NCT #: NCT02226146

CLINICAL STUDY PROTOCOL

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

Study Product:	Bertilimumab
Indication:	Moderate to Extensive Bullous Pemphigoid (BP)
Protocol Number	Immune/BRT/BP-01
Phase:	2a
Name and Address of Sponsor:	Immune Pharmaceuticals Inc. 550 Sylvan Avenue, Suite 101 Englewood Cliffs, NJ 07632 Tel: (201) 464-2677 Fax: (201) 464-2677
GCP Statement:	This study will be performed in compliance with GCP, including the archiving of essential documents.
Version Number and Date:	Version 8.0 February 28, 2018

PROTOCOL SIGNATURE PAGE

Protocol Title:	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
Protocol Identification:	Immune/BRT/BP-01
Study Phase:	2a
Sponsor:	Immune Pharmaceuticals, Inc., USA

Sponsor Representative:

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

[redacted]

Name, Title | Signature | Date

Principal Investigator

By signing below, I, the Investigator, approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, CRF and any protocol-related documents. I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Immune Pharmaceuticals, Inc. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, or by me, at my center, if it becomes necessary in my opinion, to protect the best interests of the study patients.

Name | Investigator Signature | Date

Center Name | City, Country

PROTOCOL VERSION HISTORY

Version	Main Changes
1.0	Original
2.0	• Sponsor addresses updated to reflect new offices in USA and Israel • Sponsor representative changed to [redacted] • Sponsor name (Immune Pharmaceuticals Inc/Ltd.) updated to reflect offices in USA and Israel • Inclusion of Protocol Version History • Addition of wording to allow inclusion of sites in Europe and/or the US in the event of slow recruitment • Simplification of primary objective wording • Increase in concomitant steroid starting dose from 0.3 mg/kg/day to 30 mg/day and replacement of tapering regime with clinical standard allowing investigator to decide on dose reduction according to clinical response. • Addition of pruritus visual analogue scale and QOL questionnaire to assessments during treatment and follow-up period. • Number of patients increased from 10 to "up to 15". • Addition of BP severity definitions to inclusion criterion 4 and exclusion criteria 5. • Deletion of inclusion criterion 7 and addition of exclusion criterion 9 to exclude young, childless males or those planning to have more children in the future. • Addition of exclusion criteria relating to prior treatment with macrolides or tetracyclines, and inclusion of these drugs in the list of prohibited medications during the study (section 6.8.3). • Increase in bertilimumab dose from 5 mg/kg to 10 mg/kg. Section 1.3.1 (Rationale for Dose Selection) and 6.6 (Storage and Instructions for Preparation and Infusion of the Investigational Product) updated accordingly. • Clarification of rescue therapy in synopsis and section 6.8.2. • BPDAI moved to primary efficacy endpoint. Addition of steroid dose at visit 7 as co-primary endpoint and further secondary endpoints related to disease control, pruritus visual analogue scale and QOL questionnaire. Deletion of clinical remission as primary endpoint and duration of initial hospitalization as secondary endpoint. • Addition of wording to section 1.1 related to poor compliance associated with use of topical steroids in the elderly. • Deleted Figure 1, Study design schematic.

Version	Main Changes
	• Section 5.6 amended to reflect addition of pruritus visual analogue scale and QOL questionnaire and amended efficacy endpoints. • Section 10.0 updated due to incorporation of electronic data capture system. • Addition of references 18 and 9. • Appendix A, Schedule of Activities, updated to reflect changes in protocol. • Deletion of Appendix C, Declaration of Helsinki. • Definitions for additional acronyms added to the glossary.
3.0	• Change in Sponsor Representative • Removal of drug preparation instructions from section 6 and insertion of reference to pharmacy manual.
4.0	• Updated Immune Pharmaceuticals, Ltd., Israel location • Revised number of clinical sites and countries for clinical study conduct • Revised primary objective and endpoints to evaluate the safety of bertilimumab in patients with newly diagnosed, moderate to extensive BP only • Revised secondary objectives and endpoints to include the evaluation of clinical efficacy and pharmacokinetics. Added an exploratory objective and endpoint for PBMC biomarkers. • Change of treatment period from 2 weeks to 4 weeks (revision of Day 28 from a follow-up to a treatment visit). • Addition of follow-up visits at Day 70, Day 84 and Day 118 • Change of dosing from two IV infusions at 2-week intervals to three IV infusions at 2-week intervals • Addition of pharmacokinetics (PK) assessments from Day 0 to Day 84 • Addition of PBMC biomarker assessments at Day 0, Day 42 and Day 84 • Addition of post-treatment skin punch biopsies, including eosinophil count and IF on Day 42 (Visit 6) • Revision of patient population to include males or females ≥ 60 years of age • Revision of inclusion criteria to include males who have had a vasectomy or have declared that they have no interest in fertility in the future. • Revision of oral corticosteroid tapering regimen • Revision of study visit 7 from Day 60 to Day 56 • Revision of procedure to include semen analyses for any fertile male in the trial at Days 0, 14 and 28 pre-dose (baseline) as well as at maximal dose (approximately 30 minutes post-dose). Note: the pre-dosing samples can be taken up to 2 days prior to dosing.

Version	Main Changes
	• Revision of safety laboratory assessments to include semen analysis for the evaluation of sperm count, morphology and azoospermia. • For fertile males who have had abnormal semen analysis results on Day 0, Day 14 or Day 28, additional semen assessment after one spermatogenic cycle (3 months following the last administered dose (Day 118) or at early discontinuation will be followed up for an assessment of reversibility. • Revision of procedure to include a serum pregnancy test at screening, and urine pregnancy tests on Day 0, Day 7, Day 14, Day 28, Day 42 and Day 84 for women of childbearing potential • Administrative changes such as fax number addition to SAE reporting procedures and definitions for additional acronyms added to the glossary • Addition of a +/- 2 day visit window for all visits • Addition of screening for HIV, Hepatitis B, Hepatitis C and CMV infection at Screening • Addition of exclusion criterion #5 for detailing clinically significant abnormal laboratory results • Addition of serum eotaxin-1 level measurement at Day 0, Day 7, Day 14, Day 28, Day 42, Day 56, Day 70 and Day 84 • Change in exclusion criterion #13 from superpotent to class 1 and 2 topical steroids. Clarified that use of other topical steroids (other than class 1 and 2) is allowed throughout the study at the discretion of the investigator. • Addition of language to allow re-screening of patients and repeat labs for spurious test results • Clarified procedure windows • Added QOL questionnaire, pruritis visual analog scale and BPDAI to all study visits (except Screening) • Added ECG and hematology and biochemistry to Day 7, Day 28, Day 42 and Day 84 • Added anti-bertilimumab antibodies and BP180 and BP230 auto antibodies to all study visits (except Screening) • Clarified analysis at local vs. central laboratory, source document and document retention requirements • Addition of Appendix D: Topical Steroids Potency Class Table
5.0	• Deletion of principal investigator information due to protocol template format change.

Version	Main Changes
	• Deletion of Immune Pharmaceuticals, Ltd., Israel information due to administrative reasons. It has been confirmed that Immune Pharmaceuticals, Inc. alone will be the sponsor for the study. • Updated PBMC biomarker objective to be less specific since it is an exploratory objective. • Included more specific definition of 'newly diagnosed' and added specific diagnostic procedures that will be analyzed centrally, where possible. • Included more detail and clarity to the definition of moderate to extensive bullous pemphigoid. Also, included the assessment of BP severity in order to document the number of new bullae and/or uticarial plaques. • Extension of screening from 2 weeks to 4 weeks. • Day 7 Visit deleted as the visit was deemed unnecessary. It is felt that no safety or efficacy issues should be detected at study day 7. All visit numbers have been adjusted accordingly. • Clarified exclusion criteria #1 to state that investigator can determine whether or not medical conditions, including mental impairment and dementia, is severe enough to disqualify the patient. • Updated exclusion criteria to be consistent with point of reference to be Visit 2 – Day 0 rather than baseline, except where otherwise stated. • Further clarified and amended systemic oral corticosteroid usage guidelines including the allowance of systemic oral corticosteroid usage up to 4 weeks prior to Visit 2 – Day 0 up to doses of 40mg/day prednidone equivalent. • Expanded 'infusion site reactions' to all 'infusion reactions'. • Updated BPDAI to be the current validated version. Pruritis VAS is part of the BPDAI. • Further clarified the efficacy endpoints. • Moved 4-hour post-dose assessments up to 2-hour post-dose assessments to shorten the length of visits. It is felt that any safety issues would be identified by 2 hours after treatment infusion. • Included the 'Procedures for Enrollment of Eligible Patients' in section 5.2. • Included that any prior treatments taken within 90 days of screening should be documented.

Version	Main Changes
	• Limited the number of ECG assessments as it was felt that these would not identify any safety issues. • Clarified which labs will be done centrally versus locally. • Updated semen analysis testing: post-dose sample collection will now occur as close to the completion of treatment infusion, rather than 30 minutes following the initiation of treatment infusion, due to logistical difficulties of sample collection. Also stated that infertile males or those who have religious constraints will not have to provide samples • Clarified TB screening requirements. • Included 'Assessment of lesion healing' in section 5.3.9 in order to perform a thorough evalution of control of disease activity. • Left details of photography to be included in the Photography User Manual rather than in the protocol. • Updated that systemic oral corticosteroid usage can be modified during a phone call follow-up rather than at a clinic visit. • Updated SAE section 7.2 to include more details regarding SAE collection procedures. • Corrected fax number for medical monitor. • Deleted some details regarding data management as these are better left in data management plans. • Deleted PBMC analysis from Visit 9. • Schedule of Events updated to reflect updated assessment schedule.
6.0	• Change of title: removal of "Newly Diagnosed" and addition of "Newly Diagnosed Patients and Patients Resistant to Corticosteroid Tapering" • Addition of patients resistant to corticosteroid tapering as inclusion criterion #3 • Addition of a post treatment follow up call 2 and 4 months after Visit 8 (Day 84) • Change in the secondary endpoint: Proportion of patients who have tapered to prednisone dose of ≤10 mg/day at Visit 8 (Day 84) and/or 2 and 4 months after Visit 8 (Day 84) • Exclusion Criterion #11 "Use of previoustreatment for bullous pemphigoid" revised to remove redundancy with inclusion criterion #3

Version	Main Changes
	• Exclusion criterion #15 revised: Treatment with a full course of macrolides or tetracyclines within 4 weeks prior to the first treatment administration (Visit 2 - Day 0) • Change in inclusion criterion #2 to "Patients with a Karnofsky performance status >40%" to allow for patients who may require a caregiver • Confirmaton of diagnosis of moderate to extensive BP on 3 separate occasions during the 4 week period (as opposed to on 3 consecutive days) and removal of requirement for "new" bullae and urticarial plaques as long as criteria of "moderate to extensive" are met. • Doing the BPDAI, VAS, and ABQOL at the screening visit • The assessmentBPDAI, Pruritus VAS, and ABQOL will be made in relation to: o Screening, if patient is resistant to corticosteroid tapering o Visit 2 (Day 0), if patient is newly diagnosed • Schedule of Events updated to reflect updated assessment schedule.
7.0	• Cover page updated to include new Sponsor Address • Page 2 revised with new Sponsor Representative information for [redacted] • Page 50 updated with [redacted] information as Sponsor Contact for notification of serious or unexpected adverse events
7.1	Submitted to [redacted] /Site No. [redacted] in Israel, only (all changes noted in this version appear in the version 8.0, detailed below, provided to all sites).
8.0	• Cover page updated to include corrected Sponsor Address and contact information • Page 2- protocol signature page, updated with new corrected Sponsor Representative Information for [redacted] • Page 50, SAE Notification Page, updated with new corrected Sponsor Information with [redacted] contact data provided as Sponsor Contact for notification of serious or unexpected adverse events • Appendix B- Assessment of BP Severity- updated with corrected form to assess BP severity during screening; omitted in error from previous protocol versions

Version	Main Changes
	• Appendix D- Bullous Pemphigoid Disease Area Index- updated with corrected form; typographical errors were present in the previous protocol versions • Several editorial changes inserted as necessary to ensure consistency within all sections of the text and between the text and Appendix A- Schedule of Evaluations • Several minor language/grammatical/punctuation changes inserted as necessary to ensure accuracy and clearer comprehension by the reader

PROTOCOL SYNOPSIS

Study Title	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
Protocol No.	Immune/BRT/BP-01
Clinical Sites	Up to 10 sites in Israel and US Additional sites may be added as necessary to complete enrollment
Study Phase	2a
Indication	Moderate to extensive Bullous Pemphigoid (BP)
Study Objectives	**Primary Objective:** • To evaluate the safety of bertilimumab in newly diagnosed patients and patients resistant to corticosteroid tapering with moderate to extensive BP **Secondary Objective:** • To evaluate the preliminary evidence of clinical efficacy, pharmacokinetics (PK) and the pharmacodynamic (PD) effect of bertilimumab newly diagnosed and patients resistant to corticosteroid tapering with moderate to extensive BP **Exploratory Objective:** • To determine change from baseline of PBMC biomarkers
Study Design	This is an open-label, proof-of-concept, single group study in adult newly diagnosed patients and patients resistant to corticosteroid tapering with moderate to extensive BP. Eligible patients are those who: a. Ideally, have not been previously treated for BP. However, the following treatments are permitted for newly diagnosed patients • Systemic oral corticosteroids ≤40.0 mg/day (prednisone equivalent) within 4 weeks prior to the first treatment administration (Visit 2 - Day 0) • Topical corticosteroids other than those that are Class 1 or Class 2 (See Appendix F) within 2 weeks prior to the first treatment administration (Visit 2 - Day 0) b. Have been previously diagnosed with BP, and are resistant to corticosteroid tapering, in which case other corticosteroid regimens are permitted. No wash-out period is required. c. Have been diagnosed by the following assessments: • Clinical evaluation confirming BP

	• Hematoxylin and eosin (H&E) staining of a skin punch biopsy from the edge of a lesion to check the eosinophil make-up (including eosinophil count) of the inflammatory infiltrate • Serum testing for anti BP180 and anti BP230 autoantibodies • Direct immunofluorescence (DIF) on salt split skin of a skin punch biopsy from a perilesional area to check the linear deposition of IgG and/or C3 on the blister roof (epidermal side) • Indirect immunofluorescence (IIF) of the patient's serum to check for the presence of IgG circulating autoantibodies Although all of these assessments must be performed, ultimate determination of a positive BP diagnosis is up to the investigator. In newly-diagnosed patients, if any of these assessments have been performed previously within 4 weeks prior to first treatment administration, the specific assessment will not have to be repeated. In patients resistant to corticosteroid tapering, if either DIF or IIF immunofluorescence assessments have been performed previously, the specific assessment will not have to be repeated. Moderate to extensive bullous pemphigoid is defined by the mean number of bullae and/or urticarial plaques that appear on the patient's body, as documented on 3 separate occasions during the 4 week screening period, by the investigator, referring physician or reported by the patient or caregiver. To meet this criterion, it must be documentated that the patient has "moderate to extensive BP", on three separate occasions, where moderate disease is defined by 2-10 bullae and/or $\geq$ 5 urticarial plaques and extensive disease is defined by >10 bullae and/or urticarial plaques [3]. 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 (or 90 days for males who have had abnormal semen analysis results for post-dose Visit 2 (Day 0), Visit 3 (Day 14) or Visit 4 (Day 28) compared to the pre-dose Visit 2 (Day 0) results), plus a follow-up phone call at 2 and 4 months following Visit 8 (Day 84)

	Screening – Visit 1 (Day -28 to Day -1) Following signing of informed consent, patients will be screened for study eligibility (assessment of inclusion and exclusion criteria). The following assessments will be performed: collection of demographic information, medical history, prior and concomitant medications, and adverse event data. Karnofsky performance status, physical examination, height and weight, vital signs, ECG, screening for active/latent tuberculosis (TB), skin punch biopsy for DIF on salt split skin, skin punch biopsy for H&E including eosinophil count, serum collection for IIF and BP180 & BP230 autoantibodies, assessment of BP severity, photography, BP Disease Area Index (BPDAI) including Pruritus VAS and MD assessment of lesions, ABQOL, and laboratory evaluations (hematology, biochemistry, serology and serum pregnancy test (for females of childbearing potential)). BP Disease Area Index (BPDAI) including Pruritus VAS and MD assessment of lesions and ABQOL should be performed if possible prior to commencement of corticosteroid regimen. Corticosteroid usage will be managed and documented during the screening period. Corticosteroid management can occur either during a scheduled visit, unscheduled visit, or phone-call follow-up based on the investigator's discretion. The screening visit may be conducted over multiple days. Patients who meet all the inclusion criteria and none of the exclusion criteria may be enrolled in the study. If subjects fail screening, the subject may be rescreened once at the discretion of the investigator. Rescreened subjects will get a new study identification number on rescreening. A lab assessment during the screening period may be repeated at the discretion of the investigator if deemed spurious without repeating the entire set of screening requirements. In this particular case, the subject will not get a new study identification number. **Treatment Period[a] – Visit 2 (Day 0, baseline), Visit 3 (Day 14) and Visit 4 (Day 28)** At Visit 2, inclusion and exclusion criteria will be reviewed. The following assessments will be performed on Visit 2 (Day 0), Visit 3 (Day 14), and Visit 4 (Day 28) prior to administration of bertilimumab: collection of concomitant treatment and adverse event data, physical examination (including weight), vital signs, BP Disease Area Index (BPDAI) including Pruritus VAS, physician's assessment of lesion healing, completion of Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire, photography, urine pregnancy test (for females of childbearing potential), serum collection for BP180 and BP230 autoantibodies, serum eotaxin-1 levels, anti-bertilimumab antibodies, safety laboratory evaluations (hematology, biochemistry), PBMC biomarkers (Visit 2 only), PK sampling (pre-dose timepoint), and semen analysis (Note: the pre-dosing semen analysis samples can be taken up to 2 days prior to dosing). On Visit 2 (Day 0), Visit 3 (Day 14), and Visit 4 (Day 28), following completion of pre-dose assessments, bertilimumab will be administered by IV infusion over 30 minutes of infusion time. Vital signs will be assessed and PK post-dose samples will be collected at the completion of treatment infusion (approximately 30 minutes following the initiation of study drug infusion) and approximately 2 hours following initiation of

	study drug infusion. Semen analysis will first be performed at the completion of treatment infusion (approximately 30 minutes following the initiation) or as close to this time as possible. Assessment for evidence of infusion reaction will be conducted at the completion of treatment infusion (approximately 30 minutes following the initiation) and approximately 2 hours following initiation of dosing, and adverse events and concomitant medications will be recorded. Corticosteroid usage will be managed and documented as necessary. Corticosteroid management can occur either during a scheduled visit, unscheduled visit, or phone-call follow-up based on the investigator's discretion. **Follow-Up Period [b] - Visit 5 (Day 42), Visit 6 (Day 56), Visit 7 (Day 70), Visit 8 (Day 84), Visit 9 (Day 118), and Phone Call Follow-up approximately 2 and 4 months after Visit 8 (Day 84)** The following assessments will be performed at the follow-up clinic visits except for Visit 9 (Day 118): physical examination (including weight), BPDAI including Pruritus VAS, physician's assessment of lesion healing, completion of ABQOL questionnaire, photography, vital signs, AE and concomitant medication recording and serum collection for BP180 and BP230 autoantibody titres, PK, blood sample collection for measurement of serum eotaxin-1 and anti-bertilimumab antibodies. Skin punch biopsy for H&E staining and eosinophil count in tissue will be conducted (Visit 5 only). Urine pregnancy test (Visit 5 and Visit 8) for females of childbearing potential only), PBMC biomarker blood sampling (Visit 5 only) and safety laboratory evaluations (hematology, biochemistry) will be performed (Visits 5 and 8 only). ECG will be performed at Visit 8 (Day 84). The only assessments that will be performed on Visit 9 (Day 118) are collection of concomitant medication and adverse event information, and semen analysis for males who have had abnormal semen analysis results at Visit 2 (Day 0) post-dose, Visit 3 (Day 14) or Visit 4 (Day 28) compared to baseline pre-dose Visit 2 results. Corticosteroid usage will be documented and managed as necessary. Corticosteroid management can occur either during a scheduled visit, unscheduled visit, or phone-call follow-up based on the investigator's discretion. **Phone call follow-up (Approximately 2 and 4 months after Visit 8 (-Day 84)** The following assessments will be performed: completion of ABQOL questionnaire, adverse event assessment, and concomitant medication. Corticosteroid usage will be documented and managed as necessary.
Study Duration	Study duration for each patient (following the screening period) will be up to approximately 204 days Screening period: Up to 4 weeks Treatment period: 28 days (± 2 days) Follow-up period: 56 days (± 2 days) or 90 days (± 2 days) for males who have had abnormal semen analysis results post-dose Visit

[a,b] Study 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)

	2 (Day 0), Visit 3 (Day 14) or Visit 4 (Day 28) compared to pre-dose Visit 2 (Day 0) results; 2 and 4 months follow-up phone call after Visit 8 (Day 84).
Number of Patients	Up to 15 patients are expected to be enrolled in this study. Recruitment will be competitive.
Inclusion Criteria	1. Males or females, ≥ 60 years of age 2. Patients with a Karnofsy Performance Status > 40% 3. Eligible patients are defined as follows: a. Ideally, those who have not been previously treated for BP (newly diagnosed). However, the following treatments are permitted: • Systemic oral corticosteroids ≤40.0 mg/day (prednisone equivalent) within 4 weeks prior to the first treatment administration (Visit 2 - Day 0) • Topical corticosteroids other than those that are Class 1 or Class 2 (See Appendix F) within 2 weeks prior to the first treatment administration (Visit 2 - Day 0) b. Previously diagnosed BP patients, who are resistant to corticosteroid tapering, in which case other corticosteroid regimens are permitted. No wash-out period is required. c. All patients, must be diagnosed by the following assessments during the screening period: • Clinical evaluation confirming BP • Hematoxylin and eosin (H&E) staining of a skin punch biopsy from the edge of a lesion to check the eosinophil make-up (including eosinophil count) of the inflammatory infiltrate • Serum testing for anti BP180 and anti BP230 autoantibodies • Direct immunofluorescence (DIF) on salt split skin of a skin punch biopsy from a perilesional area to check the linear deposition of IgG and/or C3 on the blister roof (epidermal side) • Indirect immunofluorescence (IIF) of the patient's serum to check for the presence of IgG circulating autoantibodies Though all of these assessments must be performed, ultimate determination of a positive BP diagnosis, based on the composite of these inicators, is up to the investigator. In newly-diagnosed patients, if any of these assessments have been performed previously within 4 weeks prior to first treatment administration, the specific assessment will not have to be repeated. In patients resistant to corticosteroid tapering, if either DIF or IIF immunofluorescence assessments have been performed previously, the specific assessment will not have to be repeated. BP

	Disease Area Index (BPDAI) including Pruritus VAS, physician's assessment of lesions and ABQOL should be performed prior to administration of corticosteroids if possible. 4. Moderate to extensive bullous pemphigoid is defined by the mean number of bullae and/or urticarial plaques that have appeared on 3 separate occasions during screening as determined by the investigator, the referring physician or reported by the patient or caregiver. Moderate disease is defined by 2-10 bullae and/or ≥5 urticarial plaques. Extensive disease is defined by >10 bullae and/or urticarial plaques [3]. 5. Systemic corticosteroids for reasons other than bullous pemphigoid may be used with a washout period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0). 6. Adequate cardiac, renal and hepatic function as determined by the investigator and demonstrated by screening laboratory evaluations, vital sign measurement, ECG recording and physical examination results 7. Females who, in the opinion of the investigator, are of childbearing potential must have a negative serum pregnancy test at screening and agree to use effective contraception (hormonal contraception or two forms of barrier contraception) consistently throughout the study. 8. Males must have had a vasectomy or have expressed that they have no interest in fertility in the future. 9. Fertile males (males with no history of infertility or vasectomy) must agree to use effective contraception (e.g., condoms, spermicides) consistently throughout the study and for a period of four months following the end of treatment administration. 10. Patients must be willing and able to adhere to the study visit schedule and other protocol requirements. 11. Patients must be willing and able to provide voluntary written informed consent or written informed consent from a legally authorized representative.
Exclusion criteria	1. Patients with severe medical or surgical conditions at screening or Visit 2 (Day 0) including, but not limited to, severe dementia or mental impairment, severe stroke, severe cardiac insufficiency, severe arterial hypertension, severe or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric, or any other severe acute or chronic medical condition that, in the opinion of the investigator, may increase the risk associated with study participation/treatment or may interfere with the interpretation of study results and would make the patient inappropriate for study entry 2. Presence of any malignancy that has been under active treatment (e.g., radiotherapy or chemotherapy) within the 2 years prior to baseline or is anticipated to require treatment during the study period (including follow up) with the exception of patients with removal of uncomplicated basal cell carcinoma or cutaneous squamous cell carcinoma, who may take part in the study

	3. Congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, organ transplantation) 4. Clinically significant vital sign measurements or ECG findings as determined by the investigator 5. Clinically significant abnormal laboratory test results at screening as defined by the investigator, including, but not limited to: • Hemoglobin level <.100 g/dL • White blood cell count <3 x 10^3/µL • Lymphocyte count <0.5 x 10^3/µL • Platelet count <100 x 10^3/µL or >1200 x 10^3/µL • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN) • Alkaline phosphatase >3 × ULN • Serum creatinine >2 × ULN 6. Concomitant skin conditions preventing physical evaluation of BP 7. Active or recent history of clinically significant infection within 1 month of the first treatment administration (Visit 2 – Day 0) 8. Patients who are pregnant or breast-feeding, or planning to become pregnant during the study 9. Participation in a clinical trial of an investigational (unapproved) product within 4 weeks prior to the first treatment administration (Visit 2 – Day 0) 10. Patients who are known to have hypersensitivity to bertilimumab or any of the drug excipients 11. Use of any previous treatment for bullous pemphigoid (other than the oral/topical corticosteroid regimens allowed as described above in inclusion criteria #3a and #3b, and other than those treatments described in exclusion criteria #13-15 below, for which the appropriate wash-out periods were applied). 12. Treatment with systemic corticosteroids at any dose for reasons other than bullous pemphigoid within 4 weeks prior to the first treatment administration (Visit 2 - Day 0) 13. Treatment with immunosuppressants (e.g., azathioprine, methotrexate) within 4 weeks prior to the first treatment administration (Visit 2 - Day 0) 14. Treatment with biologics (e.g., etanercept, adalimumab, ustekinumab, infliximab, intravenous Ig) within 4 months prior to the first treatment administration (Visit 2 - Day 0). Patients who have received rituximab within 1 year prior to the first treatment administration (Visit 2 - Day 0) will be excluded from study participation.

	15. Treatment with a full course of macrolides or tetracyclines within 4 weeks prior to the first treatment administration (Visit 2 - Day 0) 16. Subjects who received a vaccine or other immunostimulator within 4 weeks prior to the first treatment administration (Visit 2 - Day 0) 17. Subjects who have clinical, radiographic, or laboratory evidence of active or latent mycobacterium tuberculosis (TB) infection 18. Evidence of an active disease of hepatitis B (HBsAg or HBcAb positive) or hepatitis C (HCV Ab positive), CMV (IgM positive) or human immunodeficiency virus (HIV) infection (HIV1/2 Ab positive) 19. Active abuse of alcohol or drugs 20. Any other condition, which, in the opinion of the investigator, would place the patient at an unacceptable risk if participating in the study protocol
Investigational Product Route and Dosage Form	Bertilimumab is a recombinant human immunoglobulin G (IgG_4) monoclonal antibody that neutralizes human eotaxin-1 (eotaxin); the drug product consists of bertilimumab formulated in phosphate buffered saline (PBS) at a concentration of 10 mg/mL, presented as a sterile, clear, colorless solution in 10 mL clear glass vials. Bertilimumab 10 mg/kg will be administered by IV over 30 minutes of infusion time at Visit 2 (Day 0), Visit 3 (Day 14), and Visit 4 (Day 28). The weight used for dose calculation at all dosing days is the weight measured at screening.
Systemic Corticosteroid Usage	Due to the potential effects of long-term and/or high-dose systemic corticosteroid usage on bullous pemphigoid, newly diagnosed patients will be permitted to take systemic oral corticosteroids specifically for bullous pemphigoid only for a period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0) at doses no greater than 40 mg/day prednisone equivalent. Specifically: <u>Patients who are newly diagnosed:</u> • Who have taken systemic corticosteroids for bullous pemphigoid longer than 4 weeks prior to the first treatment administration (Visit 2 - Day 0) or at doses greater than 40 mg/day prednisone equivalent at any time are excluded from the study. • For patients who have used systemic corticosteroids for reasons other than bullous pemphigoid, a washout period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0) is required. • For newly diagnosed patients who are taking systemic corticosteroids at a daily dose between 40 mg/day and 30 mg/day prednisone equivalent for BP within 4 weeks prior to the first treatment administration (Visit 2 - Day 0), tapering of systemic corticosteroids is at the discretion of the investigator. However, those patients must be on 30 mg/day prednisone equivalent for the first treatment administration (Visit 2 - Day 0). For newly diagnosed patients who are taking less than 30 mg/day prednisone equivalent prior to the first administration day (Visit 2 - Day 0), a stable

<table>
<tr><td></td><td>dose of systemic corticosteroids should be maintained until Visit 2 (Day 0).

<u>Patients who are resistant to corticosteroid tapering:</u>

• Are not required to be washed out from oral corticosteroid treatment prior to Visit 2 – Day 0.

The tapering schedule depicted in Table 1 is recommended for all patients for the remainder of the study.

Table 1: Recommended Corticosteroid Tapering Regimen
<table><tr><th>Systemic corticosteroid dose (prednisone equivalent) per day</th><th>Tapering schedule</th></tr><tr><td>≥30.0-10.1 mg/day</td><td>Decrease by 5 mg each week</td></tr><tr><td>10.0 – 0 mg/day</td><td>Decrease by 2.5 mg each week</td></tr></table>
Corticosteroid management can occur either during a scheduled visit, unscheduled visit, or phone-call follow-up as per the investigator's discretion.</td></tr>
<tr><td>Rescue Therapy</td><td>If necessary, rescue therapy is permitted at any point during the study at the discretion of the investigator. The patient can continue in the study as long as the rescue therapy is clearly documented.</td></tr>
<tr><td>Outcome Measures</td><td>PRIMARY ENDPOINTS

SAFETY ENDPOINTS

Safety will be evaluated on the basis of the following parameters:

• Adverse events (AE)
• Infusion reactions
• Injection site reactions
• Physical examination
• Vital signs (blood pressure, heart rate, temperature)
• ECG
• Concomitant medications
• Laboratory evaluation (hematology, biochemistry, anti-bertilimumab antibodies)

SECONDARY ENDPOINTS

EFFICACY ENDPOINTS</td></tr>
</table>

- Proportion of patients who achieve a reduction in the Total Activity Score of the BPDAI score of at least **50%, 75% and 90%** at visits 5 (Day 42), 6 (Day 56), 7 (Day 70), or 8 (Day 84) compared to:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed.
- Proportion of patients who have tapered to prednisone dose of ≤ 10 mg/day at Visit 8 (Day 84) and/or 2 and 4 months after Visit 8 (Day 84)
- Proportion of patients who achieve control of disease activity at Visits 5 (Day 42), 6 (Day 56),7 (Day 70), or 8 (Day 84)
  - 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. Control of disease activity will be assessed by the BPDAI and the investigator's assessment of lesion healing.
- Mean time to control of disease activity from:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed
- Change in BPDAI score at each scheduled measurement timepoint compared to:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed
- Change in BPDAI pruritis component (Visual Analogue Scale) at each scheduled measurement timepoint compared to:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed
- Change in ABQOL score at each scheduled measurement timepoint compared to:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed

PHARMACOKINETICS (PK) ENDPOINTS

- PK analysis for bertilimumab concentration: blood samples will be collected three times on dosing days: pre-dose, at the completion of treatment infusion(approximately 30 minutes following infusion initiation) and at 2 hours following initiation of study drug infusion, and once at the remaining study visits (excluding screening). The following PK parameters will be calculated, to the degree possible given the number of timepoints: C_{max}, T_{max}, C_{avg}, C_{min} and $t_{1/2}$. Additional standard and exploratory PK parameters will be calculated if deemed necessary.

	PHARMACODYNAMIC (PD) ENDPOINTS • Change in BP180 and BP230 autoantibody titres at each scheduled sampling timepoint compared to Visit 2 (Day 0) • Change in blood eosinophil count at each scheduled sampling timepoint compared to Visit 2 (Day 0) • Change in tissue eosinophil count assessed on biopsy at the scheduled timepoint (Visit 5) compared to screening • Change in serum eotaxin-1 level at each scheduled sampling timepoint compared to Visit 2 (Day 0) ***EXPLORATORY ENDPOINT:*** • Change in PBMC biomarkers at Visit 5 compared to Visit 2 (Day 0)
Statistical Methods	This is an open-label study. Thus, only descriptive statistics and narratives of individual patient case studies are planned. All data collected on the case report forms (CRFs) will be summarized for the clinical study report (CSR). All continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum, maximum, 25th percentile and 75th percentile). Summary statistics for categorical variables will include frequency counts and percentages. Summaries will be presented for all patients and by Treatment Phase and Follow-up Evaluation.

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GLOSSARY

Abbreviation/Term	Definition
β-hCG	Beta-human chorionic gonadotrophin
µg	Microgram
ABQOL	Autoimmune Bullous Disease Quality of Life
AE	Adverse event
ASI	Application Setup Instructions
BMZ	Basement Membrane Zone
BP	Bullous Pemphigoid
BPDAI	Bullous Pemphigoid Disease Area Index
CDM	Clinical Data Management / Manager
CDMoP	Clinical Data Monitoring Plan
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CMV	Cytomegalovirus
CRF	Case report form (also eCRF for electronic CRF)
CRO	Contract research organization
CSR	Clinical Study Report
CV%	Coefficient of variance
DIF	Direct Immunofluorescence
DM	Data Management
DVP	Data Validation Plan
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HPF	High Power Field
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IF	Immunofluorescence
IgG	Immunoglobulin G
IRB	Institutional Review Board

Abbreviation/Term	Definition
IV	Intravenous
kg	Kilogram
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mM	Millimolar
MOH	Ministry of Health
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate buffered saline
PD	Pharmacodynamic
PK	Pharmacokinetic
PPD	Purified Protein Derivative
QA	Quality Assurance
QOL	Quality of life
SAE	Serious adverse event
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
WHO	World Health Organization

1.0 INTRODUCTION

1.1 BULLOUS PEMPHIGOID

Bullous pemphigoid (BP) is an inflammatory, autoimmune blistering disease of the skin that mainly affects people over 60 years of age. The overall incidence is increasing in Europe and the US with an incidence rate between 20-30 new cases per million inhabitants per year and an incidence rate up to 350 new cases per million inhabitants per year among the population aged 80 years and older [4, 5]. To date, the only effective treatment for BP is high dose steroids, which are associated with side effects such as increased morbidity risk, particularly in the elderly population. It is therefore necessary to develop a safe, efficacious treatment for this rare disease and/or treatment which will enable steroid tapering.

BP is characterized by deposits of IgG antibodies and/or complement component 3 (C3) along the epidermal basement membrane zone (BMZ) [6, 7, 8]. Following antibody binding to hemidesmosomal antigens (BP180 and BP230) in the BMZ, complement activation occurs and inflammatory cells infiltrate the subepidermis causing tense blisters to form mainly on the flexor surfaces of arms and legs, axillae, groin, and abdomen. The blisters of BP are filled with a clear fluid, which tend to develop on the edge of erythematous plaques and may be widespread or local, and intense itching is common [9].

High dose oral corticosteroids (prednisone, 1 mg/kg/day) have been considered the mainstay of treatment for many years. It has been clearly demonstrated that these high doses are deleterious and directly responsible for a high rate of treatment side effects and a high mortality rate [3, 10, 11]. Super potent topical corticosteroids have been demonstrated to be more effective and safer than high dose oral corticosteroids, reducing the frequency of steroid-related side effects and mortality rate, while controlling BP lesions in between 95% to 100% of patients in two randomized controlled studies of more than 700 patients [3, 12]. Despite their high efficacy, topical corticosteroids are often considered inconvenient, necessitating the assistance of relatives or a nurse to apply the cream on the whole body surface for extended periods of time and their use is associated with poor compliance in an elderly population [18].

Immunosuppressants are poorly tolerated in elderly BP patients. Randomized controlled studies have failed to demonstrate a corticosteroid sparing effect, but revealed a higher rate of treatment side effects in patients receiving combined treatment compared with those treated with corticosteroid alone.

Antibiotics (tetracycline, dapsone) are considered safer than oral corticosteroids. However, their efficacy is controversial and has not been clearly demonstrated.

In summary, although BP lesions can be adequately and rapidly controlled with either oral or topical corticosteroids, due to significant associated side effects and poor compliance with use of steroid creams over large body surface areas, there is a significant need for novel, efficacious treatments.

1.1.1 The Role of Eotaxin and Eosinophils in Bullous Pemphigoid

Eotaxin-1 is an eosinophil-selective chemokine produced by a variety of cell types including eosinophils, epithelial cells, fibroblasts, endothelial cells, T-lymphocytes, monocytes and macrophages following induction by pro-inflammatory mediators [13]. Eotaxin is known to play

a significant role in the tissue accumulation of eosinophils that accompanies allergic inflammation. While eosinophils are an important component of innate immunity, the accumulation of eosinophils in tissues can be detrimental. Eosinophil degranulation products have significant cytotoxic effects on tissues, and cytokines known to be released by eosinophils enhance inflammatory signaling.

The cellular infiltrate that characterizes BP is comprised mainly of eosinophils, but also includes mast cells and lymphocytes. High levels of Th2 cytokines are found in BP tissue and blister fluid. Eosinophil infiltration and Th2-associated chemokines play a key role in the pathogenesis of BP [14]. The presence of eosinophils in BP skin lesions is well documented, and the chemotactic factors responsible for eosinophil recruitment into the tissue have been identified.

Immunoreactivity to eotaxin, localized to the epidermis and eosinophil granules, has been found in tissue biopsies from BP patients and in blister fluid [7, 14-16], consistent with increased chemotaxis of Th2 cells toward the blister fluid. Eotaxin and interleukin (IL-5), another Th2 cytokine, cooperate to activate and recruit eosinophils, ultimately contributing to the tissue damage characteristic of BP [15].

Compared to suction blister fluids obtained experimentally in healthy individuals, blister fluids from BP patients contain significantly higher amounts of eotaxin-1 [17], indicating substantial production of eotaxin-1 at sites of tissue damage and suggesting that eotaxin-1 is responsible for chemotaxis of both eosinophils and Th2 cells. From early stages of the disease via local production and release of cytokines (such as IL-4, IL-5) and eotaxin-1 itself, the immunological processes underlying blister formation are amplified and maintained [7].

These studies provide strong rationale for the use of therapeutic agents targeting eosinophils and molecules that regulate eosinophil function such as eotaxin-1 in the treatment of BP.

1.2 INVESTIGATIONAL THERAPY

Bertilimumab is a human monoclonal IgG_4 antibody that neutralizes human eotaxin-1 and inhibits its function. The product is manufactured in a mammalian cell line engineered using recombinant DNA technology to produce the antibody.

1.2.1 Nonclinical Studies

A single-dose toxicity study with bertilimumab was conducted in Rhesus monkeys (6 per dose group). Monkeys were administered a single IV infusion of bertilimumab at a dose of 10 or 100 mg/kg and observed for 28 and 7 days, respectively. No effects on morbidity or mortality were observed. Body weights and food consumption were not impacted by bertilimumab treatment and all clinical chemistry and hematological parameters examined were unaffected. In a repeat-dose toxicity study, Rhesus monkeys (6 per dose group) were administered 10, 30 or 100 mg/kg bertilimumab twice weekly by IV infusion for 28 days. There were no deaths or significant morbidity following treatment with bertilimumab. No effects on clinical chemistry, ophthalmoscopic or hematological parameters or body weight were observed. At sacrifice (end of study period), there were no treatment-related changes in organ weight or macroscopic/ microscopic observations.

For detailed information on pre-clinical studies, please refer to the Investigator's Brochure.

1.2.2 Clinical Studies

Three clinical studies of bertilimumab were conducted in Europe: a Phase 1 study in healthy volunteers (study CAT-213-0101), and Phase 2 studies in patients with allergic rhinitis and allergic conjunctivitis (studies CAT-213-0103 and CAT-213-0203, respectively). Ninety nine (99) individuals have received bertilimumab: 45 via the IV (45/99, 45%), eight (8) via the intranasal (8/99, 8%), and 46 via the topical ocular (46/99, 46%) routes of administration. Thirteen individuals received IV bertilimumab at doses ≥500 mg (maximum dose administered: 770 mg). In these studies, bertilimumab was well tolerated and no dose-related adverse events (AEs) were noted. To date, no clinical studies of bertilimumab have been conducted in patients with BP.

For additional information on these clinical studies, please refer to the Investigator's Brochure.

1.3 STUDY RATIONALE

Bertilimumab is the first monoclonal antibody to specifically neutralize human eotaxin-1. Bertilimumab has been shown to inhibit eotaxin-stimulated migration of cells and may therefore be useful in the treatment of human diseases such as 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. A positive proof of concept in this study would be supportive of further development via randomized control trial(s) to demonstrate that bertilimumab is an adequate candidate for maintenance therapy in newly diagnosed patients and patients resistant to corticosteroid tapering with moderate to extensive BP. Its efficacy in newly diagnosed patients would be proven by allowing reduced initial doses of corticosteroids and 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.

It has been demonstrated that relatively low doses of corticosteroids (e.g., 30 mg/day) are only partially effective in achieving disease control or complete remission. The rapid onset of steroid action is desired in order to alleviate patient symptoms as quickly as possible while the slower acting biologic takes effect. A key focus in this treatment is the goal is to taper the steroids as rapidly as possible, a difficult feat to achieve with steroids in isolation. Initial treatment with prednisone has therefore been added to bertilimumab treatment. This study is designed to demonstrate that the successful tapering of corticosteroids over a shorter period of time than physicians have been accustomed to will be possible with the administration of bertilimumab, thereby mitigating risks associated with long term steroid use.

1.3.1 Rationale for Dose Selection

Immune Pharmaceuticals has chosen to evaluate the 10 mg/kg IV dose of bertilimumab based on the following safety, pharmacokinetic and PD data:

- No safety concerns were identified in Study CAT-213-0101, in which subjects received a single IV bertilimumab dose of up to 10 mg/kg (corresponding to absolute doses of 570 to 770 mg in four patients), or in Study CAT-213-0103, in which patients received a single IV bertilimumab dose of up to 500 mg.
- The PD endpoint in Study CAT-213-0101, eotaxin-induced eosinophil shape change, was inhibited by serum in all subjects who received bertilimumab doses of 1 mg/kg and higher, with nearly 100% inhibition in the 5 mg/kg and 10 mg/kg dose groups. A shape change in eosinophils is considered a requisite process in chemotaxis, and can be taken as evidence of an impending migratory response. Maximum inhibition occurred at concentrations of ~40 µg/mL. At 35 days post-dose, high levels of inhibition were still observed despite low concentrations of bertilimumab, suggesting that the PD response was prolonged when compared with the bertilimumab plasma concentrations.
- In Study CAT-213-0101, after a single dose of 5 mg/kg, unbound bertilimumab had a mean half-life of 211 hours (CV% 30.5); the mean half-life after a single 10 mg/kg dose was 194 hours (CV% 27.1).
    - The data from this study also suggest dose proportionality in bertilimumab exposure between these two doses.
- No antibodies to bertilimumab were detected in any of the three previous single-dose clinical trials.

In the healthy volunteer and patient studies performed to date, bertilimumab doses up to 10 mg/kg have not been associated with any dose-related adverse effects.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

Primary Objective

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

Secondary Objectives

- To evaluate the preliminary evidence of clinical efficacy and PK and PD effect of bertilimumab in newly diagnosed and patients resistant to corticosteroid tapering with moderate to extensive BP

Exploratory Objective:

- To determine change from Visit 2 (Day 0) to Visit 5 of PBMC biomarkers

2.2 STUDY ENDPOINTS AND OUTCOMES

Primary Endpoints

- Safety Endpoints

  Safety will be evaluated on the basis of the following parameters:

  - Adverse events (AE)
  - Infusion reactions
  - Injection site reactions
  - Physical examination
  - Vital signs (blood pressure, heart rate, temperature)
  - ECG
  - Concomitant medications
  - Laboratory evaluation (hematology, biochemistry, anti-bertilimumab antibodies)

Secondary Endpoints

Efficacy Endpoints

- Proportion of patients who achieve a reduction in the Total Activity Score of the BPDAI score of at least **50%, 75% and 90%** at visits 5 (Day 42), 6 (Day 56), 7 (Day 70), or 8 (Day 84) compared to:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed.
- Proportion of patients who have tapered to prednisone dose of ≤10 mg/day at Visit 8 (Day 84) and/or 2 and 4 months after Visit 8 (Day 84)
- Proportion of patients who achieve control of disease activity at Visits 5 (Day 42), 6 (Day 56), 7 (Day 70), or 8 (Day 84)
  - 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. Control of disease activity will be assessed by the BPDAI and the investigator's assessment of lesion healing.
- Mean time to control of disease activity from:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed
- Change in BPDAI score at each scheduled measurement timepoint compared to:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed
- Change in BPDAI pruritis component (Visual Analogue Scale) at each scheduled measurement timepoint compared to:

- Screening, if patient is resistant to corticosteroid tapering
- Visit 2 (Day 0), if patient is newly diagnosed

- Change in ABQOL score at each scheduled measurement timepoint compared to:
  - Screening, if patient is resistant to corticosteroid tapering
  - Visit 2 (Day 0), if patient is newly diagnosed

Pharmacokinetic (PK) Endpoints

- PK analysis for bertilimumab concentration: blood samples will be collected three times on dosing days: pre-dose, at the completion of treatment infusion (approximately 30 minutes following the initiation) and at 2 hours following initiation of study drug infusion, and once at the remaining study visits (excluding screening). The PK parameters will be calculated, to the degree possible given the number of timepoints: C_{max}, T_{max}, C_{avg}, C_{min} and $t_{1/2}$. Additional standard and exploratory PK parameters will be calculated if deemed necessary.

Pharmacodynamic (PD) Endpoints

- Change in BP180 and BP230 autoantibody titers at each scheduled sampling timepoint compared to Visit 2 (Day 0)
- Change in blood eosinophil count at each scheduled sampling timepoint compared to Visit 2 (Day 0)
- Change in tissue eosinophil count assessed on biopsy at the scheduled timepoint (Visit 5) compared to screening
- Change in serum eotaxin-1 level at each scheduled timepoint compared to Visit 2 (Day 0)

Exploratory Endpoint

- Change in PBMC biomarkers at Visit 5 compared to Visit 2 (Day 0)

3.0 STUDY DESIGN

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.

Eligible patients are those who:

a. Ideally, have not been previously treated for BP. However, the following treatments are permitted for newly diagnosed patients:
   - Systemic oral corticosteroids ≤40.0 mg/day (prednisone equivalent) within 4 weeks prior to the first treatment administration (Visit 2 - Day 0)
   - Topical corticosteroids other than those that are Class 1 or Class 2 (See Appendix F) within 2 weeks prior to the first treatment administration (Visit 2 - Day 0).

b. Are considered by the investigator to be resistant to corticosteroid tapering, in which case other corticosteroid regimens are permitted. No washout period is required

c. Have been diagnosed by the following assessments:

- Clinical evaluation confirming BP
- Hematoxylin and eosin (H&E) staining of a skin punch biopsy from the edge of a lesion to check the eosinophil make-up (including eosinophil count) of the inflammatory infiltrate
- Serum testing for anti BP180 and anti BP230 autoantibodies
- Direct immunofluorescence (DIF) on salt split skin of a skin punch biopsy from a perilesional area to check the linear deposition of IgG and/or C3 on the blister roof (epidermal side)
- Indirect immunofluorescence (IIF) of the patient's serum to check for the presence of IgG circulating autoantibodies

Although all of these assessments must be performed, ultimate determination of a positive BP diagnosis based on the composite of these indicators is up to the investigator.

In newly diagnosed patients, if any of these assessments have been performed within 4 weeks prior to first treatment administration, the specific assessment will not have to be repeated. In patients resistant to corticosteroid tapering, if either DIF or IIF immunofluorescence assessments have been performed previously, the specific assessment will not have to be repeated.

Moderate to extensive bullous pemphigoid is defined by the mean number of bullae and/or urticarial plaques that have appeared on 3 separate occasions during screening as determined by the investigator, the referring physician or reported by the patient or caregiver. Moderate disease is defined by 2-10 bullae and/or ≥5 urticarial plaques. Extensive disease is defined by >10 bullae and/or urticarial plaques [3].

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 (or 90 days for males who have had abnormal semen analysis results for post-dose Visit 2 (Day 0), Visit 3 (Day 14) or Visit 4 (Day 28) compared to pre-dose Visit 2 (Day 0) results); plus a follow-up phone call 2 and 4 months following Visit 8 (Day 84)

Due to the potential effects of long-term and/or high-dose systemic corticosteroid usage on bullous pemphigoid, newly diagnosed patients will be permitted to take systemic oral corticosteroids specifically for bullous pemphigoid only for a period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0) at doses no greater than 40 mg/day prednisone equivalent.

Newly diagnosed patients who have taken systemic oral corticosteroid for bullous pemphigoid longer than 4 weeks prior to the first treatment administration (Visit 2 - Day 0) or at doses greater than 40 mg/day prednisone equivalent at any time are excluded from the study.

For newly diagnosed patients who have used systemic oral corticosteroids for reasons other than bullous pemphigoid, a washout period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0) is required.

For newly diagnosed patients who are taking systemic oral corticosteroids at a daily dose between 40 mg/day and 30 mg/day prednisone equivalent for BP within 4 weeks prior to the first treatment administration (Visit 2 - Day 0), tapering of systemic corticosteroids will be conducted at the discretion of the investigator. However, patients must be on 30 mg/day prednisone equivalent for the first treatment administration (Visit 2 - Day 0). For newly diagnosed patients who are taking less than 30 mg/day prednisone equivalent prior to the first administration day (Visit 2 - Day 0), a stable dose of systemic corticosteroids should be maintained until Visit 2 (Day 0).

Patients who are resistant to corticosteroid tapering are not required to be washed out from oral corticosteroid treatment prior to Visit 2 – Day 0.

The tapering schedule depicted in Table 1 is recommended for the remainder of the study.

Table 1: Recommended Corticosteroid Tapering Regimen

Systemic corticosteroid dose (prednisone equivalent) per day	Tapering schedule
≥30.0-10.1 mg/day	Decrease by 5 mg each week
10.0 – 0 mg/day	Decrease by 2.5 mg each week

Corticosteroid management can occur either during a scheduled visit, unscheduled visit, or phone-call follow-up based on the investigator's discretion.

4.0 STUDY POPULATION

The study will be conducted in patients aged ≥60 years diagnosed with moderate to extensive BP. Patients who meet all the inclusion criteria and none of the exclusion criteria will be enrolled.

4.1 INCLUSION CRITERIA

1. Males or females, ≥60 years of age
2. Patients with a Karnofsy Performance Status >40%
3. Eligible patients are defined as follows:
   a. Ideally, those who have not been previously treated for BP. However, the following treatments are permitted for newly diagnosed patients:
      - Systemic oral corticosteroids ≤40.0 mg/day (prednisone equivalent) within 4 weeks prior to the first treatment administration (Visit 2 - Day 0)
      - Topical corticosteroids other than those that are Class 1 or Class 2 (See Appendix F) within 2 weeks prior to the first treatment administration (Visit 2 - Day 0)

b. Those patients considered by the investigator to be resistant to corticosteroid tapering, in which case other corticosteroid regimens are permitted including oral and topical corticosteroids. No wash-out period is required.

c. Have been diagnosed by the following assessments.

- Clinical evaluation confirming BP
- Hematoxylin and eosin (H&E) staining of a skin punch biopsy from the edge of a lesion to check the eosinophil make-up (including eosinophil count) of the inflammatory infiltrate
- Serum testing for anti BP180 and anti BP230 autoantibodies
- Direct immunofluorescence (DIF) on salt split skin of a skin punch biopsy from a perilesional area to check the linear deposition of IgG and/or C3 on the blister roof (epidermal side)
- Indirect immunofluorescence (IIF) of the patient's serum to check for the presence of IgG circulating autoantibodies

Although all of these assessments must be performed, ultimate determination of a positive BP diagnosis based on the composite of these indicators is up to the investigator.

In newly diagnosed patients, if any of these assessments have been performed within 4 weeks prior to first treatment administration, the specific assessment will not have to be repeated. In patients resistant to corticosteroid tapering, if either DIF or IIF immunofluorescence assessments have been performed previously, the specific assessment will not have to be repeated. BP Disease Area Index (BPDAI) including Pruritus VAS and MD assessment of lesions and ABQOL should be performed prior to administration of corticosteroids if possible.

4. Patients who have moderate to extensive bullous pemphigoid is defined by the mean number of bullae and/or urticarial plaques that have appeared on 3 separate occasions during screening as determined by the investigator, the referring physician or reported by the patient or caregiver. Moderate disease is defined by 2-10 bullae and/or ≥5 urticarial plaques. Extensive disease is defined by >10 bullae and/or urticarial plaques [3].
5. Systemic corticosteroids for reasons other than bullous pemphigoid may be used with a washout period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0).
6. Adequate cardiac, renal and hepatic function as determined by the investigator and demonstrated by screening laboratory evaluations, vital sign measurement, ECG recording and physical examination results.
7. Females who, in the opinion of the investigator, are of childbearing potential, must have a negative serum pregnancy test at screening and agree to use effective contraception (hormonal contraception or two forms of barrier contraception) consistently throughout the study.
8. Males must have had a vasectomy or have expressed that they have no interest in fertility in the future.

9. Fertile males (males with no history of infertility or vasectomy) must agree to use effective contraception (e.g.,. condoms, spermicides) consistently throughout the study and for a period of four months following the end of treatment administration.
10. Patients must be willing and able to adhere to the study visit schedule and other protocol requirements.
11. Patients must be willing and able to provide voluntary written informed consent or written informed consent from a legally authorized representative with assent from the patient.

4.2 EXCLUSION CRITERIA

1. Patients with severe medical or surgical conditions at screening or Visit 2 (Day 0) including, but not limited to, severe dementia or mental impairment, severe stroke, severe cardiac insufficiency, severe arterial hypertension, severe or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric, or any other severe acute or chronic medical condition that, in the opinion of the investigator, may increase the risk associated with study participation/treatment or may interfere with the interpretation of study results and would make the patient inappropriate for study entry
2. Presence of any malignancy that has been under active treatment (e.g., radiotherapy or chemotherapy) within the 2 years prior to baseline or is anticipated to require treatment during the study period (including follow up) with the exception of patients with removal of uncomplicated basal cell carcinoma or cutaneous squamous cell carcinoma, who may take part in the study
3. Congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, organ transplantation)
4. Clinically significant vital sign measurements or ECG findings as determined by the investigator
5. Clinically significant abnormal laboratory test results at screening as defined by the investigator, including, but not limited to:
   - Hemoglobin level <10.0 g/dL
   - White blood cell count < 3 x 10^3/µL
   - Lymphocyte count < 0.5 x 10^3/µL
   - Platelet count <100 x 10^3/µL or >1200 x 10^3/µL
   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN)
   - Alkaline phosphatase >3 × ULN
   - Serum creatinine >2 × ULN
6. Concomitant skin conditions preventing physical evaluation of BP.
7. Active or recent history of clinically significant infection within 1 month of the first treatment administration (Visit 2 – Day 0).

8. Patients who are pregnant or breast-feeding, or planning to become pregnant during the study
9. Participation in a clinical trial of an investigational (unapproved) product within 4 weeks prior to the first treatment administration (Visit 2 – Day 0)
10. Patients who are known to have hypersensitivity to bertilimumab or any of the drug excipients
11. Use of any previous treatments for bullous pemphigoid *(other than the oral/topical corticosteroid regimens allowed as described above in inclusion criteria #3a, #3b, and other than those treatments described in exclusion criteria #13-15 below, for which the appropriate wash-out periods were applied).*
12. Treatment with systemic corticosteroids at any dose for reasons other than bullous pemphigoid within 4 weeks prior to the first treatment administration (Visit 2 - Day 0)
13. Treatment with immunosuppressants (e.g., azathioprine, methotrexate) within 4 weeks prior to the first treatment administration (Visit 2 - Day 0)
14. Treatment with biologics (e.g., etanercept, adalimumab, ustekinumab, infliximab, intravenous Ig) within 4 months prior to the first treatment administration (Visit 2 - Day 0). Patients who have received rituximab within 1 year prior to the first treatment administration (Visit 2 - Day 0) will be excluded from study participation
15. Treatment with a full course of macrolides or tetracyclines within 4 weeks prior to the first treatment administration (Visit 2 - Day 0)
16. Subjects who received a vaccine or other immunostimulator within 4 weeks prior to the first treatment administration (Visit 2 - Day 0)
17. Subjects who have clinical, radiographic, or laboratory evidence of active or latent mycobacterium tuberculosis (TB) infection
18. Evidence of an active disease of hepatitis B (HBsAg or HBcAb positive) or hepatitis C (HCV Ab positive), CMV (IgM positive) or human immunodeficiency virus (HIV) infection (HIV1/2 Ab positive)
19. Active abuse of alcohol or drugs
20. Any other condition, which, in the opinion of the investigator, would place the patient at an unacceptable risk if participating in the study protocol

4.3 PATIENT IDENTIFICATION

At screening, all patients who signed informed consent will be identified by a subject number, their initials and birth date.

4.4 SCREENING FAILURES

Patients who fail to meet the eligibility criteria at any stage prior to administration of the first dose of study drug (Visit 2 - Day 0) are defined as screen failures. All screen failures will be documented on the screening log, which documents the screening number, patient's initials, birth date, and reason(s) for screen failure. The screening log will be kept in the Investigator's Site File.

If subjects fail screening, they may be re-screened once at the discretion of the investigator. Subjects will get a new study identification number on re-screening. A lab result during the screening period may be repeated at the discretion of the investigator if deemed spurious without repeating the entire set of screening requirements. In this particular case, the subject will not get a new study identification number.

4.5 REMOVAL, REPLACEMENT, OR EARLY DISCONTINUATION OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients are free to discontinue their participation in the study at any time and without prejudice to further treatment. The investigator must withdraw any patient from the study if that patient requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the patient. Withdrawn patients will not be replaced once treatment has been administered.

The following are examples of reasons why a patient's participation in this study may be discontinued:

- Patient withdraws consent
- Intolerable adverse event
- The investigator decides that continuing in the study would not be in the patient's best interest
- The patient is noncompliant with the protocol
- The patient becomes pregnant
- Upon the decision of relevant Regulatory Authorities and/or the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

4.5.1 Handling of Early Discontinuation

If a patient is withdrawn from the study, either at his or her request or at the investigator's discretion, or fails to return, every effort should be made to determine the reason. This information will be recorded on the patient's case report form (CRF). All patients who withdraw from the study prematurely, regardless of cause, should undergo Early Discontinuation Study Visit (see Section 5.8). It is important to obtain follow-up data for any patient withdrawn due to an AE or abnormal laboratory test finding. In any case, every effort must be made to undertake safety follow-up procedures.

Premature withdrawal may occur for any of the following reasons:

- Death
- Pregnancy
- AE
- Patient request
- Investigator request
- Sponsor request

Any serious AE (SAE) must be entered into the CRF and reported to the Sponsor or Sponsor's designee by email and/or fax within 24 hours and to the IRB/IEC according to site's regulations (for SAE notification procedures, refer to Section 7.4).

In the event of any AEs considered clinically significant by the investigator, patients will be provided with appropriate medical management until the outcome is determined or stabilized, according to the investigator's clinical judgment. All follow-up information will be recorded in the patient's CRF until the close of the study. Subsequent follow-up will be documented in the patient's personal file.

Patients who fail to respond to study treatment or experience a flare will be able to receive local standard-of-care at the investigator's discretion.

4.5.2 Sponsor's Termination of Study

The Sponsor reserves the right to discontinue the study at any time at the participating centers for any reason.

Regulatory Authorities also have the right to terminate the study for any reason.

5.0 STUDY PROCEDURES AND ASSESSMENTS

The schedule of events for this study is shown in Appendix A. No protocol related procedures, including cessation of prohibited concomitant medications, should be performed before patients provide written informed consent. Study related events and activities including specific instructions, procedures, concomitant medications, dispensing of study medication, and descriptions of AEs should be recorded in the appropriate source documents and CRF.

5.1 SCREENING PERIOD (VISIT 1, DAY -28 TO DAY -1)

All patients or their legally authorized representative must sign and date the most current IRB/IEC-approved written informed consent before any study specific assessments or procedures are performed. An original signed consent form will be retained by the investigator and the patient will receive a copy to take home.

Patients will be screened according to the assessments and procedures in the Schedule of Events in Appendix A. These must be completed and evaluated for patient eligibility prior to treatment administration. The screening visit may be conducted over multiple days. Patients who meet all the inclusion criteria and none of the exclusion criteria will be enrolled in the study.

5.2 PROCEDURES FOR ENROLLMENT OF ELIGIBLE PATIENTS

Only patients who fulfill all entry criteria are eligible for enrollment into the study. Once the screening process is complete, the site should complete the Eligibility form in the CRF for review by the Medical Monitor. Once the Medical Monitor confirms eligibility in the CRF, shipment of IP will be triggered.

5.3 SAFETY ASSESSMENTS

Safety assessments will be based on AEs, prior and concomitant medication use, vital signs, ECG, physical examination, and laboratory assessments (hematology, blood chemistry, and anti-

bertilimumab antibodies, etc.). Measurements of all safety parameters should be performed as described in the Schedule of Events (Appendix A) and the following sections.

5.3.1 Adverse Events (AEs)

Adverse events will be assessed by the investigator throughout the study. Any AE that occurs after the informed consent is signed by the patient will be recorded in the patients' medical files as well as on the appropriate CRF page. (See Section 5.3.4).

AEs should be checked at each visit and recorded. Patients should be instructed to report any new AE that occurs between scheduled visits.

AEs will be coded by Data Management using Medical Dictionary for Regulatory Activities (MedDRA®) version 17.0 or higher.

5.3.2 Prior and Concomitant Medications

Recording of concomitant medication use will be conducted at all study visits. All treatments used by patients within 90 days prior to screening should be recorded. Any dose modification of concomitant medications should be checked at each visit and recorded. There will be a separate CRF page specifically for the entry of oral corticosteroid therapy for bullous pemphigoid.

5.3.3 Vital Signs

Vital signs will be measured at all visits except for Visit 9 (Day 118) as indicated in the Schedule of Events (Appendix A). At treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), vital signs will be taken pre-dose (any time prior to the initiation of treatment infusion), at the completion of treatment infusion (approximately 30 minutes following the initiation of treatment infusion), and approximately 2 hours following the initiation of treatment infusion. All vital signs are to be obtained prior to any biopsies, treatment infusion, or laboratory/PK sampling collection if these procedures are scheduled at the same visit.

Vital signs will include blood pressure, pulse rate and oral temperature after at least 5 minutes of rest. Significant findings which meet the definition of an AE must be recorded on the AE CRF module.

5.3.4 ECG

ECG will be performed at Screening and Visit 8 (Day 84) as indicated in Appendix A. ECGs should be obtained prior to any biopsies or laboratory/PK sampling collection if these procedures are scheduled at the same visit.

The patient should rest for at least 10 minutes before measurement is taken. The ECG will be evaluated by the investigator (signed and dated) and the printout should be kept in the source documentation file.

When potentially clinically significant findings are detected by the site investigator, a cardiologist should be consulted for a definitive interpretation and treatment, if necessary. The investigator and local cardiologist are responsible to determine whether the ECG findings are of clinical significance. Significant findings made after the informed consent is signed which meet the definition of an AE must be recorded on the AE CRF. All abnormalities will be closely monitored until stabilized or resolved.

5.3.5 Physical Examination

Physical examination will be performed at all study visits except for Visit 9 (Day 118) as indicated in the Schedule of Events (Appendix A). On treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), a physical examination will be performed prior to the initiation of the treatment infusion. Height will be recorded at Visit 1 (screening) only.

Physical examination will include weight and height (at screening only) measurements, assessment of head, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system and, where appropriate, other body systems as indicated in the study schedule.

Information about the physical examination must be recorded in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant findings made after the start of study drug, which meet the definition of an AE, must be recorded on the AE CRF.

5.3.6 Infusion Reactions

Infusion reactions should be assessed on treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28) as indicated in the Schedule of Events (Appendix A). At these visits, evidence for infusion reactions will be evaluated at the completion of treatment infusion (approximately 30 minutes following the initiation of treatment infusion) and at 2 hours following the initiation of treatment infusion.

5.3.7 Safety Laboratory Assessments

Safety laboratory assessments will be performed according to the Schedule of Events (Appendix A).

Hematology and Biochemistry will be performed at all visits with the exception of Visits 6 (Day 56), 7 (Day 70), and 9 (Day 118) as indicated in the Schedule of Events (Appendix A). At treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), these samples will be taken pre-dose (any time prior to the initiation of treatment infusion). For screening, hematology and chemistry will be evaluated locally and at a central laboratory for all other visits.

Serology will be evaluated locally only at Screening.

Pregnancy will be evaluated locally by serum at Screening and locally by urine testing at all other visits with the exception of Visits 6 (Day 56) and 7 (Day 70).

Anti-bertilimumab antibodies will be evaluated at all visits with the exception of screening and Visit 9 (Day 118). At treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), anti-bertilumamb samples will be collected pre-dose (any time prior to the initiation of treatment infusion). Anti-bertilumamb antibodies will be evaluated centrally.

The following parameters will be tested for each assessment:

Evaluations	Parameters
Hematology	Hematocrit, hemoglobin, platelet count, red blood cell count, reticulocytes, white blood cell count with differential count, monocytes
Biochemistry	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, calcium, cholesterol, creatinine, gamma-glutamyl transferase, glucose, potassium, sodium, total bilirubin, triglycerides, urea or BUN
Immunology	Anti-bertilimumab antibodies
Pregnancy test	Serum β-hCG Urine β-hCG
Serology	For HBV (HBsAg or HBcAb), HCV (HCV Ab), HIV (HIV1/2 Ab), CMV (IgM)

All laboratory tests with abnormal values which are considered clinically significant and are detected after the informed consent is signed will be repeated as clinically indicated until the values return to normal, or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered clinically important by the investigator will be reported as an AE in the AE CRF.

Laboratory results will be reported to the investigator who will review abnormal laboratory findings for clinical significance. The investigator will note any laboratory test results of clinical concern, or values that are outside normal ranges and provide details of the relationship to investigational product and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE CRF page. If no correlation is determined, the direction of change (increase or decrease) in addition to the actual value will be recorded.

Refer to the Laboratory Manual for more details.

5.3.7.1 Semen analysis testing

Semen testing will be performed at Visits 2 (Day 0), 3 (Day 14), 4 (Day 28). Visit 9 (Day 118) will only be required if any results from the previous visits are abnormal compared to pre-dose Visit 2 (Day 0). At treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), semen testing will be performed pre-dose (any time within 48 hours prior to the initiation of treatment infusion), and at the completion of treatment infusion (approximately 30 minutes following the initiation) or as close to this time as possible.

Semen analysis will be performed on all male patients participating in this study with the exception of the following:

- Infertile males
- Patients with religious constraints that prevent them from providing semen samples

5.3.7.2 Tuberculosis Evaluation

An evaluation for active/latent tuberculosis will be performed at Screening as indicated in the Schedule of Events (Appendix A). The evaluation will be performed locally either clinically, radiographically, or by laboratory (i.e., PPD, X-ray, or Quantiferon Gold). Quantiferon Gold testing will also be available centrally as an option, where applicable.

5.4 EFFICACY ASSESSMENTS

5.4.1 Bullous Pemphigoid Disease Area Index (BPDAI)

The BPDAI (See Appendix D) will be completed at all visits with the exception of Visit 9 (Day 118) as indicated in the Schedule of Events (Appendix A). At treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), the BPDAI should be completed pre-dose (any time prior the initiation of treatment infusion). In screening, the BPDAI should be performed, if possible, prior to commencement of corticosteroid regimen.

The BPDAI Pruritus Component Visual Analogue Scale (VAS) will be completed by the patient or their legally authorized representative and all other sections for the BPDAI will be completed by the investigator. Patients and investigators will be asked to complete their respective sections on the corresponding worksheets, which will serve as source documentation for this measurement. The study source documents should reflect any issues that may have occurred during completion.

5.4.2 Assessment of Lesion Healing

The assessment of lesion healing will be completed at all visits with the exception of Visit 9 (Day 118) as indicated in the Schedule of Events (Appendix A). As part of the assessment for control of disease activity, one of the efficacy endpoints, investigators will be asked to document whether established lesions have started to heal.

5.4.3 Autoimmune Bullous Disease Quality of Life (ABQOL)

The ABQOL (See Appendix E) will be completed at all visits with the exception of Visit 9 (Day118) as indicated in the Schedule of Events (Appendix A). At treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), the ABQOL should be completed pre-dose (any time prior the initiation of treatment infusion). In screening, the ABQOL should be completed, if possible, prior to commencement of corticosteroid regimen.

Patients or their legally authorized representative will be asked to complete the ABQOL on the worksheets, which will serve as source documentation for this measurement. The study source documents should reflect any issues that may have occurred during completion.

5.4.4 Photography

Photographs will be taken at all visits with the exception of Visit 9 (Day 118) as indicated in the Schedule of Events (Appendix A). At treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), the photographs should be completed pre-dose (any time prior to the initiation of treatment infusion). In screening, the photography should be conducted, if possible, prior to commencement of corticosteroid regimen.

Refer to the Photography User Manual for more details.

5.5 PHARMACOKINETIC (PK) ASSESSMENTS

PK will be measured at all visits with the exception of Screening and Visit 9 (Day 118) as indicated in the Schedule of Events (Appendix A). At treatment administration Visits 2 (Day 0), 3 (Day 14), and 4 (Day 28), PK samples will be collected pre-dose (within 30 minutes prior to the initiation of treatment infusion), at the completion of treatment infusion (approximately 30 minutes following

the initiation of treatment infusion), and 2 hours following the initiation of treatment infusion. All PK samples should be collected after vital signs, physical examination, and ECG if these procedures are scheduled at the same visit.

PK outcome refers to study drug (bertilimumab) concentration in the serum. PK parameters may include:

C_{max}	Maximum bertilimumab serum concentration
T_{max}	Time to C_{max} (peak exposure)
C_{avg}	Average bertilimumab serum concentration
C_{min}	Minimum bertilimumab serum concentration
λ_z	Elimination rate constant
$t_{1/2}$	Elimination half-life, calculated as $0.693/\lambda_z$

Additional PK parameters may be calculated if deemed necessary.

Refer to the Laboratory Manual for more details.

5.6 PHARMACODYNAMIC (PD) ASSESSMENTS

5.6.1 Eosinophil Count in Biopsy Tissue

Eosinophil count in the skin biopsy tissue will be evaluated at Screening and Visit 5 (Day 42) as indicated in the Schedule of Events (Appendix A). This assessment will be evaluated centrally, where feasible.

This biopsy should be collected using a 4-6 mm punch at the edge of a lesion or blister and should include some adjacent unaffected skin, as the sample must contain intact epithelium. At Screening and at Visit 5 (Day 42), the same biopsy sample will be used to determine eosinophil count and the eosinophil make up of the inflammatory infiltrate with hematoxylin and eosin staining. The Visit 5 (Day 42) biopsy should be taken from approximately the same location as the one from Screening.

Refer to the Laboratory Manual for more details.

5.6.2 Eosinophil count in Blood

Eosinophil count in the blood will be evaluated as part of the hematology assessment at all visits with the exception of Visits 6 (Day 56), 7 (Day 70), and 9 (Day 118) as indicated in the Schedule of Events (Appendix A). This assessment will be evaluated centrally.

5.6.3 BP180 and BP230 Autoantibodies

BP180 and BP230 autoantibodies will be evaluated at all visits with the exception of Visit 9 (Day 118) as indicated in the Schedule of Events (Appendix A). This assessment will be evaluated centrally, where feasible.

Refer to the Laboratory Manual for more details.

5.6.4 Serum Level of Eotaxin-1

Serum levels of eotaxin-1 will be evaluated at all visits except Screening and Visit 9 (Day 118) as indicated in the Schedule of Events (Appendix A). This assessment will be evaluated centrally.

Refer to the Laboratory Manual for more details.

5.7 OTHER ASSESSMENTS

5.7.1 Bullous Pemphigoid Diagnosis

In order to diagnose patients with bullous pemphigoid for this study, the following assessments will be performed at Screening. However, if any of these assessments have been performed within 4 weeks prior to screening, the assessment will not have to be repeated. With the exception of the clinical evaluation, all of these assessments, if performed during screening, will be evaluated at the central clinical laboratory, where feasible. Though all assessments have to be performed, ultimate determination of a positive diagnosis is up to the investigator.

5.7.1.1 Clinical Evaluation

Clinical evaluation of the patient for diagnosing bullous pemphigoid will be performed at Screening.

5.7.1.2 Hematoxylin and Eosin (H&E) Staining

H&E of the skin biopsy tissue will be evaluated at Screening and Visit 5 as indicated in the Schedule of Events (Appendix A).

H&E will be performed in order to determine the eosinophil make up of the inflammatory infiltrate.

This biopsy should be taken using a 4-6 mm punch at the edge of a lesion or blister and should include some adjacent unaffected skin as the sample must contain intact epithelium. At Screening and Visit 5 the same biopsy sample will be used to determine eosinophil count and the eosinophil make-up of the inflammatory infiltrate with hematoxylin and eosin staining.

See the Laboratory Manual for more details.

5.7.1.3 Direct Immunofluorescence (DIF) and Salt Split Skin

DIF on salt split skin of skin biopsy tissue will be evaluated at Screening as indicated in the Schedule of Events (Appendix A).

DIF on salt split skin will be performed to check the linear deposition of IgG and/or C3 on the blister roof (epidermal side) as part of the diagnosis for bullous pemphigoid.

The biopsy should be taken using a 4-6mm punch of erythematous perilesional skin, approximately 0.5 to 1 cm away from a fresh blister. Avoid erosions, ulcers, and bullae while obtaining tissue adjacent to active lesions.

See the Laboratory Manual for more details.

5.7.1.4 BP180 and BP230 Autoantibodies

BP180 and BP230 autoantibodies will be evaluated at Screening as indicated in the Schedule of Events (Appendix A).

Patients will be tested for the presence of BP180 and BP230 autoantibodies. At Screening, the same sample will be used to test for BP180 and BP230 autoantibodies and IgG circulating autoantibodies with IIF.

See the Laboratory Manual for more details.

5.7.1.5 Indirect Immunofluorescence (IIF)

IIF of the patient's serum will be evaluated at Screening as indicated in the Schedule of Events (Appendix A).

IIF of the patient's serum will be performed to check for the presence of IgG circulating autoantibodies. At Screening, the same sample will be used to test for BP180 and BP230 autoantibodies and the IIF.

See the Laboratory Manual for more details.

5.7.2 Assessment of BP Severity

Moderate to extensive BP will be defined by the number of bullae and/or urticarial plaques that have appeared on 3 occasions during the screening period. The number of bullae and/or urticarial plaques can be monitored at the clinical site and recorded by the investigator or it can be reported by the patient or caregiver. The number of bullae and/or urticarial plaques should be documented on the Assessment of BP Severity form (see Appendix B). The assessment should be performed at approximately the same time each day.

5.7.3 Karnofsky Performance Status Scale

The Karnofsky Performance Status Scale, an assessment tool for functional impairment (Appendix C), will be evaluated at Screening as indicated in the Schedule of Events (Appendix A).

5.7.4 Biomarkers

Biomarker sample collection will be performed at Visit 2 (Day 0) and Visit 5 (Day 42) as indicated in the Schedule of Events (Appendix A). At Visit 2 (Day 0), biomarkers will be collected pre-dose (any time prior to the initiation of treatment infusion).

5.8 EARLY DISCONTINUATION STUDY VISIT

An early discontinuation study visit will be performed for patients who withdraw from the study for the reasons specified in Section 4.5.1.

All reasons for treatment discontinuation will be documented in the source documents as well as the CRF. Only one reason (the most severe) for early discontinuation should be recorded in the CRF. If one of the reasons for discontinuation is an AE – this should be chosen as the reason. Every effort should be made to follow-up these patients for resolution of the AE.

The required assessments that are to be performed during an early discontinuation visit are indicated in the Schedule of Events (Appendix A), but assessments may be added at the discretion of the investigator.

5.9 UNSCHEDULED VISIT

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording should be performed. Appropriate procedures and evaluations will be completed as deemed necessary by the investigator and may include (but are not limited to) laboratory tests, vital signs and physical examination.

Corticosteroid use may be managed at a scheduled visit, unscheduled visit, or phone call follow-up based on investigator discretion.

5.10 PHONE CALL FOLLOW-UP

Systemic corticosteroid usage may be managed at a scheduled visit, unscheduled visit, or phone call follow-up per the discretion of the investigator. If a phone call follow-up for corticosteroid use management is performed, other concomitant treatment and AE data should also be collected.

5.11 POST TREATMENT PHONE CALL

Approximately 2 and 4 months after Visit 8 (Day 84), a follow-up phone call will be placed and the following assessments will be performed: completion of ABQOL questionnaire, adverse event assessment, and concomitant medication reporting. Corticosteroid usage (oral and topical) will be documented and managed as necessary.

6.0 INVESTIGATIONAL PRODUCT

6.1 IDENTITY OF INVESTIGATIONAL PRODUCT

Bertilimumab is a recombinant human IgG_4 monoclonal antibody that neutralizes human eotaxin-1 (eotaxin); the drug product consists of bertilimumab formulated in phosphate buffered saline (PBS) at pH 7.2 and at a concentration of 10 mg/mL, presented as a sterile, clear, colorless solution in 10 mL clear glass vials.

The formula for the PBS is sodium chloride 77 mM, monosodium phosphate 17 mM and disodium phosphate 50 mM.

6.2 STUDY DRUG ADMINISTRATION AND DOSAGE

Bertilimumab 10 mg/kg will be administered by IV over 30 minutes of infusion time. The weight used for dose calculation at all dosing days is the weight measured at screening.

6.3 MANUFACTURING OF STUDY MEDICATION

Patheon UK and Nova Laboratories Ltd, cGMP vendors, will perform the drug product manufacturing and release.

6.4 PACKAGING AND LABELLING OF STUDY MEDICATION

Bertilimumab vials will be packaged and labeled in compliance with GCP and local health authority guidelines.

Site designee(s) will be responsible for handling and preparation of the study test medication.

Refer to the IP Manual for more details.

6.5 DISTRIBUTION AND SHIPMENT OF STUDY MEDICATION

The patients' investigational drug supplies will be packed and shipped in appropriate boxes. If, upon arrival at the clinical investigation site, study drug supplies appear to be damaged, the study monitor should be contacted immediately.

Each shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment, acknowledgement of receipt and other appropriate documentation. The shipment form will assist in maintaining current and accurate inventory records. The study staff will confirm the receipt of clinical supply to the study monitor.

6.6 STORAGE AND INSTRUCTIONS FOR PREPARATION AND INFUSION OF THE INVESTIGATIONAL PRODUCT

The study medication will be stored at each site under refrigeration at 2-8°C.

Records should be kept by the designee(s) as to how much study drug was used by each patient. The study monitors must periodically check the study drug supplied to ensure expiry date and sufficient amount of study drug, ensure that drug accountability is being performed at each visit and that drug accountability logs are maintained.

All investigational products must be kept in a locked area with access to the study drug limited to designated study personnel.

Preparation of the study drug dose for administration must be carried out by a trained medical professional at the study center using aseptic technique according to the Pharmacy Manual. The number of vials used as well as the study drug volume dispensed per dose will be recorded in the study logbook. Instructions for preparation and administration of study drug are detailed in the IP Manual.

Only trained personnel are authorized to prepare and administer study drug to participating patients.

6.7 ACCOUNTABILITY AND COMPLIANCE OF INVESTIGATIONAL PRODUCT

Each delivery must be acknowledged by the study team member responsible for the investigational medicinal product by filling in the receipt record form and returned according to the instructions included in the IP shipment. Accurate, complete, and timely documentation for all distribution to the study staff and patients will be maintained by the site designee(s), which may include confirmation of receipts of clinical supply, drug accountability logs and other forms.

The site designee(s) is responsible for ensuring the supervision of the storage and allocation of these supplies, which will be forwarded to the investigator or designee at the appropriate time

before administration. Investigational drug will be administered only to patients who meet the eligibility criteria of the study.

Drug accountability records must be maintained by the clinical investigation site at all times. All used and unused investigational drug will be collected and drug accountability performed by the site designee(s). The study monitor will check these regularly during monitoring visits.

Unused drug supplies will be returned to the Sponsor, unless instructed otherwise. At the end of the study, all the clinical supply and the corresponding accountability forms must be returned to the Sponsor, the study monitor or designee for reconciliation and destruction. A photocopy of these records must be kept at the clinical investigation site.

The inventory will be made available to the study monitor who will verify accountability and verify dose during the course of the study.

Study drug orders, records of study drug receipts, dispensing records, and inventory forms located at the site will be examined and reconciled by the study monitor periodically during and at the end of the study.

6.8 CONCOMITANT THERAPY

At the screening visit, relevant treatments currently received by the patient will be recorded in the patient's file and on the patient's CRF including treatment name, indication, dose, total daily dose, and start and stop dates.

Any medications (including prescription, over-the-counter, herbal supplements, and other health store-type products) to be taken during the study must be recorded in the CRF. All concomitant medications used to treat AEs will also be recorded.

6.8.1 Concomitant Corticosteroid Therapy

- Newly diagnosed patients:

  Due to the potential effects of long-term and/or high-dose systemic corticosteroid usage on bullous pemphigoid, patients will be permitted to take systemic oral corticosteroids specifically for bullous pemphigoid only for a period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0) at doses no greater than 40 mg/day prednisone equivalent.

  Patients who have taken systemic oral corticosteroid for bullous pemphigoid longer than 4 weeks prior to the first treatment administration (Visit 2 - Day 0) or at doses greater than 40 mg/day prednisone equivalent at any time are excluded from the study.

  For patients who have used systemic corticosteroids for reasons other than bullous pemphigoid, a washout period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0) is required.

  For patients who are taking systemic oral corticosteroids at a daily dose between 40 mg/day and 30 mg/day prednisone equivalent for BP within 4 weeks prior to the first treatment administration (Visit 2 - Day 0), tapering of systemic corticosteroids is to be conducted at the discretion of the investigator. However, patients must be on 30 mg/day prednisone equivalent for the first treatment administration (Visit 2 - Day 0). For patients who are taking less than 30 mg/day prednisone equivalent prior to the first administration day (Visit 2 - Day 0), a stable dose of systemic corticosteroids should be maintained until Visit 2 (Day 0).

- Patients resistant to corticosteroid tapering:

No wash-out period is required.

The tapering schedule depicted in Table 1 is recommended for the remainder of the study.

Table 1: Recommended Corticosteroid Tapering Regimen

Systemic corticosteroid dose (prednisone equivalent) per day	Tapering schedule
≥30.0-10.1 mg/day	Decrease by 5 mg each week
10.0 – 0 mg/day	Decrease by 2.5 mg each week

Corticosteroid management can occur either during a scheduled visit, unscheduled visit, or phone-call follow-up per the investigator's discretion.

Table 2: Corticosteroid Comparison Chart

	Approximate Equivalent Dose, mg	Relative Potency
Cortisol	20	1.0
Cortisone	25	0.8
Prednisone	5	4.0
Prednisolone	5	4.0
Triamcinolone	4	5.0
Dexamethasone	0.75	30-150

Reference: Welsh GA, Manzullo EF and Nieman LK The surgical patient taking glucocorticoids. 2007 UpToDate® www.uptodate.com.

On completion of the study, patients will be treated according to local practice and at the investigator's discretion.

Other corticosteroid regimens other than those listed in Table 2 are permitted only if the patient is considered, in the opinion of the investigator, unable to taper down corticosteroid treatment. No wash-out period is required.

6.8.2 Rescue Therapy

If necessary, rescue therapy is permitted at any point during the study at the discretion of the investigator. The patient can continue in the study as long as the rescue therapy is clearly documented.

6.8.3 Prohibited Prior and Concomitant Medication

Medications having the potential to interfere with the study assessments are excluded throughout the trial and include:

- Systemic corticosteroids administered for reasons other than bullous pemphigoid without a washout period of 4 weeks prior to the first treatment administration (Visit 2 - Day 0) or at any time during the study for newly diagnosed patients.
- Systemic corticosteroids taken specifically for bullous pemphigoid at any dose (greater than 40 mg/day prednisone equivalent) within 4 weeks prior to the first treatment administration day (Visit 2 - Day 0) or greater than 40 mg/day prednisone equivalent at any time prior to the first treatment administration day or at any time during the study for newly diagnosed patients
- Treatment with class 1 and 2 topical steroids within 2 weeks prior to the first treatment administration day (Visit 2 – Day 0) or at any time during the study for newly diagnosed patients
- Immunosuppressive drugs (e.g., methotrexate, azathioprine, mycophenolate mofetil, dapsone) within 4 weeks prior to the first treatment administration day (Visit 2 – Day 0) or at any time during the study
- Biological therapies (e.g., intravenous Ig, etanercept, adalimumab, ustekinumab, infliximab) within 4 months and rituximab within 1 year prior to the first treatment administration day (Visit 2 – Day 0) or at any time during the study
- Treatment with a full course of macrolides or tetracyclines within 4 weeks prior to the first treatment administration day (Visit 2 – Day 0) or at any time during the study
- Use of vaccines or other immunostimulator within 4 weeks prior to the first treatment administration day (Visit 2 – Day 0) or at any time during the study

In the interests of patient safety and acceptable standards of medical care, the investigator may prescribe additional treatment(s) at his/her discretion, which will be recorded on the patient's CRF.

7.0 SAFETY AND PHARMACOVIGILANCE

7.1 ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subjectand which does not necessarily have to have a causal relationship with this treatment. This includes any subjective signs, symptoms or diagnosis, clinically significant deviation from baseline screening laboratory values or vital signs, or worsening (more severe, more frequent or increased in duration during the investigational product treatment) of the concomitant disease present at Visit 2 (Day 0) visit (after initiation of investigational product treatment). Stable chronic conditions that are present prior to study entry and do not worsen during the study will not be considered AEs. Disease-related adverse events will not be considered AEs unless they worsen beyond what would be expected in the normal progression of the disease. In all cases, the etiology should, as much as possible, be identified and the Sponsor notified.

An abnormal result of diagnostic procedures including abnormal laboratory or vital sign findings will be considered an AE if it:

- Results in patient's withdrawal by the investigator
- Is associated with clinical signs or symptoms

- Is considered by the physician to be of clinical significance.

Adverse events reported by the patient or observed by the investigator will be individually listed on an AE form in the CRF as follows: the specific event or condition, whether the event was present pre-study, the dates and times of occurrence, duration, severity, likelihood of relationship to study medication, specific countermeasures, and outcome.

The intensity or severity of the AE will be characterized as:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible

The Investigator will document his/her opinion regarding the relationship of the AE to the investigational product (study medication) using the following criteria:

Category	Definition
Unrelated	Clearly due only to extraneous causes, and does not meet criteria listed under possible or probable.
Unlikely	Does not follow a reasonable temporal sequence from administration. May have been produced by the patient's clinical state or by environmental factors or other therapies administered.
Possible	Follows a reasonable temporal sequence from administration, but may have been also produced by the patient's clinical state, environmental factors or other therapies administered.
Probable	Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.

7.2 SERIOUS ADVERSE EVENT

A **serious** adverse event (SAE) is any adverse event occurring after signing informed consent at any dose that suggests a significant hazard or side effect, regardless of the investigator or sponsor's opinion on the relationship to the investigational product and that results in, but may not be limited to, any of the following outcomes:

- Death (regardless of the cause)
- Life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect.

Important medical events that may not be fatal, life threatening, or require hospitalization may be **serious** when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and hospitalizations for treatment of non-adverse events (e.g., cosmetic surgery) are not considered serious adverse events. Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital) are not considered as serious adverse events.

The underlying medical condition for any surgery performed should be reported as the event term rather than the procedure itself.

Significant medical events are those which may not be immediately life threatening, but may jeopardize the patient and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an adverse event which would normally be considered serious by this criterion.

Inpatient hospitalization or prolongation of existing hospitalization refers to hospital inpatient admission and/or prolongation of hospital stay required for treatment of AE, or which occurred as a consequence of the event. Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and hospitalizations for treatment of non-adverse events (e.g., cosmetic surgery or diagnostic procedure) are not considered serious adverse events.

Any new SAE that occurs up to 30 days after the study period and is considered related (possibly/probably) to the investigational product or study participation should be recorded and reported immediately.

A **life-threatening** adverse drug experience is any adverse event that places the patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Every attempt should be made to describe the AE/SAE in terms of a diagnosis. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE/SAE on the eCRF. Once a clear diagnosis has been made, individual signs and symptoms shall not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

7.3 DEFINITION OF AN UNEXPECTED ADVERSE EVENT

An **unexpected** adverse drug experience (event) is any adverse event of specificity or severity not reported in the current Investigator's Brochure.

7.4 NOTIFICATION ABOUT SERIOUS OR UNEXPECTED ADVERSE EVENTS

All SAEs must be reported **immediately** to the Immune Pharmaceuticals representative as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

Immune Pharmaceuticals Representative:

[redacted]
Telephone: [redacted] **ext** [redacted]
Mobile: [redacted]
Fax: [redacted]
E-mail: [redacted]

These preliminary reports will be followed within 24 hours by detailed descriptions that will include a completed SAE form, copies of hospital case reports, autopsy reports, and other documents, when requested and applicable.

In addition, all AEs/SAEs/Suspected Unexpected Serious Adverse Reaction (SUSARs) will be reported to the local EC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

Preliminary Reports must include:

- An identifiable patient (e.g., subject number)
- An identifiable reporting source
- All related adverse events
- The suspect medicinal product
- Follow-up of SAEs/SUSARs

Follow-up of SAEs/ SUSARs that occur during the study will continue until satisfactory resolution or stabilization.

If and when supplementary information is available, a follow-up SAE Report Form must be completed by the site and faxed within 24 hours to Sponsor.

The contact information for follow up SAE reporting is the same as for initial SAE reports (see Section 7.4).

Once faxed, the SAE form and accompanying documentation should be placed in the SAE section of the investigator's file. If supplementary information on a SAE has to be sent, the SAE form has to be used marked as "Follow-Up Report."

SAEs may be reported through an EDC system with a paper form used as back up.

Follow-Up Reports on non-serious AE

All AEs must be followed until resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" by the investigator and sponsor's decision.

8.0 STATISTICAL ANALYSIS

This is an open-label study. Thus, only descriptive statistics are planned. All data collected on the case report forms (CRFs) will be summarized for the clinical study report (CSR).

All continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile).

Summary statistics for categorical variables will include frequency counts and percentages. Summaries will be presented for all patients and by Treatment Phase and Follow-up Evaluation.

Details will be specified in the statistical analysis plan.

9.0 ETHICS

9.1 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

Prior to initiation of the study, the investigator will submit the study protocol and amendments, sample Informed Consent Form (ICF), and any other documents that may be requested to the IRB/IEC for review and approval. The investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. The investigator will not begin the study until the protocol and ICF have been approved by the IRB/IEC. The investigator must agree to make any required progress reports to the IRB, as well as reports of SAEs, life-threatening conditions, or death.

9.2 ETHICAL CONDUCT OF THE STUDY

All clinical work conducted under this protocol is subject to GCP guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996)
- Declaration of Helsinki: Brazil, 2013
- Israeli MOH guidelines (February 2016)
- Guidelines from the country-specific National Competent Authority as appropriate

9.3 PROTOCOL REVISIONS AND/OR DEVIATIONS

Changes to the protocol may be made only by the Sponsor. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements and, if required, to Regulatory Agencies, either as an amendment or a notification. Approval for amendments must be granted before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial study patients, or when the changes involve only logistical or administrative aspects of the trial. No approval will be required for notifications.

9.4 STUDY PATIENT INFORMATION AND CONSENT

Prior to study screening, each study patient will be informed in detail about the study drug to be administered and the nature of the clinical investigation with its expected risks and discomforts. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. Written consent will be obtained from each study patient or their legally authorized representative to be involved in the clinical trial by using the IRB/IEC-approved ICF prior to the conduct of any study-related activity. Each study patient will be given a copy of the

written ICF. The study patients will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Each study patient's chart will include the signed ICF for study participation. When the study treatment is completed and the CRF has been monitored, the ICF will be kept in the investigator's central study file for the required period. Regulatory authorities may check the existence of the signed ICF in this central study folder if not confirmed during the study.

9.5 STUDY PATIENT INSURANCE

The Sponsor has an insurance policy for the total duration of the study covering the patients and investigators in respect of the risks involved in conducting this study according to this protocol. The certificate of insurance will be filed in the investigator's file or can be made available to the investigator and to the IRB/IEC upon request.

9.6 PERSONAL DATA PROTECTION

The Sponsor complies with the principle of study patient's right to protection against invasion of privacy. Throughout this trial, all data will be identified only by a subject number and study patient initials. The identifying patient data will be blinded in all data analyses. However, the patient must be informed and consent is required that authorized personnel of the Sponsor and/or designee (Study Monitor, Auditor, etc.) and relevant health regulatory agency will have direct access to personal medical data to assure a high quality standard of the study.

10.0 DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

10.1 AUDITS AND INSPECTIONS

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its designees or to regulatory authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

10.2 STUDY MONITORING

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO or a contract monitor. The study monitor will advise the investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements. Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the investigator. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the investigator's study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate period. The investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection and respond to inquiries.

10.2.1 Source Data and Records

Source data/records contain all the information which is necessary for the reconstruction and evaluation of the study. Source data/records are 1) original records, 2) certified copies of original records, 3) observations, 4) laboratory reports, 5) paper Case Report Forms (CRFs) and/or data sheets. Source data/records are to be kept within the control of the investigator until the end of the contractual retention period. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

10.3 QUALITY LABORATORY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the local institution laboratory and central laboratories.

10.4 DATA COLLECTION AND MANAGEMENT

All aspects of the study will be monitored by Immune Pharmaceuticals and their designees according to Good Clinical Practices (GCP) and Standard Operating Procedures (SOPs) for compliance with applicable government regulation (i.e., Informed Consent Regulations [US 21CFR, Part 50] and Institutional Review Board regulations [US 21CFR, Part 45.103]). Access to all records, both during the trial and after trial completion, should be made available to Immune Pharmaceuticals at any time for review and audit to ensure the integrity of the data.

The investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data is not recorded per protocol, the reasons must be clearly documented in the CRF and site records.

Prior to the study, an Immune Pharmaceuticals representative will review the protocol and study procedures and processes to include IP receipt, storage, and accountability; investigator responsibilities and staff adequacy; event reporting timelines; monitoring and audit requirements; study documentation responsibilities; subject enrollment procedures; and CRF requirements to include system training with the investigator and site staff. Additional tasks and activities may be completed as needed for the study.

During the study, all protocol-specified data will be recorded in the source documents and data will be entered on the CRF from the source documents. Checks will be performed by the study monitor and data management to ensure the quality, consistency, and completeness of the data. Instances of missing or un-interpretable data will be resolved with the site staff. Site personnel will be responsible for providing resolutions to the data queries and to correct the CRFs, as appropriate.

10.4.1 Electronic Case Report Forms

Data for this study will be recorded using an electronic CRF. Sites will receive training for appropriate CRF completion and sites will be responsible for data entry into the eCRF. In the event of discrepant data, the Sponsor or designee will request clarification from the sites. The sites will resolve discrepant data electronically in the CRF. An Immune Pharmaceuticals representative, or a designee, will perform final data review and external data reconciliations prior to all major milestones, including database close and lock. CRFs and correction documentation will be

maintained in the CRF's audit trail. Records retention for the study data will be consistent with the SOPs of the Sponsor or designee.

A CRF must be completed for each screened subject. For each screen-failed subject, the reason for screen failure will also be collected in the CRF. The corresponding forms for the activities and assessments performed should be entered into EDC for screen-failed patients. The entire casebook of data must be reviewed and electronically signed by the investigator.

11.0 STUDY ADMINISTRATION

11.1 PARTICIPATING CENTERS

Up to 10 sites in Israel and US will participate in this study. Additional sites may be added as necessary to complete enrollment. A list of the Principal Investigators will be maintained in the trial master file.

11.2 CLINICAL TRIAL SUPPLIES

The investigator and designee(s) will be responsible for administering, inventory, and accountability of all clinical trial supplies, and exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study, the investigator will keep the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned. **Under no circumstances will the investigator allow the study drugs or other study-related supplies to be used other than as directed by this protocol.**

11.3 INVESTIGATOR SITE FILE

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor and regulatory agencies.

11.4 FINAL REPORT

A final study report will be prepared after the study has been completed and database has been cleaned, locked and analyzed. The report will be prepared according to the ICH E3 guidelines.

11.5 RETENTION OF STUDY RECORDS

The investigator will retain study documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor. If the investigator is unable to retain the study documents for the required amount of time, Sponsor or designee must be informed of the individual who will be assuming this responsibility.

These files must be made available for inspection upon reasonable request by authorized representatives of Sponsor and/or the relevant regulatory agencies.

11.6 CONFIDENTIALITY AND PUBLICATION

Study patient medical information obtained by the study is confidential and disclosure to third parties other than those noted below is prohibited. Throughout the study, all data will be identified only by the subject number, and where applicable, the study patient's initials and birthdate.

At the study patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. The personal physician will be notified by site personnel of study patient participation in the study.

All information supplied by Immune Pharmaceuticals, Inc. in association with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, the protocol, CRFs, and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain sole property of Immune Pharmaceuticals, shall not be disclosed to others without the written consent of Immune Pharmaceuticals, and shall not be used except in the performance of this study.

The information developed during the conduct of this study is also considered confidential, and will be used by Immune Pharmaceuticals, Inc. This information may be disclosed as deemed necessary by Immune Pharmaceuticals, Inc. To allow the use of this information derived from this study, the investigator is obliged to provide Immune Pharmaceuticals with complete test results and all data developed in this study.

12.0 REFERENCES

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13.0 APPENDICES

Appendix A: Schedule of Activities

Study Procedures	Screening	Treatment Period			Follow-up Period[a]						Early Discontinuation[b]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9°**	**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°	X°	X°							
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 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 value at Visit 2 (Day 0)
[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.

Appendix B: Assessment of BP Severity*

*Assessment to be done on three occasions during the screening period

Date of Assessment	Assessor Initials	Number of bullae that are present at the time of the assessment	Number of urticarial plaques that are present at the time of the assessment	BP Severity
				☐ Moderate ☐ Extensive ☐ Other
				☐ Moderate ☐ Extensive ☐ Other
				☐ Moderate ☐ Extensive ☐ Other
				☐ Moderate ☐ Extensive ☐ Other
				☐ Moderate ☐ Extensive ☐ Other
				☐ Moderate ☐ Extensive ☐ Other
				☐ Moderate ☐ Extensive ☐ Other

Appendix C: Karnofsky Performance Status

	KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%)	CRITERIA
Able to carry on normal activity and to work; No special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; Minor signs or symptoms of disease.
	80	Normal activity with efforts; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; Requires equivalent of institutional or hospital care; diseases may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; Active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Oxford Textbook of Palliative Medicine. Oxford University Press. 1993;109.

Appendix D: Bullous Pemphigoid Disease Area Index [1]

BPDAI					
SKIN	**ACTIVITY**		**ACTIVITY**		**DAMAGE**
Anatomical location	Erosions/Blisters	Number of Lesions if <3	Urticaria/ Erythema / Other	Number of Lesions if <3	Pigmentation/ Other
	0 absent		**0** absent		Absent 0, present 1
	1 1-3 lesions, none > 1 cm diameter		**1** 1-3 lesions, none >6 cm diamter		
	2 1-3 lesions, at least one > 1 cm diameter		**2** 1-3 lesions, at least one lesion > 6 cm diameter		
	3 >3 lesions, none > 2 cm diameter		**3** >3 lesions, or at least one lesion > 10 cm diameter		
	5 >3 lesions, and at least one >2 cm		**5** >3 lesions and at least one lesion > 25 cm diameter		
	10 >3 lesions, and at least one lesion >5 cm diameter or entire area		**10** >3 lesions and at least one lesion > 50 cm diameter or entire area		
Head					
Neck					
Chest					
Left arm					
Right arm					
Hands					
Abdomen					
Genitals					
Back/Buttocks					
Left leg					
Right leg					
Feet					
Total skin	/120		/120		
MUCOSA	Erosions/Blisters				
	1 1 lesion				
	2 2-3 lesions				
	5 >3 lesions, or 2 lesions >2cm				
	10 entire area				
Eyes					
Nose					
Buccal mucosa					
Hard palate					
Soft palate					
Upper gingiva					
Lower gingiva					
Tongue					
Floor of Mouth					
Labial Mucosa					
Posterior Pharynx					
Anogenital					
Total Mucosa	/120				

TOTAL ACTIVITY SCORE _____

TOTAL DAMAGE SCORE _____

BPDAI Pruritus Component- VAS

☐	Baseline	☐	Beginning Consolidation
☐	Consolidation phase	☐	End of Consolidation
☐	Tapering phase	☐	Partial remission on minimal therapy
☐	Complete remission on minimal therapy	☐	Partial remission off therapy
☐	Complete remission off therapy	☐	Flare

A. How severe has your itching been over the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
None										Severe

Score out of 10=

B. How severe has your itching been over the past week?

0	1	2	3	4	5	6	7	8	9	10
None										Severe

Score out of 10=

B. How severe has your itching been over the past month

0	1	2	3	4	5	6	7	8	9	10
None										Severe

Score out of 10=

Average INTENSITY SCORE FOR PAST MONTH = (A+B+C)=

OR

For BP patients with impaired mental functioning:

No evidence of itch (no excoriations)	0
Mild itch (isolated excoriations up to two body sites)	10
Moderate itch (excoriations on ≥ 3 body sites, impairment of daily activity)	20
Severe itch (generalized excoriations, sleep impairment)	30
TOTAL SCORE	/30

Appendix E: Autoimmune Bullous Disease Quality of Life

ABQOL Questionnaire

Not Done, specify reason: ☐

Date of Assessment	☐ ☐ (dd Month yyyy)

1. In regards to your blistering disease, does your skin burn, sting or hurt in any way?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never
2. In regards to your blistering disease, does your skin itch?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never
3. Have you had to change your clothing because of your blistering disease?	o 3 I have to be very careful with how tight my clothing is and what materials they are made of – I have had to change what I wear all the time o 2 I have had to change most of the things I wear o 1 I have had to change some of the things I wear o 0 I have never had to change what I wear
4. Do you notice your skin heals slowly?	o 3 I notice this all the time o 2 I notice this sometimes o 1 I notice this occasionally o 0 I have never had this problem
5. Do you have difficulty bathing or showering because of your blistering disease?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never
6. In regards to your blistering disease, does your mouth have erosions which are painful?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never

7. In regards to your blistering disease, do your gums bleed easily?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never
8. Does your blistering disease result in you having to avoid food or drinks that you enjoy?	o 3 I can no longer eat any of the foods I used to enjoy o 2 I can eat some of the foods I enjoy o 1 I can eat most of the foods I enjoy o 0 I can eat anything I like
9. As a result of your blistering disease, are you embarrassed about your appearance?	o 3 All the time o 2 Sometimes o 1Occasionally o 0 Never
10. Do you feel depressed or angry because of your blistering disease?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never
11. Do you feel anxious or cannot relax as a result of your blistering disease?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never
12. Do you worry that friends and family find your blistering skin condition tiresome?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never
13. Is your blistering disease causing sexual difficulties?	o 3 All the time o 2 Sometimes o 1 Occasionally o 0 Never

14. Does your blistering disease affect relationships with friends or loved ones?	o 3 I have had to end a relationship because of my disease OR I cannot have a relationship because of my disease o 2 Relationships are very difficult o 1 Relationships are a little difficult o 0 This has not affected my relationships
15. Does your blistering disease affect your social life?	o 3 I cannot go out to socialize any more o 2 I can only go to some social events o 1 I can go to most social events o 0 My social life is not affected
16. Does your blistering disease affect your work or study?	o 3 Yes, I can no longer work or study o 2 Yes, I find it difficult to work or study o 1 Yes, it is a little harder than before to work or study o 0 No, I am not affected **OR** N/A
17. Do employers discriminate against you because of your blistering disease?	o 3 I cannot find a job due to my blistering disease o 2 I have had to change jobs due to my blistering disease o 1 I still have my job but it is more difficult than before o 0 My employers are completely understanding **OR** N/A

Appendix F: Topical Steroids Potency Class Table

Class	Generic Name	Formulation
Class 1 Very High Potency		
	Betamethasone dipropionate	0.05% G O (diprolene)
	Clobetasol	0.05% C F G L O
	Diflorasone diacetate	0.05% O
	Halobetasol propionate	0.05% C O
Class 2 High Potency		
	Amcinonide	0.1% O
	Betamethasone dipropionate	0.05% C (diprolene)
	Desoximetasone	0.05% G, 0.25% C O
	Fluocinonide	0.05% C G O S
	Halcinonide	0.1% C
	Mometasone furoate	0.1% O
Class 3 High Potency		
	Amcinonide	0.1% C L
	Betamethasone dipropionate	0.05% C (non-diprolene)
	Betamethasone valerate	0.1% O
	Desoximetasone	0.05% C
	Diflorasone diacetate	0.05% C
	Fluticasone propionate	0.005% O
	Halcinonide	0.1% O S
	Triamcinolone	0.1% O
Class 4 Mid Potency		
	Betamethasone valerate	0.12% F
	Flucinolone acetonide	0.025% O
	Flurandrenolide	0.05% O
	Hydrocortisone valerate	0.2% O
	Mometasone furoate	0.1% C
	Triamcinolone	0.1% C
Class 5 Mid Potency		
	Betamethasone dipropionate	0.05% L
	Betamethasone valerate	0.1% C
	Flucinolone acetonide	0.025% C
	Fluticasone propionate	0.05% C
	Flurandrenolide	0.05% C
	Hydrocortisone butyrate	0.1% C
	Hydrocortisone valerate	0.2% C
Class 6 Low Potency		
	Alcometasone dipropionate	0.05% C O
	Betamethasone valerate	0.1% L
	Desonide	0.05% C L O
	Flucinolone acetonide	0.01% C S
Class 7 Low Potency		
	Hydrocortisone acetate	0.5% C L O, 1% C O F
	Hydrocortisone hydrochloride	0.25% C L, 0.5% C L O S, 1% C L O S, 2% L, 2.5% C L O S

C = Cream, F = Foam, G = Gel, L = Lotion, O = Ointment, S = Solution

Source: Dermatol Nurs © 2006 Jannetti Publications, Inc.