of OCS until they have achieved control of disease activity. Control of disease activity is expected to occur by 2 weeks after randomization with the aforementioned doses of OCS, but some patients may take longer, usually no longer than 4 weeks (Joly, 2002) (Simon, 2019).

Although the majority (~95%) of moderate BP patients achieve control of disease activity on 0.5 mg/kg/day of prednisone (or prednisolone), a few may require higher doses (Joly, 2002). For moderate BP patients who are not showing signs of disease control (eg, continued blister or urticarial plaque formation) 2 weeks after randomization (week 2), the dose of OCS may be increased to [redacted] of prednisone (or prednisolone).

It is recommended that tapering of OCS should begin when there has been 2 weeks of sustained control of disease activity. This coincides with the "end of the consolidation phase" which is defined as the time at which there has been control of disease activity for a minimum of 2 weeks and when tapering of OCS should begin (Murrell, 2012). Oral corticosteroid tapering may therefore start at week 4 or up to week 6 depending on when initial control of disease activity is achieved (eg, if initial control of disease activity occurs at week 4, OCS tapering should begin at week 6).

[redacted]

- [redacted]
- [redacted]
- [redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

8.3. Rescue Treatments

Patients requiring doses greater than [redacted] of prednisone (or prednisolone) and those who do not achieve control of disease activity by week 4 will be considered treatment failures. These patients should receive rescue treatment per investigator's discretion.

During the OCS taper period, [redacted] will be considered treatment failures, but will be allowed to increase the prednisone (or prednisolone) dose to the dose level where there was control of disease activity before resuming the predefined OCS tapering regimen (as described in Section 8.2). If a patient fails to [redacted], they should be considered for rescue. Following the OCS taper period, there will be a remission period of at least 36 weeks where patients will be observed for relapses off OCS.

A 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 (Murrell, 2012).

Patients who experience a relapse after completely tapering off OCS may also be rescued, including with re-initiation of OCS. Rescue treatment may include treatment with high-potency topical corticosteroids, OCS (eg, increases of OCS doses during the taper regimen, or re-initiation of OCS after tapering completely off OCS), and systemic non-steroidal immunosuppressive drugs or immunomodulating biologics.

If topical or oral corticosteroids are used as rescue treatments, patients may continue study treatment. If a patient receives rescue treatment with a systemic non-steroidal immunosuppressive drug or immunomodulating biologic (including, but not limited to, omalizumab, rituximab, mycophenolate-mofetil, azathioprine, methotrexate), study treatment will be permanently discontinued immediately.

Unless permanently discontinued from the study, all patients will be requested to complete the scheduled study visits and assessments, whether or not they complete study drug treatment and whether or not they receive rescue treatment.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

Dose modification of study drug for an individual patient is not allowed.

8.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2.

8.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction (eg, Hy's law is met (Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation FDA, 2009)
- Patient withdraws consent
- Treatment with an investigational drug (other than dupilumab)
- Treatment with an immunomodulating biologic (eg, omalizumab, intravenous immunoglobulin [IVIG])
- Treatment with a systemic non-steroidal immunosuppressive drug (including but not limited to mycophenolate-mofetil, azathioprine, methotrexate)
- Diagnosis of a malignancy during study other than non-melanoma skin cancer or carcinoma in situ of the cervix that can be treated with curative local surgery
- Any infection that is opportunistic, such as tuberculosis and other infections whose nature or course may suggest an immunocompromised status
- Severe laboratory abnormalities assessed as related to study drug*:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values >3x × ULN with total bilirubin >2x × ULN, excluding confirmed Gilbert's Syndrome
  - Confirmed AST and/or ALT >5x × ULN (for more than 2 weeks)

*If the laboratory abnormality is considered causally related to study drug, study treatment will be permanently discontinued. In cases in which a causal relationship to study drug can be reasonably excluded, (ie, an alternative cause is evident), study treatment will be

suspended but it may be resumed when the laboratory abnormality is sufficiently normalized. A decision to resume study treatment will be made jointly by the investigator and medical monitor (medical monitor's written approval is required).

- Treatment with a live attenuated vaccine (refer to Section 8.10.1)

The investigator may discontinue study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation.

If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron Pharmaceuticals, Inc. medical monitor (except for illness requiring prompt treatment).

8.4.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing will be temporarily discontinued in the event of:

- Clinically important laboratory abnormalities, such as:
  - ALT or AST >3x × ULN
  - Neutrophil count <1.5 × 10^3/μL but >0.5 × 10^3/μL
  - Platelet count ≤100 × 10^3/μL but >50 × 10^3/μL
- Helminth infection not responding to antihelminth therapy

After the condition leading to suspension of dosing resolves, study treatment may resume at the discretion of the investigator in consultation with the medical monitor. A decision to temporarily discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor.

The investigator may suspend study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation.

8.5. Management of Acute Reactions

8.5.1. Acute Injection Reactions

8.5.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as adverse events (AEs) (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4.

Acute systemic reactions following injection of study drug (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.5.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4.

8.6. Method of Treatment Assignment

Approximately 98 patients will be randomized in a 1:1 ratio to receive either a loading dose of [redacted] SC followed by [redacted] dupilumab every 2 weeks (q2w), or a matching placebo loading dose and SC placebo injections q2w, according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified by [redacted]. All patients will receive a standard regimen of OCS (prednisone or prednisolone) on day 1/baseline visit to obtain control of disease. [redacted]

8.7. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

Blinded study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody, drug concentration results, and biomarker results (eg, [redacted] will not be communicated to the sites, and the sponsor's blinded operational team will not have access to results associated with patient identification until after the database is locked.

8.8. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded/unmasked (Section 8.4.2)

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the

investigator for the site will unblind/unmask the patient. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.

– The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site [redacted]; storage instructions will be provided in the pharmacy manual.

8.9.1. Supply and Disposition of Treatments

Study drug will be shipped [redacted] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug can be destroyed on site after sponsor approval or returned to the sponsor/designee.

8.9.2. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.9.3. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.10. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the final study will be recorded. This includes medications that were started before the study and are ongoing during the study.

8.10.1. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited during the study:

- Topical corticosteroids
- Topical calcineurin inhibitors
- Topical crisaborole
- Treatment with immunomodulating biologics (eg, omalizumab, rituximab, IVIG)
- Treatment with a systemic non-steroidal immunosuppressive drug (including but not limited to mycophenolate-mofetil, azathioprine, methotrexate)
- Treatment with any BP-directed therapy, which includes dapsone or tetracycline class of antibiotics (unless being used to treat an infection suspected or known to be sensitive to dapsone or tetracycline class of antibiotics)
- Initiation, discontinuation, or change in the dosages of treatments known to cause or exacerbate BP (eg, angiotensin-converting enzyme inhibitors, penicillamine, furosemide, phenacetin, dipeptidyl peptidase 4 inhibitor) must be discussed with the medical monitor.
- Initiation, discontinuation, or change in the dosage regimen of systemic antihistamines after baseline
- Treatment with an investigational drug (other than dupilumab)
- Treatment with nicotinamide directed at the treatment of BP (note: use of multivitamins containing nicotinamide is allowed)
- Initial treatment with a live (attenuated) vaccine:

Chickenpox (varicella)	Oral typhoid
FluMist® (influenza)	Rubella
Intranasal (influenza)	Smallpox (vaccinia)
Measles (rubeola)	Yellow fever
Measles-mumps-rubella combination	Bacille Calmette-Guerin
Measles-mumps-rubella-varicella combination	Rotavirus
Mumps	Varicella zoster (shingles) (use of Zostavax® is prohibited as it is live attenuated; use of Shingrix® is allowed as it is non-live)
Oral polio (Sabin)	

Note: If rescue consists of topical agents (eg, high-potency topical corticosteroids), patients may continue study treatment (see Section 8.3). If a patient receives rescue treatment with a systemic non-steroidal immunosuppressive drug or immunomodulating biologic (including, but not limited to, omalizumab, rituximab, mycophenolate-mofetil, azathioprine, methotrexate), study treatment will be permanently discontinued immediately.

The following concomitant procedures are prohibited during study treatment:

- Major elective surgical procedures

8.10.1.1. Adverse Events Requiring the Use of Systemic Corticosteroids

If the patient develops an AE for a condition not related to BP that requires a corticosteroid dose modification (eg, increase or decrease of current concomitant oral prednisone or equivalent), or the introduction of a new oral or systemic steroid medication, the sponsor must be notified at the time of the steroid dose modification to verify that the patient can continue to participate in the study. Furthermore, the dosage modification and AE must be recorded on the patient electronic case report form (eCRF). Intranasal, inhaled, and ophthalmic corticosteroids as per label are permitted, as needed throughout the course of the study.

8.10.2. Permitted Medications

Other than the prohibited medications listed in Section 8.10.1, treatment with concomitant medications are permitted during the study. Medications used to treat chronic disease such as diabetes, hypertension, and asthma are also permitted. Treatment with drugs, including biologics that do not have an immunosuppressive/immunomodulating effect and are not intended for the treatment of BP are permitted (eg, Praluent). If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

8.10.3. Glucocorticoid-Induced Osteopenia/Osteoporosis Prevention and Treatment

Oral calcium, 25-hydroxy vitamin D supplementation, and bisphosphonate therapy (eg, alendronate 70 mg weekly or zoledronate 4 mg annually) for the prevention or treatment of glucocorticoid-induced osteoporosis are permitted. The doses and treatment duration should comply with local practice or clinical guidelines at the discretion of the investigator.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1 and Table 2.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19, are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 1: 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
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
[redacted]																				
BPDAI Pruritus	X	X								X										X
[redacted]																				
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																				
[redacted]																				

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
[redacted]																				
BP180, BP230 Autoantibodies	X[27]	X		X						X										X
Optional FBR Samples																				
Serum		X								X										X
Plasma		X								X										X
[redacted]																				

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
[redacted]								
BPDAI Pruritus				X				X
[redacted]								
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								
[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
[redacted]								

ABQOL: Autoimmune bullous disease quality of life; BP: Bullous pemphigoid; BPDAI: Bullous Pemphigoid Disease Area Index; BSA: Body surface area; [redacted]; 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; [redacted]; PK: Pharmacokinetic; [redacted]; TB: Tuberculosis; WOCBP: women of childbearing potential.

Table 2: 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						
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
[redacted]						
BPDAI Pruritus			X	X	X	X
[redacted]						
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
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

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			
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						
[redacted]						
BP180, BP230 Autoantibodies			X	X	X	X
Optional FBR Samples						
Serum			X			
Plasma			X			
[redacted]						

ABQOL: Autoimmune bullous disease quality of life; BP: Bullous pemphigoid; BPDAI: Bullous Pemphigoid Disease Area Index; BSA: Body surface area; [redacted]; FBR: Future biomedical research; [redacted]; NRS: Numerical rating score; OCS: oral corticosteroids; [redacted]; PK: Pharmacokinetic; [redacted]; WOCBP: women of childbearing potential.

9.1.1. Footnotes for the Schedule of Events Tables

9.1.1.1. Table 1 Schedule of Events Footnotes

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 [redacted] at select study sites only], [redacted]), 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).
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) 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. [redacted]
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).
28. [redacted]
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).

9.1.1.2. Table 2 Schedule of Events Footnotes

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 [redacted] at select study sites only], [redacted]), 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 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. [redacted]
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.

9.1.2. Early Termination Visit

Patients who are withdrawn from the study will be asked to return to the clinic for an early termination visit consisting of the early termination assessments described in Table 2.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

9.1.3.1. Unscheduled Visits for BP Relapse

These visits allow for an assessment for BP relapse after week 16 when a BP flare (worsening of disease) has been reported by a patient during the phone visits which start at week 18. If a BP flare is suspected during these phone visits, then the patient must return for assessments and procedures specified in Table 2 for an unscheduled visit for BP relapse.

9.2. Study Procedures

Assessments/procedures at the clinic visit should be performed in the following order:

1. Patient-reported outcomes
2. Investigator assessments (performed only by adequately trained and qualified investigators or sub-investigators; it is recommended that the same investigator or sub-investigator perform all the evaluations for a given patient throughout the entire study period)

3. Safety and laboratory assessments (including sample collection for ADA, PK, biomarker, and optional [redacted]).
4. Administration of study drug

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: Inclusion/exclusion criteria, medical history, demographics, and patient e-diary training (Pruritus, Pain, and Sleep Quality NRS assessments).

A biopsy and assessments for diagnosis of BP based on histopathology, immunopathology, and serology will be performed during screening for the BP diagnostic criteria unless a ≤6-month-old biopsy report (from the screening visit) for histology and direct immunofluorescence is available (see Section 7.2.1 Inclusion Criteria, Inclusion Criterion #2.

9.2.2. Efficacy Procedures

9.2.2.1. Body Surface Area

Body surface area 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. Patients will undergo this assessment at time points according to Table 1 and Table 2. The BSA assessment tool is provided in the study reference manual/site binder or file.

9.2.2.2. Pruritus Numerical Rating Scale

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a 24-hour recall period. Patients will be instructed on using the patient diary to record their Pruritus NRS score at the screening and baseline visits. Patients will complete the rating scale DAILY according to the time points in Table 1 and Table 2. Clinical sites will check and remind patients to complete the diary at each visit.

9.2.2.3. Skin Pain Numerical Rating Scale

Skin pain will be 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. Clinical sites will check and remind the patient to complete the scale according to the time points in Table 1 and Table 2. Patients will be instructed on using the scale to record their skin pain score at the screening visit. Clinical sites will check patient data collected using an e-diary for protocol compliance and remind patients to complete their e-diary throughout the study.

9.2.2.4. Sleep Numerical Rating Scale

Sleep quality will be 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 will be asked to select the number that best describes the quality of their sleep during the previous night.

Clinical sites will check and remind the patients to complete the scale according to the time points in Table 1 and Table 2. Patients will be instructed on using the scale to record their sleep quality score at the screening visit. Clinical sites will check patient data collected using an e-diary.

9.2.2.5. Bullous Pemphigoid Disease Area Index Activity Score

The BPDAI activity score is a well-developed and 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. The minimal clinically important difference (MCID) in the BPDAI activity score is 4 points for assessing clinical improvement and 3 points for deterioration. Patients will undergo this assessment at time points according to Table 1 and Table 2.

9.2.2.6. 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 analog scale where 0 represents no itch and 10 represents maximal itching. Patient mark 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. Patients will undergo this assessment at time points according to Table 1 and Table 2.

9.2.2.7. Patient Global Assessment of Disease Severity

Patients will rate their overall wellbeing based on a 5-point scale. Patients will be 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". Patients will undergo this assessment at time points according to Table 1 and Table 2.

The assessment tool is provided in the study reference manual.

9.2.2.8. Patient Global Assessment of Treatment

Patients will rate their satisfaction with the study treatment based on a 5-point scale. Patients will be 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". Patients will undergo this assessment at time points according to Table 1 and Table 2.

The assessment tool is provided in the study reference manual.

9.2.2.9. Patient-Assessed [redacted]

[redacted]

9.2.2.10. 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 maximum ABQOL score is 51. Patients will undergo this assessment at time points according to Table 1 and Table 2.

9.2.2.11. Blister and Urticaria/Eczematous Plaque Count

The number of blisters (or erosions) and urticarial/eczematous lesions will be collected for each anatomical location (eg, head, neck, chest). Patients will undergo this assessment at time points according to Table 1 and Table 2.

9.2.2.12. Bullous Pemphigoid Clinical Assessment

The investigator will be required for completing the overall evaluation of BP clinical activity, which may include the following:

- Control of disease activity (Note: 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.
- Achievement of complete remission (Note: complete remission is defined as absence of new lesions and epithelialization of old lesions).
- Assessment of adherence to the protocol-defined prednisone taper regimen (see Section 8.2).

- Assessment of disease relapse (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)
- Need for rescue therapy (see Section 8.3).

Evaluation of the above should be based on the signs of BP, which include the presence (or absence) of blisters, erosions, urticarial and eczematous plaques. Once a lesion has been epithelialized, the lesion should no longer be considered a blister or erosion. Further, the presence of scarring or post-inflammatory hyperpigmentation or hypopigmentation should not be considered as active disease.

To ensure consistency of assessments, the same investigator or sub-investigator should perform all the evaluations for a given patient throughout the entire study period. Patients will undergo this assessment at time points according to Table 1 and Table 2.

9.2.2.13. Bullous Pemphigoid Area Photographs

At select study sites, photographs will be taken of a representative area of BP involvement. Subsequent photographs of the same area will be taken at time points according to Table 1 and Table 2.

Instructions for taking the photographs are provided in the photography reference manual.

9.2.2.14. Assessment of Bullous Pemphigoid Flare

During phone visits, patients will be asked to report any worsening of their disease. If worsening of a patient's disease is suspected, the patient should return to the clinic for an unscheduled visit for BP relapse (Table 2). At this visit, the assessments and procedures specified in Table 2 should be performed.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including heart rate, blood pressure, respiration rate, and body temperature will be collected pre-dose at each clinic visit, as noted in Table 1 and Table 2. Heart rate and blood pressure will be measured with the patient in a sitting position after the patient has rested comfortably for at least 5 minutes.

9.2.3.2. Body Weight and Height

Body weight will be measured at time points according to Table 1 and Table 2. Height will be measured according to Table 1.

9.2.3.3. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1 and Table 2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.4. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 1 and Table 2. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT intervals will be recorded. The ECG strips or reports will be retained with the source.

9.2.3.5. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 1 and Table 2. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol[2]
Chloride	Blood urea nitrogen	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase[3]
Glucose	Alkaline phosphatase	Hemoglobin A1c
Albumin	Lactate dehydrogenase	hs-CRP

1 Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN.
2 Low-density lipoprotein and high-density lipoprotein
3 CPK isoenzymes will be measured when CPK >5× the ULN

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Serum and urine pregnancy testing will be performed for all female patients of childbearing potential according to Table 1 and Table 2.

The following additional laboratory tests will be performed at screening: HIV; HBsAg; HBsAb; HBcAb; HBV DNA (only in patients who are HBsAg negative, HBsAb negative, and HBcAb positive); hepatitis C antibody; HCV RNA (only in patients who are HCV Ab positive); tuberculosis (will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards).

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical/study director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Drug Concentration and Measurements

Samples for measuring functional dupilumab concentrations will be collected at visits listed in Table 1 and Table 2.

9.2.5. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 1 and Table 2. Samples positive in the ADA assay will be analyzed for the presence of neutralizing antibody in the NAb assay.

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore how dupilumab may modify the underlying disease process in BP. Biomarker samples will be collected at time points according to Table 1 and Table 2. Biomarker measurements will be performed to determine effects on relevant physiological and pathogenic processes.

[redacted]

Serum anti-BP180 and anti-BP230 autoantibodies of the IgG subclass concentration measurement

Serum anti-BP180 and anti-BP230 IgG increase during BP disease flares are markers of disease activity. The concentration of anti-BP180 and anti-BP230 IgG are measured at screening as part of the inclusion criteria and monitored during the treatment period in the study, as described in Table 1 and Table 2.

[redacted]

9.2.6.1. Exploratory Research

Research samples ([redacted]) will be collected for exploratory research related to immunology of BP. Samples may also be used to evaluate the effects of dupilumab on the inflammatory profile in circulation, as measured by serum and plasma chemokines/cytokines [redacted]

The list may be altered or expanded as it is recognized that more relevant or novel biomarkers may be discovered during the course of this study. Banked research plasma samples (serum/plasma), as well as any unused samples for study-related research (including PK and ADA samples), will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for the scope of research described above. After 15 years, any residual samples will be destroyed. Results of these exploratory analyses will not be reported in the clinical study report.

Residual tissue block from the screening punch biopsies (if performed) may be used for exploratory biomarker research, including [redacted] analysis.

Skin biopsies collection (at select study sites only)**:** Punch biopsies will be collected from the affected areas of BP lesions. The skin biopsies may be used to evaluate [redacted]

9.2.7. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Additional samples will be collected for FBR. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.7.1. [redacted] Analysis (Optional)

Patients who agree to participate in the [redacted] sub-study will be required to consent to this optional sub-study before collection of the samples. [redacted]. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements

involving the [redacted] analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

[redacted]

Research findings from the optional [redacted] sub-study will not be disclosed to the patient or principal investigator, even if these findings have implications for a patient's health and management. [redacted] results from this sub-study are for research purposes only and not for medical diagnosis or for [redacted].

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period, from the time of signing the informed consent form (ICF) to the end of the study. Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, lead to dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of study) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF and retained at the study center, and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **AESIs**; serious and nonserious**:** Adverse events of special interest for this study include the following:
    1. Anaphylactic reactions
    2. Systemic hypersensitivity reactions
    3. Helminthic infections
    4. Any severe type of conjunctivitis or blepharitis
    5. Keratitis
    6. Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female during the study or within 12 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event**. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. 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.

10.2.4. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade):

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires emergency room visit or hospitalization; necrosis or exfoliative dermatitis

10.2.5. Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the AE, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs. time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction

- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications), or other external factors.

Causality to the study conduct (protocol-specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications), or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical/study director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic, cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, Ethics Committees (ECs)/Institutional Review Board (IRBs), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (dupilumab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Event expectedness for study drug (dupilumab) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and ECs/IRBs as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the SAP for the study.

Data collected through the implementation of new CRFs regarding the impact of the COVID-19 pandemic on the patients will be summarized (eg, discontinuation due to COVID-19). Handling missing data due to COVID-19 pandemic and any additional analyses and methods required to investigate the impact of COVID-19 on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

The primary analyses of the study will compare the treatment effect of dupilumab [redacted] q2w against placebo on the proportion of patients achieving sustained remission at week 36 as defined in Section 4.1.1. The following hypothesis of the primary endpoint will be tested:

- 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)

11.2. Justification of Sample Size

[redacted]

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) is defined as all randomized patients analyzed according to the treatment group allocated by randomization 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.

11.3.2. Safety Analysis Set

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

In addition:

- For patients who receive any dose of active study drug(dupilumab) during the trial, the treatment group allocation for as-treated analysis will be the dupilumab group.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis set 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.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received any study drug and had at least 1 non-missing ADA result following the first dose.

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or have at least 1 non-missing result in the NAb assay following the first dose. Patients who are ADA negative are set to negative in the NAb analysis set.

11.4. Statistical Methods

For continuous variables, the following information will be provided: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum. Continuous variables will be described by visit and as change from baseline, if applicable.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

For the time-to-event data, Kaplan-Meier curves and estimates, and median time along with 95% confidence interval (CI), will be provided.

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.

All statistical tests will be performed 2-sided with a type I error rate of 5% unless otherwise stated.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients who have signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- The total number of patients who completed week 36 and week 52, respectively
- The total number of patients who took rescue medications

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

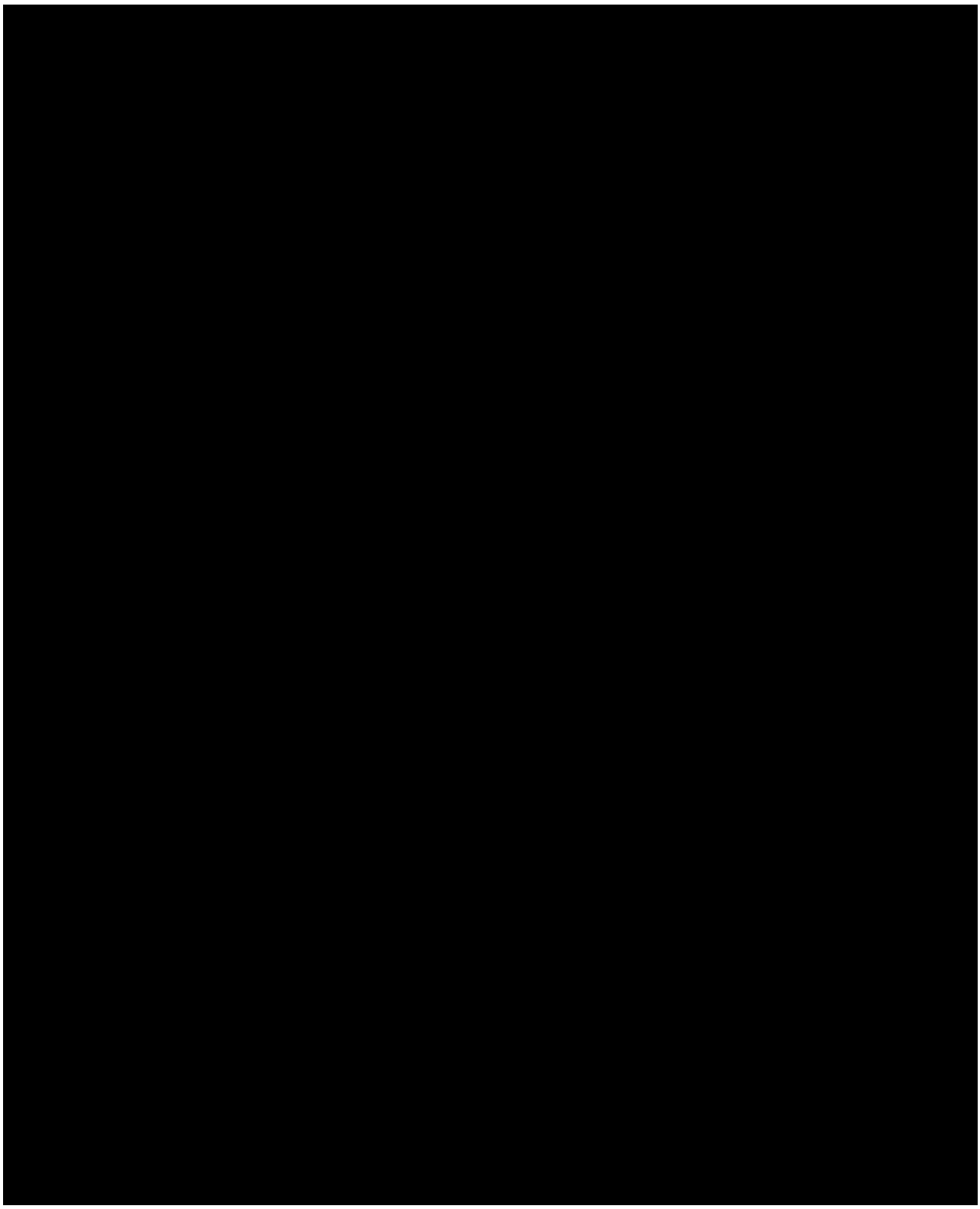
11.4.3.1. Primary Efficacy Analysis

[redacted]

[redacted]

11.4.3.2. Secondary Efficacy Analysis

[redacted]



[redacted]

11.4.3.3. Subgroup Analysis

[redacted]

11.4.4. Control of Multiplicity

[redacted]

11.4.5. Safety Analysis

All safety analyses will be performed on the SAF and the summary of safety results will be presented by treatment group. The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs, and 12-lead ECG.

Thresholds for treatment-emergent potentially clinically significant values (PCSVs) in laboratory variables and vital signs are defined as abnormal values considered medically important by the sponsor based on a review of the literature. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment period.

11.4.5.1. Adverse Events

Definitions

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

The pre-treatment AE and TEAE are defined in the following 3 observation periods:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug. Pre-treatment signs and symptoms (pre-treatment AEs) are AEs that developed or worsened in severity during the pre-treatment period.
- The on-treatment period during the 52-week treatment period are AEs with onset after the first dose up to the week 52 visit date (study day 365 if the week 52 visit date is missing) or early termination visit, whichever is earlier. TEAEs that have an onset during the 52-week treatment period and continue afterwards into the follow-up period will be counted only once as TEAEs during the 52-week treatment period.
- The post-treatment period (follow-up period) is AEs with onset after the week 52 visit date up to the end of study

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment and follow-up periods.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by system organ class (SOC) and preferred term (PT)
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- TEAEs leading to permanent treatment discontinuation, presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a treatment-emergent PCSV will be summarized for each vital sign variable. The criteria for treatment-emergent PCSV will be defined in the SAP.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a PCSV at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest. The criteria for treatment-emergent PCSV will be defined in the SAP.

Listings will be provided with flags indicating the out of laboratory range values.

11.4.5.3. Treatment Exposure

The duration of exposure during the study will be presented by treatment group and calculated as:

- last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations.

The number (%) of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, standard deviation, minimums, Q1, medians, Q3, and maximums. A summary of the number of doses by treatment group will be provided.

11.4.5.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

- Treatment Compliance = (Number of study drug injections during exposure period)/(Number of planned study drug injections during exposure period) × 100%

The treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

No formal statistical analysis will be performed. Trough functional dupilumab concentration in serum (C_{trough} time point) will be summarized at each time point using descriptive statistics. The data may be combined with data from other adult dupilumab studies (eg, AD) for analysis using population methods. Any population PK analysis will be reported separately.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by ADA, titer, and NAb responses observed:

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers, and NAb positivity presented by patient, time point, and dose cohort/group will be provided. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.5. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) system.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical analysis system (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- Digital archive system for photographs

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current, approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and is accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF/eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRFs/eCRFs that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP, the Japanese GCP, and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original, signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and health authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study 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

Protocol Number: R668-BP-1902

Protocol Version: R668-BP-1902 Amendment 3

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00337156 v1.0

Approval/eSignature	[redacted] 01-Mar-2024 15:43:55 GMT+0000

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