Statistical Analysis Plan

Immune Pharmaceuticals

An Open-Label, Proof of Concept Study Designed to Evaluate the Safety, Efficacy and Pharmacodynamic Effect of Bertilimumab in Newly Diagnosed Patients and Patients Resistant to Corticosteroid Tapering with Moderate to Extensive Bullous Pemphigoid

Final

6 February 2019

Signature Page

Study Name	**An Open-Label, Proof of Concept Study Designed to Evaluate the Safety, Efficacy and Pharmacodynamic Effect of Bertilimumab in Newly Diagnosed Patients and Patients Resistant to Corticosteroid Tapering with Moderate to Extensive Bullous Pemphigoid**
Sponsor	**Immune Pharmaceuticals**
SAP Date	**6 February 2019**

Written by:

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The undersigned hereby declare that they have examined the Statistical Analysis Plan document and agree to its form and content.

Represented by:

Signature [redacted]

Date:

Name:

Title:

Version History

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1.0	February 6, 2019	Final

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List of Abbreviations

ABQOL	The Autoimmune Bullous Diseases Quality of Life
AE	Adverse Event
B-hCG	Human beta chorionic gonadotropin
BMI	Body Mass Index
BP	Bullous Pemphigoid
BPDAI	Bullous Pemphigoid Disease Area Index
CMV	Cytomegalovirus
CRF	Case Report Form
CS	Clinically Significant
DIF	Direct Immunofluorescence
ECG	Electrocardiography
ECP	Eosinophil Cationic Protein
HBV	Hepatitus B Virus
HCV	Hepatitus C Virus
H&E	Hematoxylin & Eosin
HIV	Human Immunodeficiency Virus
IIF	Indirect Immunofluorescence
NCS	Non-Clinically Significant
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PK	Pharmacokinetics
PPD	Purified Protein Derivative
QFT	Quantiferon Test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TB	Tuberculosis
VAS	Visual Analogue Scale

1 Introduction

1.1 General

Bertilimumab is the first monoclonal antibody to specifically neutralize human eotaxin-1 (eotaxin). Bertilimumab has been shown to inhibit eotaxin-stimulated migration of cells and may therefore be useful in the treatment of human diseases such as Bullous Pemphigoid (BP), where eosinophil accumulation is an important feature.

The purpose of this study is to provide proof of concept for the treatment of BP with bertilimumab. This study will provide both safety and efficacy data for internal decision-making regarding further development of bertilimumab in BP. Its efficacy in newly diagnosed patients would be proven by allowing reduced initial doses of corticosteroids and a reduced cumulative dose of corticosteroids by facilitating rapid tapering to 10 mg prednisone equivalent or lower after initial control of BP lesions. Its efficacy in patients resistant to corticosteroid tapering would be proven by allowing patients to be tapered down from corticosteroids without flaring and/or allowing smaller doses of oral corticosteroids to control the disease.

The study will investigate newly diagnosed adult patients and adult patients resistant to corticosteroid tapering with moderate to extensive BP. The treatment period will include three IV infusions of 10 mg/kg bertilimumab on study Days 0, 14 (±2 days) and 28 (±2 days) and a follow-up period up to Day 84 (or Day 118 for males who have had abnormal semen analysis results on Day 0, Day 14 or Day 28) relative to pre-dose Visit 2. Patients will receive concomitant oral steroids during the treatment and follow-up period.

1.2 Study Design Configuration

This is an open-label, proof-of-concept, single group study in newly diagnosed adult patients and adult patients resistant to corticosteroid tapering with moderate to extensive BP.

The study will consist of three periods:

- A screening period of up to 4 weeks
- An open-label treatment period lasting 4 weeks consisting of IV infusion of bertilimumab at Visit 2 (Day 0), Visit 3 (Day 14) and Visit 4 (Day 28)
- A safety and efficacy follow-up period of approximately 56 days plus a follow-up phone call 2 and 4 months following Visit 8 (Day 84)

2 Centers

This is a multicenter trial. Up to 10 sites in Israel and US will participate in this study.

3 Study Objectives

3.1 Primary Objective

To evaluate the safety of bertilimumab in newly diagnosed patients and patients resistant to corticosteroid tapering with moderate to extensive BP.

3.2 Secondary Objectives

To evaluate the preliminary evidence of clinical efficacy, pharmacokinetics (PK) and pharmacodynamic (PD) effect of bertilimumab in newly diagnosed patients and patients resistant to corticosteroid tapering with moderate to extensive BP.

3.3 Exploratory Objectives

To determine the change from Visit 2 (Day 0) to Visit 5 of Peripheral Blood Mononuclear Cell (PBMC) biomarkers.

4 Treatment Groups

This is a single arm trial, where all eligible patients will be treated with investigational product - Bertilimumab.

5 Study Schedule

Table 1 Schedule of Study Events

Study Procedures	**Screening**	**Treatment Period**			**Follow-up Period[a]**						**Early Discontinuation[b]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[o]**	**Phone call**	**-**
Study Day (visit window +/- 2 day)	**-28 to -1**	**0**	**14 (+/-2)**	**28 (+/-2)**	**42 (+/-2)**	**56 (+/-2)**	**70 (+/-2)**	**84 (+/-2)**	**118 (+/-2)**	**Approx. days 144 and 204**	**-**
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographic & medical history	X										
Karnofsky performance status	X										
Physical examination[c]	X[c]	X*	X*	X*	X	X	X	X			X
Vital signs	X	X[d]	X[d]	X[d]	X	X	X	X			X
ECG	X							X			X
Hematology (including eosinophil count) and biochemistry[e]	X[f]	X*	X*	X*	X			X			X
Serum eotaxin-1		X*	X*	X*	X	X	X	X			X
Screen for active/latent tuberculosis[, g]	X										
Skin punch biopsy for H&E and eosinophil count	X				X[h]						
Skin punch biopsy for DIF on salt split skin	X										
IIF and BP180 & BP230 auto antibodies	X[j]	X*	X*	X*	X	X	X	X			X
Assessment of BP severity	X										
Serology (HIV, HBV, HCV, CMV) [e]	X										
Urine β-hCG[i]		X*	X*	X*	X			X			
Anti-bertilimumab antibodies		X*	X*	X*	X	X	X	X			X
PK (bertilimumab) blood sampling		X[k]	X[k]	X[k]	X	X	X	X			X
PBMC biomarker blood sampling		X*			X						
Semen analysis		X[l]	X[l]	X[l]					X		X[m]
Bertilimumab infusion		X	X	X							
BPDAI (including Pruritus evaluation) and lesion healing assessment	X**	X*	X*	X*	X	X	X	X			X
ABQOL questionnaire	X**	X*	X*	X*	X	X	X	X			X
Corticosteroid management	X	X	X	X	X	X	X	X	X	X	

Prior and concomitant medications	X	X*[n]	X*[n]	X*[n]	X	X	X	X	X	X	X
Adverse events	X	X*[n]	X*[n]	X*[n]	X	X	X	X	X	X	X
Infusion reaction assessment		X[o]	X[o]	X[o]							
Photography	X	X*	X*	X*	X	X	X	X			X

Note: Ability to taper steroids during scheduled or unscheduled visits will be determined by the investigator based on patient response.
* Denotes assessment will be done pre-dose
** To be performed if possible prior to commencement of corticosteroid regimen
a Visits 3 through 9 have a ±2-day window. The window is calculated from the actual visit day compared to baseline (Day 0), (e.g.,. for Visit 6 (Day 56) the window would be Day 54 to Day 58).
b At this visit, the activities to be performed will relate to the study period at which time the patient discontinued.
c Physical examination including weight; height measurement at screening only.
d Vital signs will be measured pre-dose (any time prior to the initiation of treatment infusion), immediately at the completion of treatment infusion (approximately 30 minutes after initiation) and approximately 2 hours following initiation of treatment infusion.
e Clinical laboratory assessments will be performed by a local laboratory for the screening visit and a central laboratory for every subsequent visit.
f Biochemistry will include serum β-hCG at screening for females of childbearing potential only.
g The patient should be evaluated for active/latent TB as applicable (e.g.,. PPD, QFT, and/or chest x-ray)
h The Visit 5 (Day 42) punch biopsies should be taken in the area of the previous biopsies, as much as possible.
i Females of childbearing potential only.
j IIF only at screening
k Blood samples for bertilimumab (PK analysis) will be collected pre-dose and at the completion of treatment infusion (approximately 30 minutes after the initiation) and 2 or 4 hours following the initiation of treatment infusion. PK samples 30 minutes post-infusion should be taken as close to this time as possible.
l Semen analysis will be performed for males pre-dose and close to the completion of infusion as possible. Pre-dosing samples can be taken up to 2 days prior to dosing.
m Only for males with abnormal semen analysis results from Day 0, Day 14 or Day 28 compared to pre-dose at Visit 2 (Day 0). It should be noted that in practice semen samples were not collected.
n Adverse events and concomitant medication information to be recorded pre-dose and 2 hours after the initiation of infusion.
o Infusion reactions should be assessed at the completion of infusion (approximately 30 minutes after the initiation) and 2 hours following the initiation of treatment infusion

6 Analysis Populations

6.1 Safety Analysis Population

The Safety analysis population will consist of all patients enrolled in the trial who received at least one infusion of bertilimumab 10 mg/kg.

Specifically, at least one CRF item "Date of Drug Administration" is completed.

6.2 Efficacy Analysis Populations

6.2.1 PK Population

The PK population will include patients from whom PK samples were collected. Samples were collected at three timepoints: pre-dose, 30 minutes post-infusion and 2 or 4 hours post-infusion (depending on the protocol version executed) and at the follow-up visits. The following PK parameters will be calculated Cmax, Tmax, Cavg, Cmin, $\boldsymbol{\lambda_z}$ and t1/2. Additional PK parameters will be calculated if deemed necessary.

6.2.2 Efficacy Population

The Efficacy population will be a subset of the Safety population. All patients in the Efficacy population will have the visit score on the Bullous Pemphigoid Disease Area Index (BPDAI) at baseline and at least one post baseline BPDAI score.

“Baseline” is defined as the last measurement obtained *before* the treatment initiation.

Handling of missing data:

Missing data will not be imputed, i.e. only observed data will be used.

7 Definition of Endpoints

7.1 Safety Endpoints

7.1.1 Main Safety Endpoints

- Treatment related (possibly and probably) AEs
- Serious AEs (SAEs)
- Infusion reactions

7.1.2 Additional Safety Endpoints

- Treatment emergent AEs (occurring at or after the treatment initiation)
- Physical examination
- Vital signs (blood pressure, heart rate, temperature)
- ECG
- Concomitant medications
- Laboratory evaluation:
    - Hematology
    - Biochemistry
    - Anti-bertilimumab antibodies

7.2 Efficacy Endpoints

7.2.1 Main Efficacy Endpoints

Following are the study main efficacy endpoints:

Bullous Pemphigoid Disease Area Index (BPDAI)

The following three activity sub-scores will be defined:

Activity Sub-Score I: Total Activity Cutaneous Erosions/Blisters defined as:

Total Erosions/Blisters Activity Score (auto calculated in the CRF) + 0.3(The corresponding total number of erosions/blisters)*

If a body region is scored 3 or higher, the number of lesions = 0.

In other words, only if a body region is scored 1 or 2 the number of lesions should be provided.

Activity Sub-Score II: Total Activity Cutaneous Urticaria/Erythema/Other defined as:

Total Urticaria/Erythema Activity Score (auto calculated in the CRF) + 0.3(The corresponding total number of urticarial/erythematous lesions)*

If a body region is scored 3 or higher, the number of lesions = 0.

In other words, only if a body region is scored 1 or 2 the number of lesions should be provided.

Activity Sub-Score III: Total Activity Mucosa Erosions/Blisters defined as:

Total Activity Score (auto calculated in the CRF)

There is no lesion count for Mucosa.

Note (a) the number of lesions reported for each of 12 areas could vary between 1 to 3. Thus, the maximal possible total number of lesions is 36; (b) lesion counts are ONLY reported for a score of 1 (Erosions/Blisters: "1-3 lesions, none>1cm;" Urticaria/Erythema: "1-3 lesions, none >6cm") or 2 (Erosions/Blisters: "1-3 lesions, at least one>1cm;" Urticaria/Erythema: "1-3 lesions, at least one >6cm").

Total Activity Score of the BPDAI

Total activity score is defined as sum over the three activities sub-scores defined above. Higher scores indicate greater disease activity.

BPDAI Damage / Pigmentation Total Score

BPDAI Damage / Pigmentation Total Score, ranging from 0 to 12, where higher scores indicate greater disease activity.

Note that the Damage/Pigmentation score generally rises over shorter time periods (months) because it represents post-inflammatory hyperpigmentation that can take over one year to resolve.

Damage scores that were not filled should be replaced by zero.

Total BPDAI Score

Total BPDAI score is defined as sum of the Total Activity scores and BPDAI Damage / Pigmentation Score. Higher scores indicate greater disease activity.

- Change in **Total Activity Score** of BPDAI from Baseline to all subsequent visits

  Change in Total Activity Score =

  (Baseline Total Activity BPDAI - Visit *t* Total Activity BPDAI)

- Change in **Total BPDAI Score** from Baseline to all subsequent visits

  Change in Total BPDAI Score = (Baseline Total BPDAI - Visit *t* Total BPDAI)

Note: larger positive difference indicates greater improvement.

- Percent change in Total Activity Score of BPDAI from Baseline to all subsequent visits

  Percent Change in Total Score = 100*(Baseline Total Activity BPDAI – Visit t Total Activity BPDAI) / Baseline Total Activity BPDAI

- Percent change in Total BPDAI Score from Baseline to all subsequent visits

  Percent Change in Total BPDAI Score = 100*(Baseline Total BPDAI – Visit t Total BPDAI) / Baseline Total BPDAI

Note: larger positive difference indicates greater improvement.

In addition, percent change in Total Activity score of BDPAI will be further divided into 4 categories:

1. # subjects with >= 90% reduction in BPDAI total activity score
2. # subjects with >=75% reduction in BPDAI total activity score
3. # subjects with >=70% reduction in BPDAI total activity score
4. # subjects with >= 50% reduction in BPDAI total activity score

Prednisone Dose

All prednisone doses are summarized in either the Concomitant Medications form or the Corticosteroid Therapy Form depending on the protocol version used. Note that modification of prednisone doses at any time during the study was acceptable. Therefore, both the mean dose throughout the trial and the cumulative dose will be of interest.

The following prednisone dose summaries will be provided:

1. For each patient, divide the relevant form records into the periods which are consistent with the study periods:
   a. Prednisone dose at Visit 2 will be based on all records done between the Visit 2 (including) and Visit 3 (not including). A single (long) record could be split into several records to fit the trial periods. For example, if a record starts before Visit 2 and ends before Visit 3, only the relative part from Visit 2 date onwards will be related to Visit 2.
   b. Similarly, all other trial visits will be defined, up to Visit 8.
2. For each patient and each trial period, calculate the total prednisone dose (mg) taken during this period. Frequency and the length of exposure should be considered in this calculation. (For example, Dose*Frequency*Number of Days)

3. The mean prednisone dose (mg/day) for each period will be calculated as the total dose in the previous step divided by the period duration (days).
4. The cumulative prednisone dose (mg) for each period will be calculated as the sum of the total prednisone dose (mg) over all preceding periods, starting at Visit 2.
5. Calculations similar to those described in steps (3) and (4) will be repeated, but with dose adjusted for a patient's weight. The mean weight adjusted prednisone dose (mg/kg/day) for each period will be calculated as the total dose in step (2) divided by the period duration (days) and divided by the subject's weight (kg) obtained at this visit (or the most recent available). The cumulative weight adjusted prednisone dose (mg/kg) for each period will be calculated as the cumulative sum over weight adjusted doses over all preceding visits.

- Reduction (measured continuously) in prednisone mean dose (mg/day) from Visit 2 (Day 0) to each subsequent visit
- Dichotomous reduction in prednisone mean dose (mg/day) will be defined as
    - Success "1", if the dose at Visit 8 (Day 84) does not exceed 10 mg/day
    - Failure "0", otherwise

7.2.2 Additional Efficacy Endpoints

BPDAI Pruritus Component (VAS) Score

The following three VAS sub-scores will be defined:

- **VAS Sub-Score I:** How severe has your itching been over the last 24 hours
- **VAS Sub-Score II:** How severe has your itching been over the past week
- **VAS Sub-Score III:** How severe has your itching been over the past month

The Total Pruritus VAS score is defined as the sum over the three sub-scores. If at least one of the sub-scores is missing, the total is not defined.

- Change in BPDAI Pruritus Component (VAS) (sub-scores and total) from baseline to all subsequent visits

Control of Disease Activity

Control of Disease Activity is defined as the time when at least two of the following occur: New lesions cease to form, established lesions begin to heal and/or pruritic symptoms start to abate. The information needed for this endpoint was not collected for

all subjects. Consequently, data will be presented for the individual subjects where the data is available.

Quality of Life

- The autoimmune bullous diseases quality of life (ABQOL) questionnaire total score (auto-calculated in the CRF), by visit
- Change in ABQOL total score from baseline to all subsequent visits.

Flares

Frequency distribution of patients experiencing a flare, by visit. This data will be provided by assessing the site's completion of the top section of the BPDAI/Pruritus VAS at each visit for each subject.

7.3 Pharmacokinetic (PK) Analysis

Descriptive statistics of PK parameters as described in Section 6.2.1 will be performed by Certara, a vendor chosen by Immune Pharmaceuticals. A final report of PK analysis including the definition of each PK parameter will be issued by Certara and included in the final CSR.

7.4 PD Endpoints

Following are the study PD endpoints.

If more than one value is obtained per-patient, per-test or per-time point, the average will be calculated.

- Eosinophil Absolute Count (serum), by visit; and change in Eosinophil Absolute Count compared to Baseline
- Hematoxylin and Eosin (from biopsy tissue); and change in Hematoxylin and Eosin compared to Screening
- Eotaxin-1 (serum concentration); and change in serum Eotaxin-1 level at each scheduled timepoint compared to Baseline
- BP 180 autoantibody (serum concentration); and change in BP 180 autoantibody compared to Baseline
- BP 230 autoantibody (serum concentration); and change in BP 230 autoantibody compared to Baseline
- Eosinophil Cationic Protein (ECP) (serum concentration); and change in ECP compared to Baseline

- IgE (serum concentration); and change in IgE compared to Baseline
  It should be noted that ECP and IgE data were collected from samples already available and the decision to test for these markers was made after the study was completed, so the protocol was not updated to include them.

7.5 Exploratory Endpoints

- Peripheral Blood Mononuclear Cell (PBMC) biomarkers
- Change in PBMC biomarkers at Visit 5 compared to Visit 2 (Day 0)

8 Data Derivation and Transformation

Data not originally part of CRF will be derived as follows:

- Subjects age [years] = [Date of Informed Consent – Date of Birth] / 365.25
- Study Duration [days]= Date of Last Visit – Date of First Visit + 1.
- BMI = Weight (kg) / Height $(m)^2$
- Temperature [C°] = (Temperature [F°] - 32) × 5/9
- Weight (kg) = Weight (lb)* 0.45359237

9 Statistical Analysis

Numerical variables will be tabulated using mean, standard deviation, minimum, median, maximum and number of observations. Categorical variables will be tabulated using number of observations and percentages.

9.1 Subject Disposition

The following will be provided:

- Number and percent of subjects in each of the analysis populations (Safety, PK, Efficacy) by center and overall.
- Listing of subjects excluded from each of the analysis populations along with reason for exclusion.
- Consort flow diagram

- Number and percent of subjects who meet all inclusion / exclusion criteria at Visit 2
- Number and percent of subjects who were found eligible (approved by medical monitor) to participate in the study.
  For non-eligible subjects, by-subject listing, including site reason for non-eligibility.

Study Termination:

- Number and percent of subjects who completed the study.

Note, a subject is considered as early terminated the study if the CRF item "Indicate if the subject completed the trial or the primary reason for premature discontinuation" is not marked as "1" (Subject completed the trial).

- Frequency of premature termination reasons
- Listing of all dropouts along with the reason for termination and the time between termination and signing the informed consent form.

Protocol Deviations

- Listing of protocol deviations including subject ID, date of deviation, visit/CRF term and protocol deviation.

9.2 Baseline Characteristics

Baseline characteristics will be analyzed using the safety analysis population.
The following will be provided:

- Descriptive statistics of demographic characteristics (Age, Weight, Height, BMI, Gender, Race, Ethnicity)
- Frequency distribution of Karnofsky performance status
- Number and percent of patients who have any relevant medical history.
- By-subject listing of medical history including Subject ID, Center, Diagnosis/Symptoms, Start Date, End Date, whether Ongoing.

Tuberculosis Screen

- Number and percent of patients' current TB status: Active, Inactive- No evidence of active TB, Inactive- Latent.

- For patients with latent TB, number and percent of patients who were adequately treated or controlled.
- For patients with latent TB, number and percent of patients in the risk for reactivation.
- By-subject listing of assessments performed to confirm TB status, with the corresponding results.

Pregnancy Test

Frequency distribution of serum pregnancy test results.

Serology Test at Screening

Results will be divided into the following categories based on the normal ranges provided by the sites:

- ✓ Clinically significant below the normal range (CS below)
- ✓ Non-clinically significant below the normal range (NCS below)
- ✓ Within the normal range (Normal)
- ✓ Non-clinically significant above the normal range (NCS above)
- ✓ Clinically significant above the normal range (CS above)

Note: The above is relevant for all tests where the normal ranges are applicable.

Frequency distribution of Serology evaluation will be presented using the above categories.

DIF on Salt Split Skin at Screening (provided by Sponsor externally to the CRF)

The following DIF parameters will be provided externally to the CRF by the Sponsor (based on narrative reports) and presented in listing form: Immunoglobulin type (IgG, IgA, IgM, IgE – could be more than one), C3 deposition (yes/no), staining pattern (linear, granular, lace-like), site of staining (intercellular, basement membrane zone), extent of staining (diffuse vs focal), diagnosis (consistent with BP or not), unusual findings or notes. All data may not be available for all patients.

IIF Data at Screening (provided by Sponsor externally to the CRF)

The following IIF parameters from subjects' screening blood samples will be provided externally to the CRF by the Sponsor and presented in listing form: Dermal IgG Ab; Anti-Dermal Abs Area; Salt split skin IIF; BP230 Ab; BP180 Ab; Desmoglein 1 Ab; Desmoglein 3 Ab.

9.3 Safety

All safety analyses will be performed on the safety analysis population.

9.3.1 Main Safety Analysis

Treatment Related AEs

- Adverse Events that are possibly or probably related to treatment (including serious) will be tabulated using frequency tables with - Number of Subjects and Percentage of Subjects by:
    - Overall by System Organ Class (SOC) and Preferred Term
    - Maximal Severity by System Organ Class (SOC) and Preferred Term
    - By subject listing of treatment related Adverse Events

Serious Adverse Events (SAEs):

All SAEs will be tabulated using frequency tables with - Number of Subjects and Percentage of Subjects by:

- Overall by System Organ Class (SOC), Preferred Term and maximal severity
- Overall by System Organ Class (SOC), Preferred Term and maximal relation to study drug
- By subject listing of SAEs

Infusion Reaction Assessment (including injection site reactions)

- By subject listing of any infusion reactions (all responses except "no reaction"), including visit and time point.

9.3.2 Additional Safety Analysis

The following will be provided:

Adverse Events (AEs):

All Adverse Events (including serious) will be tabulated using Frequency tables with - Number of Incidents, Number of Subjects and Percentage of Subjects by:

- Overall by System Organ Class (SOC) and Preferred Term
- Severity by System Organ Class (SOC) and Preferred Term
- Relation to study drug by System Organ Class (SOC) and Preferred Term
- Severity and Relation to study drug

- By subject listing of Adverse Events

Physical Examination

- Frequency distribution of evaluation (normal/abnormal non-clinically significant (NCS)/abnormal clinically significant (CS)/not done) by body system and visit.
- By-subject listings of CS abnormal physical examination results, including patient ID, Center, Visit, Body System and Abnormality Description.
- Shift table of normal/abnormal non-clinically significant (NCS)/abnormal clinically significant (CS) transitions from Screening to Visit 4 (last infusion) and Visit 8 (last planned FU).

Body Measurements

- Descriptive statistics of Weight (kg), Height (m), BMI (kg/m^2), by visit
  Note: Height is presented only at Screening.

Vital Signs

- Descriptive statistics of blood pressure (systolic / diastolic), pulse and temperature by visit and by time point
- For each treatment visit, visits 2, 3 and 4, descriptive statistics of change from pre-dose to 30 minutes, 2 and/or 4 hours post-dose will be provided
- For visits 5, 6, 7 and 8, descriptive statistics of change from baseline pre-dose (visit 2) to each subsequent visit measure will be provided.

ECG

- Descriptive statistics of ECG parameters (heart rate, RR, PR, QRS, QT, QTc) by visit and by time point
- Frequency distribution of overall evaluation of ECG (normal/abnormal non-clinically significant (NCS)/abnormal clinically significant (CS)/not done)
- Descriptive statistics of change from Screening to last available visit
- By-subject listings of CS abnormal ECG results, including patient ID, center, visit, heart rate, RR, PR, QRS, QT, QTc, and abnormality description.

Anti-bertilimumab

- Descriptive statistics of anti-bertilimumab antibodies by visit
- Change from Baseline pre-dosing (at Visit 2) to each subsequent visit

Hematology / Chemistry

All hematology and chemistry tests will be divided into the following categories based on the normal ranges provided by the sites:

- ✓ Clinically significant below the normal range (CS below)
- ✓ Non-clinically significant below the normal range (NCS below)
- ✓ Within the normal range (Normal)
- ✓ Non-clinically significant above the normal range (NCS above)
- ✓ Clinically significant above the normal range (CS above)

  Note: The above is relevant for all tests where the normal ranges are applicable.

- By-test and by-subject listing of Hematology/ Chemistry results across visits. Note: The results will be presented using the above categories, where CS results will be highlighted. Screening data will not be presented as it was collected by separate local labs for screening purposes only and is, thus, not comparable to other rest results analyzed centrally (at one US and one Israeli central lab).
- By-subject listing of clinically significant abnormal hematology / urinalysis results.

Urine Pregnancy Test

- Frequencies of urine pregnancy test result (positive / negative / not done) by visit

Exposure

- Frequency distribution of number of infusions received

Concomitant medications

- By-subject listing of past and concomitant medication including subject ID, site, medication generic name or therapy, dose, units, frequency, route, start date, end date, whether ongoing, indication.
- By-subject listing of Corticosteroid Therapy for Bullous Pemphigoid including subject ID, site, Corticosteroid Name, dose, units, frequency, route, start date, end date, whether ongoing.

9.4 Efficacy

All efficacy analyses will be done on efficacy population.

9.4.1 Main Efficacy Analysis

Bullous Pemphigoid Disease Area Index (BPDAI)

- Descriptive statistics of main efficacy endpoints listed in Section 7.2.1. (three activity sub-scores, Total Activity BPDAI score, Damage / Pigmentation sub-score, Total BPDAI score, change from baseline in Total Activity and Total BPDAI score, percent change from baseline in Total Activity and Total BPDAI score, categorized change in Total Activity score.).
- Mean plots for the Total Activity BPDAI score and Total BPDAI score over time
- If applicable, the covariate analysis will be done to examine the reduction over time in Total Activity BPDAI score and Total BPDAI score, adjusted for the baseline value. Specifically, the following model will be fit:

  Reduction at Visit 4 = Baseline value,

  This model will be applied on both change and percent change, for total activity and total BPDAI scores.

Prednisone dose

- Descriptive statistics of prednisone doses (mean dose, weight adjusted mean dose, cumulative dose and weight adjusted cumulative dose) will be presented by visit.
- Descriptive statistics of reduction in mean dose and weight adjusted mean dose will be presented by visit.
- Frequency distribution of dichotomous reduction in mean dose will be presented by visit.
- Mean plots for mean dose (mg/day), weight adjusted mean dose (mg/kg/day), cumulative dose (mg) and weight adjusted cumulative dose (mg/kg).

9.4.2 Additional Efficacy Analysis

BPDAI Pruritus Component (VAS) Score

- Descriptive statistics of Pruritus VAS sub-scores, and the total score, by visit.

- Descriptive statistics of change from baseline in Pruritus VAS sub-scores, and the total score, by visit.
- Mean plot of total pruritus score over visits.

Quality of Life

- Descriptive statistics of ABQOL total score, by visit.
- Descriptive statistics of change from baseline in ABQOL total score, by visit

Flares

Frequency distribution of patients experiencing a flare, by visit. This data will be provided by assessing the site's completion of the top section of the BPDAI/Pruritus VAS at each visit for each subject.

9.5 Pharmacokinetics (PK) Analysis

PK analysis will be done (by Certara) on the PK analysis set accordingly as defined in Section 6.2.1 and Section 7.3.

9.6 Pharmacodynamics (PD) Analysis

- For continuous endpoints listed in Section 7.4, descriptive statistics will be presented (by visit where relevant).
- For dichotomous endpoints listed in Section 7.4, frequency distribution will be presented (by visit where relevant).
- Raw data for all endpoints listed in Section 7.4 will be presented in mean plots over time.

9.7 Exploratory Analysis

Additional exploratory analyses may be performed, including though not limited to following analyses:

- Descriptive Statistics of levels of Peripheral Blood Mononuclear Cell (PBMC) biomarkers, by visit.
- Descriptive Statistics of change in Peripheral Blood Mononuclear Cell (PBMC) biomarkers at Visit 5 compared to Visit 2 (Day 0)
- Mean plots of Peripheral Blood Mononuclear Cell (PBMC) biomarkers over time.

9.8 Covariate Analysis

Covariate analysis will be done in an exploratory fashion, upon the Sponsor requests.

10 Data Listings

Data listings will be provided for all data available from the CRF.

11 Computer Software

All statistical analyses will be carried out using SAS® Version 9.4 or higher under Windows® 2016 Terminal.