NCT02704429

CLINICAL STUDY PROTOCOL

Protocol Title: An Open-Label, Phase 2, Pilot Study Investigating the Safety, Clinical Activity, Pharmacokinetics, and Pharmacodynamics of Oral Treatment with the BTK Inhibitor PRN1008 in Patients with Newly Diagnosed or Relapsing Pemphigus Vulgaris

Protocol No.: PRN1008-005

Development Phase: Phase 2

Investigational Product: PRN1008

No.: (IND/CTD/CTN) EudraCT No. 2015-003564-37

Protocol Date: 19 March 2019, Version 7.0

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PROTOCOL SIGNATURE PAGE

Product Name:	PRN1008
Version Number:	7.0
Release Date:	19 March 2019

The undersigned confirms that this Protocol is accurate.

Signed: 

PROTOCOL ACCEPTANCE PAGE

PROTOCOL NO.: PRN1008-005

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PROTOCOL DATE: **Amendment 7, 19 March 2019**

By signing this protocol acceptance page, I confirm that I have read, understood, and agree to conduct the study in accordance with the current protocol.

Principal Investigator Name (Printed)

Principal Investigator Signature Date

Please return original Protocol Acceptance to Principia Biopharma Australia Pty Ltd. or designee. Please retain a copy for your study files.

This study is to be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, The International Conference on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Directive 2001/20/EC and 2005/28/EC, and the Title 21 Code of Federal Regulations Parts 50, 54, 56, 312, and 314, where appropriate.

The study protocol and any amendments are to be reviewed by a Human Research Ethics Committee (HREC) before implementation.

Written informed consent is to be obtained from each study participant prior to the conduct of any procedures which exceed or differ from standard practice at the study site.

Confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without prior written consent of Principia Biopharma Australia Pty Ltd.

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STUDY SYNOPSIS

Study Title:	An Open-Label, Phase 2, Pilot Study Investigating the Safety, Clinical Activity, Pharmacokinetics, and Pharmacodynamics of Oral Treatment with the BTK Inhibitor PRN1008 in Patients with Newly Diagnosed or Relapsing Pemphigus Vulgaris
Study Number:	PRN1008-005
Indication:	Pemphigus: Pemphigus Vulgaris (PV)
Background:	PV, which is characterized by intraepidermal blisters in skin and mucosae, is known to be driven by autoantibodies to epidermal proteins and is responsive acutely to the anti-inflammatory effects of corticosteroids and chronically to B-cell depletion by anti-CD20 therapy. Principia Biopharma has developed a novel, highly selective, small molecule inhibitor of non-T cell white blood cell signaling (via B- cell receptor, FCγR, FcεR signaling of the Bruton's tyrosine kinase, i.e., BTK, pathway). In naturally occurring canine pemphigus foliaceus (PF), PRN1008, rapidly reversed disease without the need for corticosteroid treatment. In Phase 1 studies with 114 healthy volunteers, target BTK occupancy levels were safely and consistently exceeded, suggesting PRN1008 may be highly effective in human pemphigus and other autoimmune diseases.  Refer to PRN1008 Investigators' Brochure, for additional information.
Study Sites:	Multiple international sites
Study Phase:	Phase 2

Study Objectives:	**Primary Objectives:** • To evaluate the clinical safety of PRN1008 in patients with PV over a 12-week (Part A) or 24-week (Part B) treatment period • To evaluate the clinical activity of PRN1008 in patients with PV, per criteria in the European Academy of Dermatology and Venereology (EADV) 2014 Pemphigus S2 Guideline (Hertl et al. 2015)* *As modified to define CR without 2-month durability definition **Secondary Objective:** • To evaluate the pharmacokinetics (PK) and the pharmacodynamics (PD) of PRN1008 in patients with PV **Exploratory Objective:** • To evaluate the relationship of PK and PD to each other and to efficacy and safety in this patient population
Study Design:	**Part A:** Open-label cohort study, with intrapatient dose-adjustment based on clinical response and BTK occupancy, and with conventional immunosuppressive "rescue treatment", if indicated. Initial dosing will be 400 mg twice daily (*bid*). The duration of study therapy will be 12 weeks starting on Day 1 and ending on study Day 84 (total duration of individual subject participation is 28 weeks). **Part B:** Initial dosing will be 400 mg once daily (*qd*), with intra-patient dose escalation to 400 mg *bid* allowed at or after the Week 3 visit for insufficient clinical response (and then again to 600 mg bid if necessary at or after the Week 5 visit). The duration of study therapy will be 24 weeks starting on Day 1 and ending on study Day 169 (total duration of individual subject participation is approximately 32 weeks). **Both Parts:** The first dose on Day 1 of Week 1 will be supervised in the clinic and the patient observed for approximately 2 hours, at which time a PK/PD sample will be drawn. Day 2 study medication will be withheld in the morning in order to gain the trough BTK occupancy approximately 12 (when *bid* dosing) or approximately 24 hours (when *qd* dosing) after the prior dose. Where follow-up is not feasible the next day, another day in the first week of treatment may be used to get trough occupancy instead, again withholding dose on the morning of that day to get an occupancy measurement close to 12 (when *bid* dosing) or approximately 24 (when *qd* dosing) hours post dose. At other follow-up visits, BTK occupancy can be measured at any time after the usual morning dose of PRN1008. The maximum dose of PRN1008 in this study, after dose adjustment, will be 600 mg *bid*.

Corticosteroid Rescue Criteria Guidelines:	Systemic corticosteroids will be avoided during PRN1008 therapy unless "rescue criteria" are triggered, or the patient enters the study on low-dose corticosteroids (i.e., ≤ 0.5 mg/kg). Corticosteroid rescue criteria are listed in Appendix 1.
Outcome Measures:	**Primary Outcome Measures**: Safety: The incidence of treatment-emergent AEs (TEAEs), including clinically significant changes in physical examination, laboratory tests, and vital signs. Efficacy: The proportion of subjects who are able to achieve control of disease activity (CDA) within 4 weeks of starting PRN1008 treatment without the need for doses of prednis(ol)one > 0.5 mg/kg. **Secondary Outcome Measures:*** • Proportion of subjects able to achieve CDA without corticosteroids within 4 weeks • Proportion of subjects able to achieve a complete response (CR) without corticosteroids within 12 weeks (and also 24 weeks in **Part B**) • Proportion of subjects able to achieve CR without the need for doses of prednis(ol)one of greater than 0.5mg/kg within 12 weeks (and also 24 weeks in **Part B**) • Time to CDA • Time to CR • Time to end of consolidation phase • Time to relapse after PRN1008 treatment discontinuation • Cumulative corticosteroid usage over the first 12 weeks (and also 24 weeks in **Part B**) • Change from baseline in Pemphigus Disease Area Index (PDAI) and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) scores at each follow-up visit • Change from baseline in Autoimmune Bullous Diseases Quality of Life (ABQOL) and Treatment of Autoimmune Bullous Diseases Quality of Life (TABQOL) scores at each follow-up visit • Change from baseline in appetite (SNAQ score) at each follow-up visit *Clinical activity endpoints as defined by the EADV 2014 pemphigus S2 guideline (Hertl et al. 2015) **Pharmacokinetics Outcome Measure:** • Plasma concentrations of PRN1008 at approximately the time of maximum concentration on Day 1 and at varied subsequent times during outpatient dosing

	Pharmacodynamic Outcome Measures: • Percentage BTK occupancy in PBMCs at 2 & 24 hours after the first PRN1008 dose and at various subsequent times during outpatient dosing • Change from baseline in anti-dsg1-3 autoantibody levels by enzyme-linked immunosorbent assay (ELISA) at various time points. **Exploratory Outcome Measures:** Exploratory PK/PD analysis will examine the effects, if any, of covariates on PK and/or PD, and the relationship between PK, PD, and efficacy in this population.
Planned Number of Participants and Interim Analysis:	[redacted]
Participant Selection Criteria:	**Inclusion Criteria Part A and Part B (unless noted below)**: 1. Male or female patients, aged 18 to 80 years old, with biopsy-proven (positive direct immunofluorescence and appearance on H&E microscopy), mild-moderate PV in **Part A** (PDAI 8 to 45) and mild-severe PV in **Part B** (PDAI 8 to 60) 2. Newly diagnosed or relapsing patients for whom an initial period of PRN1008 monotherapy or combination therapy with low-dose corticosteroids (≤0.5 mg/kg of prednis[ol]one or equivalent), is judged clinically acceptable, provided tapering of the corticosteroid treatment regimen is anticipated with good clinical response to PRN1008 3. BMI > 17.5 and < 40 kg/m^2 **Part A only** 4. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥ 1.5 X 10^9/L, Hgb > 9 g/dL, platelet count ≥ 100 X 10^9/L, AST/ALT ≤ 1.5 x ULN, albumin ≥ 3 g/dL, creatinine ≤ ULN **(Part A)** and creatinine ≤ 1.5 x ULN (**Part B**) 5. Female patients who are of reproductive potential must agree for the duration of active treatment in the study to use an effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, condoms or sexual abstinence). Unless surgically sterile, postmenopausal females should have menopause confirmed by FSH testing 6. Able to provide written informed consent and agreeable to the schedule of assessments **Exclusion Criteria Part A and Part B**: 1. Previous use of a BTK inhibitor. *Patients enrolled in a previous version of this protocol who are still in their 12-week active treatment period with PRN1008 are eligible to continue treatment, initially with their current dose level, under this amended protocol for an additional 12 weeks, i.e.*

	*24 weeks total, following review and signature of the EC approved patient's consent. Patients who completed **Part A** and did not discontinue the study due to a medical condition that might compromise safety assessments or for a PRN1008 related adverse event may be screened for entry under **Part B**.* 2. Pregnant or lactating women 3. ECG findings of QTc > 450 msec (males) or > 470 msec (females), poorly controlled atrial fibrillation (i.e. symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities 4. A history of malignancy of any type, other than surgically excised non-melanoma skin cancers or in situ cervical cancer within 5 years before the day of dosing 5. Use of immunologic response modifiers with the following periods prior to Day 1: *as concomitant therapy*, other immunologic response modifiers not detailed in this exclusion apart from corticosteroids; *1 week*: cyclophosphamide; *4 weeks*: IVIG , Kinaret (anakinra) and Enbrel (etanercept); *12 weeks*: Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), Orencia (abatercept), Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), plasmapheresis; *6 months*: Rituxan/MabThera (rituximab), ofatumumab, any other anti-CD20 antibody, other long-acting biologics 6. More than 0.5 mg/kg of prednis(ol)one per day ("low dose corticosteroids") within the two weeks prior to Day 1 7. Use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change patient to H2 receptor blocking drugs prior to the first dose of PRN1008) 8. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A (Appendix 2) within 3 days or 5 half-lives (whichever is longer) of study drug dosing 9. Use of CYP3A-sensitive substrate drugs (Appendix 3) with a narrow therapeutic index within 3 days or 5 half-lives (whichever is longer) of study drug dosing including, but not limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or terfenadine 10. Has received any investigational drug (or is currently using an investigational device) within the 30 days before receiving the first dose of study medication, or at least 5 times the respective elimination half-life time (whichever is longer) 11. History of drug abuse within the previous 12 months 12. Alcoholism or excessive alcohol use, defined as regular consumption of *more than* approximately 3 standard drinks per day

	13. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption 14. History of anorexia nervosa or periods of three months or more of low body weight (BMI < 17.5) in the past 5 years 15. Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1 16. History of solid organ transplant 17. History of epilepsy or other forms of seizure in the last 5 years 18. Positive for screening for HIV, hepatitis B (surface and core antibodies unrelated to vaccination), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA) 19. Positive interferon-gamma release assay (IGRA) (e.g., T-spot TB Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus), at Screening. Unless, the patient has latent TB and all of the following 3 conditions are true: a) Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease b) There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease c) Documented receipt of one of the following prophylactic treatment regimens: i. Oral daily Isoniazid for 6 months or ii. Oral daily Rifampin (RIF) for 4 months or iii. Isoniazid and Rifapentine weekly for 3 months (3HP) On a case by case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to 1 of the above tests may be used for eligibility. For example, if a QuantiFERON®-TB Gold, or QuantiFERON-TB Gold Plus (QFT Plus) is positive and a local blood test or T-Spot TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor. 20. History of serious infections requiring intravenous therapy with the potential for recurrence 21. Live vaccine within 28 days prior to baseline or plan to receive one during the study

	22. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with subject safety, study evaluations, and/or study procedures
Test Product and Method of Dosing	PRN1008 300 mg and 100 mg tablets. Tablets should be taken with a glass of water and may be taken with or without food, i.e., a period of fasting is not required.
Concomitant CYP3A Inducers or Inhibitors, Clinically Relevant CYP3A Substrate Drugs, Acid-Reducing Drugs and Anticoagulant Monitoring	Inducers and inhibitors of Cytochrome P450 3A (CYP3A) should be avoided, as they may reduce or increase the exposure of PRN1008 (Appendix 2) when administered concomitantly. PRN1008 is a moderate CYP3A inhibitor and can increase the exposure of drugs metabolized by CYP3A when administered concomitantly. Narrow therapeutic index CYP3A substrate drugs should be avoided (Appendix 3) and care should be taken with other drugs metabolized by the CYP3A. Clinically relevant CYP3A substrate drugs, (e.g. "sensitive substrate" listed in Appendix 3), should be managed by administering PRN1008 on a time schedule such that CYP3A substrate drugs can be given 2 hours or more after PRN1008. Proton pump inhibitors reduce the exposure of PRN1008 by approximately 50% due to the effects of a lack of an acidic environment on tablet bioavailability. Therefore, subjects who are on proton pump inhibitors should be changed to H2 receptor blocking drugs or not enrolled in the study. PRN1008 should be given at least 2 hours before any dose of an H2 receptor blocking drug or any antacid. Anticoagulation with warfarin should be monitored actively in the first weeks of PRN1008 therapy, as the combination has not been studied previously (interaction is not suggested to be likely based on in vitro metabolism studies).
Screening Procedures Part A and Part B:	Up to 28 days before enrollment into the study, participants will be required to sign a consent form, after which screening assessments will be carried out as follows: • Review of medical history including concomitant medications • PDAI and ABSIS scoring • Review of inclusion and exclusion criteria • Measurement of height and weight • Physical examination • 12-Lead ECG • Vital signs (blood pressure, heart rate, respiration rate and temperature) • Clinical laboratory testing (hematology, coagulation, serum chemistry and urinalysis) • HIV, hepatitis B (surface antigen and core antigen and antibodies, hepatitis C (anti-HCV antibody confirmed with Hep C RNA)

	• TB screen with T-spot TB Test, or QuantiFERON®-TB Gold test, or QuantiFERON®-TB Gold Plus (QFT Plus) • FSH (in postmenopausal women only who are not surgically sterile) • Pregnancy test in women of childbearing potential (serum test done at screening, urine dip test done at other time points) • Skin biopsy if not already performed: lesional for H&E staining, perilesional for direct immunofluorescence
Randomization Procedure:	Not applicable; the study is open-label.
Study Assessments (see Schedule in Appendix 4):	**Part A**: Patients will be screened within 28 days of dosing and will return for an end-of-study assessment 84 days after receiving their final dose of study drug. During the study, patients will return at specified times on an outpatient basis for assessment of vital signs, physical examination, assessment of AEs, assessment of concomitant medication use, assessment of clinical benefit, and provision of blood samples for PK and PD, and other clinical laboratory tests. Note: Patients who are currently enrolled in this PRN1008-005 study (**Part A**) and are in the 12-week active treatment period with PRN1008 are eligible to continue treatment at their current dose up to a total of 24 weeks active treatment, as a **Part B** patient, upon review and signature of the *Part B* EC-approved Patient Informed Consent Form. Patients that completed **Part A** of the trial are also eligible to be screened as a **Part B** patient, upon review and signature of the *Part B* EC-approved Patient Informed Consent Form. **Part B:** Patients will be screened within 28 days of dosing and will return for an end-of-treatment assessment on Day 169 after receiving their final dose of study drug on the morning of Day 169. They will return for follow up 28 days later for a final, follow up visit. During the study, patients will return at specified times on an outpatient basis for assessment of vital signs, physical examination, assessment of AEs, assessment of concomitant medication use, assessment of clinical benefit, and provision of blood samples for PK and PD, and other clinical laboratory tests. **Clinical Assessments Part A and B:** • Medical history, including evaluation of any on-study AEs and periodic vital signs (body temperature, heart rate, respiratory rate, blood pressure), concomitant medication use • At screening only: height and weight, full physical examination, and 12-lead electrocardiogram (ECG) (an extra ECG may be taken at additional visits, if indicated) • Disease activity scores: PDAI, ABSIS (Appendix 5) • Standardized photography of the affected area (Optional) • Quality of Life Scores: ABQOL, TABQOL (Appendix 5) • SNAQ appetite questionnaire (Appendix 6)

	Laboratory Assessments Part A and Part B: • *Hematology:* hemoglobin, hematocrit, erythrocyte count (RBC's), thrombocyte count (platelets), leukocyte count (WBCs) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes) • *Coagulation:* PT/INR, thrombin time, aPTT, fibrinogen level • *Serum chemistry:* Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total, direct, and indirect bilirubin levels, Alkaline phosphatase (ALP), Albumin, Creatinine, Urea, Total Protein, Sodium, Chloride, Calcium, Phosphate, Potassium, Glucose (random), creatine phosphokinase (CPK) and thyroid stimulating hormone (TSH) • *PK:* Plasma PRN1008 concentration • *PD:* BTK occupancy in PBMCs and anti-desmoglein -1 and -3 autoantibody titers by ELISA • *Urinalysis:* pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocytes measured by dip stick • *Serology:* HIV, Hepatitis B (surface antigen and core antigen and antibodies) and Hepatitis C and T-spot TB® Test, QuantiFERON®-TB Gold, or QuantiFERON-TB Gold Plus (QFT Plus) testing at screening only • *FSH* for postmenopausal women who are not surgically sterile at screening only • *Pregnancy test* for women of childbearing potential
Safety and Tolerability Assessments Part A and B:	Specific assessments to evaluate treatment safety include the following: the frequency and type of AEs, clinical laboratory testing, SNAQ appetite questionnaire (Appendix 6) and vital signs. Patients will remain under observation in the clinic for 2 hours after administration of the first dose and until the PK/PD sample is drawn. A Safety Monitoring Committee (SMC) will regularly review and evaluate patient safety data including AEs, laboratory results, concomitant medications, dose modifications, and efficacy.
Statistical Analysis:	**Clinical Activity:** Given the natural history of PV to not remit spontaneously, a study of approximately 25 PV patients completing 12 weeks of treatment and approximately 25 PV patients completing 24 weeks of treatment with PRN1008 should determine a reasonable approximation of the responder rate and average time to response (e.g., estimated response rate of 50% with 80% CI of ± 13%). Where appropriate, patients from both parts will be combined in analysis. The results from this pilot study will be used to design confirmatory, pivotal clinical trials. Time course of changes in clinical and laboratory parameters will be described graphically, and at each visit using descriptive statistics.

	Safety and Tolerability: Quantitative safety data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum) by dose level. Summaries will also be presented for the change from baseline, when appropriate. **Pharmacokinetics and Pharmacodynamics:** Individual and group PK and PD data will be summarized, displayed graphically, and by descriptive statistics for each visit, where measured.
Study Duration:	Approximately 48 months from the first subject treated to last subject completing, and 28 (**Part A**) – 32 (**Part B**) weeks per subject.

GLOSSARY OF ABBREVIATIONS AND TERMS

ABBREVIATION OR TERM	DEFINITION
ABSIS	Autoimmune Bullous Skin Disorder Intensity Score
ABQOL	Autoimmune Bullous Diseases Quality of Life (assessment)
AE	Adverse event
Ae	Amount excreted unchanged in the urine
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCR	B-cell receptor
BID	Twice daily (morning and evening)
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
BTK	Bruton's Tyrosine Kinase
CA	Competent Authority
CI	Confidence Interval
CLr	Renal clearance
Cmax	Maximum observed plasma concentration
CNS	Clinical Network Services
CPK	Creatine phosphokinase
CR	Clinical Response
CRF	Case report form
CRO	Contract research organization
CTCAE	Common Terminology Criteria for AEs
CV	Coefficient of Variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DSG	Desmoglein
EC	Ethics Committee (see also HREC)
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
FSH	Follicle Stimulating Hormone
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
H2	Histamine two (receptor)
HBsAg	Hepatitis B surface antigen
HPMC	Hypromellose
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HR	Heart rate
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization

ABBREVIATION OR TERM	DEFINITION
IMP	Investigational medicinal product
IR	Immediate Release (tablet formulation)
IRB	Institutional Review Board (Human Research Ethics Committee)
IVIG	Intravenous immunoglobulin
LDL	Low density lipoprotein
LPLV	Last participant last visit
LTFU	Long-term Follow-up
MAD	Multiple ascending dose (trial)
MedDRA	Medical Dictionary for Regulatory Activities
N	Sample Size
NOEL	No observed effect level
NOAEL	No observed adverse effect level
OTC	Over the counter
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PDAI	Pemphigus Disease Area Index
PF	Pemphigus foliaceus
PK	Pharmacokinetic
PO	By Mouth
PV	Pemphigus vulgaris
Q12H	Every 12 hours
QD	Once a day
QTc	QT interval corrected for heart rate
RA	Rheumatoid arthritis
RBC	Red blood cell
RR	Resting Rate
SAD	Single ascending dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard Deviation
SI	Système international d'unités (International system of units)
SMC	Safety Monitoring Committee
SoAT	Schedule of Assessment Table
SLE	Systemic Lupus Erythematosus
SNAQ	Simplified Nutritional Appetite Questionnaire
SSR	Six-Month SUSAR Report
SUSAR	Suspected Unexpected Serious Adverse Reaction
TABQOL	Treatment of Autoimmune Bullous Diseases Quality of Life (assessment)
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TGA	Therapeutic Goods Administration
Tmax	Time of observed maximum plasma concentration
TSH	Thyroid stimulating hormone
t½	Elimination half-life
WBC	White blood cell
WHODD	World Health Organisation Drug Dictionary
XLA	X-linked agammaglobulinemia

1 BACKGROUND AND SCIENTIFIC RATIONALE FOR THE TREATMENT OF PEMPHIGUS WITH PRN1008

1.1 Background

Bruton's agammaglobulinemia tyrosine kinase (BTK) is an essential signaling element downstream of the B-cell receptor (BCR), Fc-gamma receptor (FcγR) and Fc-epsilon receptor (FcεR). BTK is a non-receptor tyrosine kinase and is a member of the TEC family of kinases. Inhibition of BTK activity in cells produces phenotypic changes consistent with blockade of the BCR. This activity results in the down-regulation of various B-cell activities including cell proliferation, differentiation, maturation, survival, and the up-regulation of apoptosis. BTK also regulates the activation of other hematopoietic cells, such as basophils, mast cells, macrophages, neutrophils, and platelets. It is not expressed in T cells, natural killer cells, and plasma cells (Sideras and Smith 1995; Mohamed, et al., 2009). A selective BTK inhibitor has the potential to target multiple pathways involved in inflammation and autoimmunity. These include modulation of BCR-mediated B-cell pathways, inhibition of FcγR-induced cytokine release from monocytes and macrophages, FcεR-induced mast cell degranulation, granulocyte migration and mediator release. These effects lead to the prediction that a BTK inhibitor could block the initiation and propagation of various inflammatory diseases and mitigate the resulting tissue damage.

Important insights into BTK function come from loss of function analyses in humans and mice. Individuals with loss of function mutations in the BTK gene develop X-linked agammaglobulinemia (XLA) characterized by a complete absence of circulating B cells and plasma cells, and very low levels of immunoglobulins of all classes (Tsukada 1993, Vetrie 1993). This indicates the potential for BTK inhibition to suppress production of autoantibodies thought to be important in development of autoimmune diseases, such as pemphigus vulgaris (PV). These individuals have decreased humoral immunity and are susceptible to pyogenic bacterial as well as enterovirus infections, requiring treatment with intravenous immunoglobulin. However, inhibition of BTK in individuals with an intact immune system is not predicted to produce similar susceptibility to infection.

Several orally administered BTK inhibitors, including ibrutinib (PCI-32765) and CC-292, are currently marketed or in clinical development for a range of indications. Ibrutinib has provided further clinical validation of the BTK target and was recently approved for human use in mantle cell lymphoma, Waldenström's macroglobulinaemia, and chronic lymphocytic leukemia by the U.S. Food and Drug Administration (U.S. FDA), and has also demonstrated activity in other hematological malignancies (Wang 2013, Byrd 2013, Imbruvica Package Insert, 2015). CC-292 has been reported to be well tolerated in a healthy volunteer population, at doses which provide 100% occupancy of the BTK enzyme (Evans 2013).

1.2 Rationale for PRN1008 Treatment in Pemphigus

PV is known to be driven by autoantibodies to epidermal proteins and is responsive acutely to the anti-inflammatory effects of corticosteroids and within 5 to 35 weeks to B- cell depletion by anti-CD20 therapy (Horvath et al. 2012).

PRN1008 is a novel, highly selective, small molecule inhibitor of non-T cell white blood cell signaling (via B- cell receptor, FCγR, FcεR signaling of the Bruton's tyrosine kinase, i.e., BTK, pathway).

In Phase 1 studies with 114 healthy volunteers, target BTK occupancy levels were safely and consistently exceeded, suggesting PRN1008 at the planned dose levels may be highly effective in human pemphigus and other autoimmune diseases.

As of January 18, 2018, PRN1008 had been administered to 21 patients with pemphigus (pemphigus vulgaris [PV] and pemphigus foliaceus [PF]), 18 of whom had 4 or more weeks of treatment with PRN1008. Of the 18 patients with efficacy data, 11 (61%) met the primary endpoint of "Control of Disease Activity" (CDA) on a CS dose of ≤ 0.5 mg/kg/day (low-dose CS) by the Week 5 visit. Three patients achieved CDA on no CS. Two patients required high-dose CS temporarily during PRN1008 treatment due to worsening of disease activity. Four patients achieved complete remission (CR) on 1 to 20 mg/day of CS; 3 achieved CR at Week 13 (25%) and one achieved CR at Week 21. PRN1008 has been well-tolerated in this study (see Section 1.4).

Refer to PRN1008 Investigators' Brochure for additional information.

1.3 Summary of PRN1008 Animal Toxicity Studies

1.3.1 13-week GLP Toxicology

In the 13-week repeat-dose GLP toxicity studies with PRN1008, doses of up to 500 mg/kg/day and 300 mg/kg/day were given to rats and dogs, respectively. The No Observed Adverse Effect Level (NOAEL) in rats was considered to be 150 mg/kg/day and the NOAEL for male dogs was 30 mg/kg/day. The NOAEL in female dogs is less than 30 mg/kg/day, based on body weight loss in one female administered 30 mg/kg/day. At doses above 150 mg/kg, the lungs of some rats showed increased macrophages and bronchoalveolar papillary hyperplasia. In dogs, PRN1008-related findings considered potentially PRN1008-related were observed in the liver and lymphoid tissues. At doses above 30 mg/kg in dogs, changes in liver function (mainly ALT and AST), loss of appetite, and associated weight loss were observed. These observations are considered clinically significant and their assessment in human subjects is included in the study procedures in this clinical protocol.

Orally administered PRN1008 did not affect the gross behavioral, physiological, or neurological state of rats at dose levels up to 500 mg/kg, and the NOAEL for effects on the cardiovascular and respiratory systems in dogs was considered to be 500 mg/kg.

PRN1008 tested negative in a battery of in vitro and in vivo genotoxicity studies.

1.3.2 6 and 9-month GLP Toxicology

In the 6-month rat oral GLP toxicology study, the no-observed-adverse-related level (NOAEL) was 50 mg/kg/day in females (AUC_{last} 5480 hr.ng/mL) and 150 mg/kg/day in males (AUC_{last} 5327 hr.ng/mL). The nature and severity of observed findings included lethality, decreased body weight gain, macroscopic and microscopic changes in the gastrointestinal tract, and neutrophilic inflammation in the brain. Adequate safety factors of ~4X are present to the rat NOAEL, assuming a maximum exposure in humans of 1360 ng.h/mL with a 600 mg bid dose, and 6X to the target exposure of 890 ng.h/mL with the 400 mg bid dose.

In the 9-month dog oral GLP toxicology study, the NOAEL for male and female animals was 30 mg/kg/day (AUC_{last} 963 hr.ng/mL), based on body weight loss that required food supplementation and the euthanasia of one male dog dosed at 50mg/kg/day. The observed findings in the dog of appetite decrease, weight loss, and reversible changes in liver function are readily monitorable in human studies.

1.3.3 Reproductive and Fertility Studies

1.3.3.1 Embryo-Fetal Development Study in Rat

There were no PRN1008-related external, visceral, or skeletal fetal malformations or variations, and there were no PRN1008-related effects on fetal ossification site averages.

Pregnant female rats were given daily oral doses of 50, 150, or 300 mg/kg/day of PRN1008 from DG 7 through 17. The maternal NOAEL was determined to be 150 mg/kg/day based upon lower body weight/gain and food consumption. There were no PRN1008-related fetal development; or fetal external, visceral, or skeletal morphology changes. Therefore, the embryo/fetal development NOAEL was considered to be 300 mg/kg/day.

1.3.3.2 Embryo-Fetal Development Study in Rabbit

There were no PRN1008-related external, visceral, or skeletal fetal malformations or variations, and there were no PRN1008-related effects on fetal ossification site averages.

Pregnant female rabbits were given daily oral doses of 10, 30, or 100 mg/kg/day of PRN1008 from DG 7 through 19. The maternal NOAEL was determined to be 30 mg/kg/day based upon lower body weight gain and food consumption at 100 mg/kg/day. There were no PRN1008-related fetal development changes, and no fetal external, visceral, or skeletal morphology changes were observed. Therefore, the embryo/fetal development NOAEL was considered to be 100 mg/kg/day.

1.3.3.2.1 Fertility and Early Embryonic Development in Rat

Administration of PRN1008 in male rats resulted in an increased incidence of rales and reduced body weight, body weight gains, and food consumption. The NOAEL in males for general toxicity parameters was considered to be 150 mg/kg/day. There were no effects on mating,

fertility, reproductive organ weights, or sperm parameters in the treated males. The reproductive NOAEL in males was 300 mg/kg/day.

Administration of PRN1008 in female rats resulted in reductions in body weights, body weight gains, and food consumption during the premating period and reductions in food consumption during the gestation period. The NOAEL for the females for maternal toxicity was considered to be 150 mg/kg/day. There were no effects on estrous cycling, mating, fertility, or ovarian and uterine parameters in the females. The reproductive and development NOAEL in females was 300 mg/kg/day.

Refer to PRN1008 Investigators' Brochure, Section 4.4 and 6 5 for a more comprehensive preclinical safety summary.

1.4 Summary of PRN1008 Clinical Experience

To date PRN1008 has been administered to 114 healthy adult volunteer subjects in five Phase I studies (PRN1008-001, PRN1008-002, PRN1008-004, PRN1008-006 and PRN1008-008) using four different formulations. Single doses, repeat single doses and periods of up to 11 days of once or twice daily dosing were studied. The maximum single dose administered was 1200 mg and the maximum multiday dose was 450 mg twice daily for 10 days (450 mg of the liquid formulation is equivalent to 648 mg of the IR tablet formulation).

As of January 18, 2018, PRN1008 has been administered to 21 patients with pemphigus using the IR tablet formulation. Study PRN1008-005, is a Phase 2, open-label cohort study of 12 weeks of PRN1008 therapy, followed by 12 weeks of follow up, using a starting dose of 400 mg twice a day, with intra-patient dose-escalation based on clinical response and BTK occupancy up to a maximum dose of 600 mg twice a day (**Part A** of this protocol).

This amendment 5.0, (**Part B**) allows 24 weeks of treatment followed by 4 weeks of follow-up. Initial dosing in Part B will be 400 mg once daily (*qd*), with intra-patient dose escalation to 400 mg *bid* allowed at or after the Week 3 visit for insufficient clinical response (and then again to 600 mg bid if necessary at or after the Week 5 visit).

A Phase 1/2 study of relapsing immune thrombocytopenia is enrolling patients at dose levels between 200 mg daily and 400 mg bid.

1.4.1 Experience in Healthy Volunteer Phase 1 Studies

In Study PRN1008-001, volunteers received single oral doses of placebo (n = 6), 50 mg (n = 6), 150 mg (n = 6), 300 mg (n = 6), 600 mg (n = 6), or 1200 mg (n = 6). The longest duration of treatment to date was in this same study, where subjects received 10 or 11 days of dosing, at dose regimens of placebo, 300 mg *qd*, 300 mg *q12h*, 600 mg *qd*, and 450 mg *q12h* (n = 8 per dose level). In Study PRN1008-002, a midazolam drug-drug interaction study, 12 subjects received single doses of 600 mg PRN1008. In both Study PRN1008-001 and Study PRN1008-002, PRN1008 was administered as a liquid formulation, under fasted conditions on all but one day. Study PRN1008-004 compared the relative bioavailability of the liquid formulation to a capsule formulation, whereby subjects (n = 12) received 300 mg single doses of both PRN1008

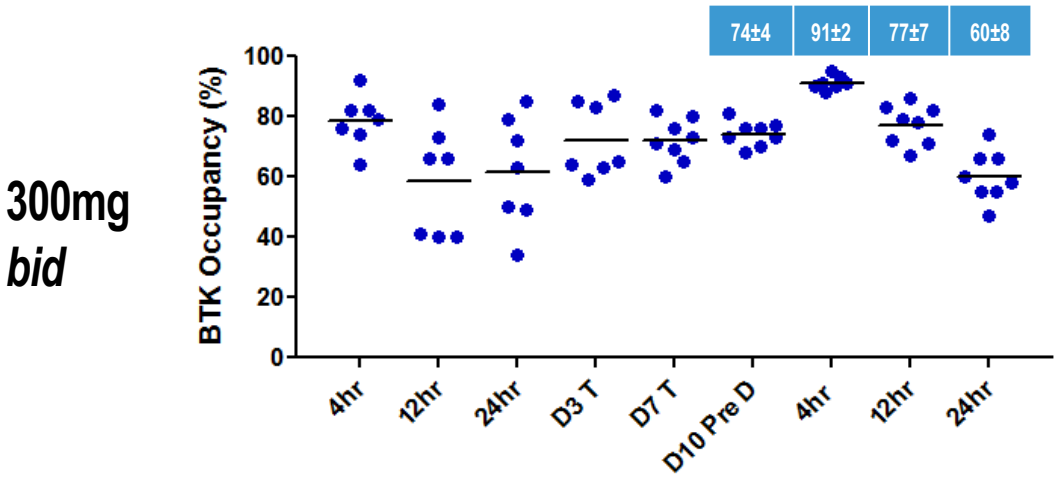
formulations. Study PRN1008-006 compared the relative bioavailability of the liquid formulation to a tablet formulation, whereby subjects (n = 12) received 300 mg single doses of both PRN1008 formulations, as well as the tablet after food and after several days of esomeprazole treatment. For additional details, refer to the PRN1008 Investigators' Brochure.

PRN1008 was safe and well tolerated at the dose levels tested). In these 114 Healthy Volunteer subjects, no severe AEs (AEs) or SAEs were reported, and no subjects required discontinuation or interruption of dosing. Reported AEs were mild or moderate in severity, with gastrointestinal AEs being most common (nausea/vomiting, loose stools) – predominantly with the liquid formulation. These AEs were more frequent at the 600 mg *qd* and 450 mg *q12h* doses. No clinically significant changes in laboratory parameters, vital signs, or ECG parameters were observed in 112/114 healthy volunteer subjects tested.

In Study PRN1008-008 of single doses of 400 mg of tablet formulations, one healthy volunteer with a low-normal baseline neutrophil count of 2100/µL experienced a single laboratory reading of 800/µL during follow up five days after a series of 4 single doses, having had a single low count of 1200/µL four days earlier after the fourth dose. The single low count had returned to 1900/µL when first remeasured four days later. In Study PRN1008-006, one subject had reversible, Grade 2 elevations of ALT during follow-up, associated with Grade 1 elevation of AST.

Following single and multiple oral doses of PRN1008 in Study PRN1008-001, mean BTK occupancy in PBMCs of more than 70% was observed 4 hours or later following doses of 300 mg or more on Day 1. Figure 1 shows clinically effective levels of BTK occupancy with a 300 mg bid dose on Day 1, with slightly reduced interpatient variability, and slightly higher Hour-4 values, observed after multiple days of dosing. Three subjects with BTK occupancies at 12 hours on Day 1 in the 40% range all had 12-hour occupancies above 60% by Day 10.

Figure 1 Individual and Mean BTK Occupancy Data from HV Study PRN1008-001 with the Liquid Formulation of PRN1008*



*Tablet equivalent doses are 428 mg twice daily after correction for relative bioavailability of ~70%. A second dose was not administered on Day 10.

1.4.2 Experience in Pemphigus Patients in Study PRN1008-005

1.4.2.1 Efficacy

As of January 18, 2018, PRN1008 had been administered to 21 patients with pemphigus (pemphigus vulgaris [PV] and pemphigus foliaceus [PF]), 18 of whom had 4 or more weeks of treatment. Of the 18 patients with efficacy data, 11 (61%) met the primary endpoint of "Control of Disease Activity" (CDA) on a CS dose of ≤ 0.5 mg/kg/day (low-dose CS) by the Week 5 visit. Three patients achieved CDA on no CS (Figure 2). Two patients required high-dose CS temporarily during PRN1008 treatment due to worsening of disease activity. Four patients achieved complete remission (CR) on 1 to 20 mg/day of CS; 3 achieved CR at Week 13 (25%) and one achieved CR at Week 21. Responses were seen in patients with both mild and moderate levels of initial disease (PDAI patient profiles, Figure 3).

Figure 2 PDAI and Clinical Response Patient Profiles of 5 Patients on Zero or Doses of CS ≤ 5 mg

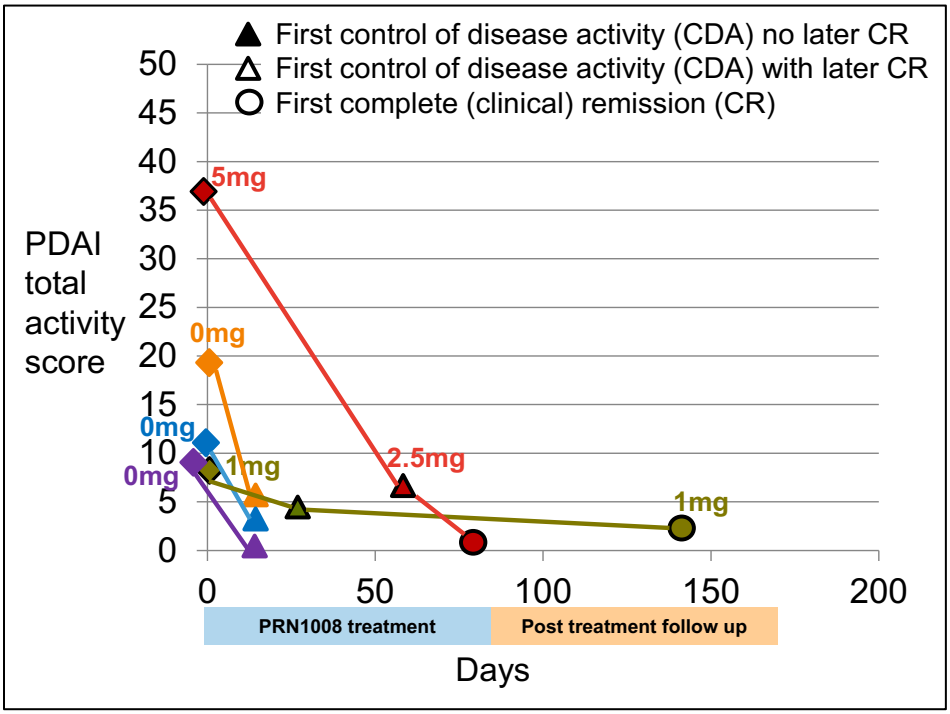
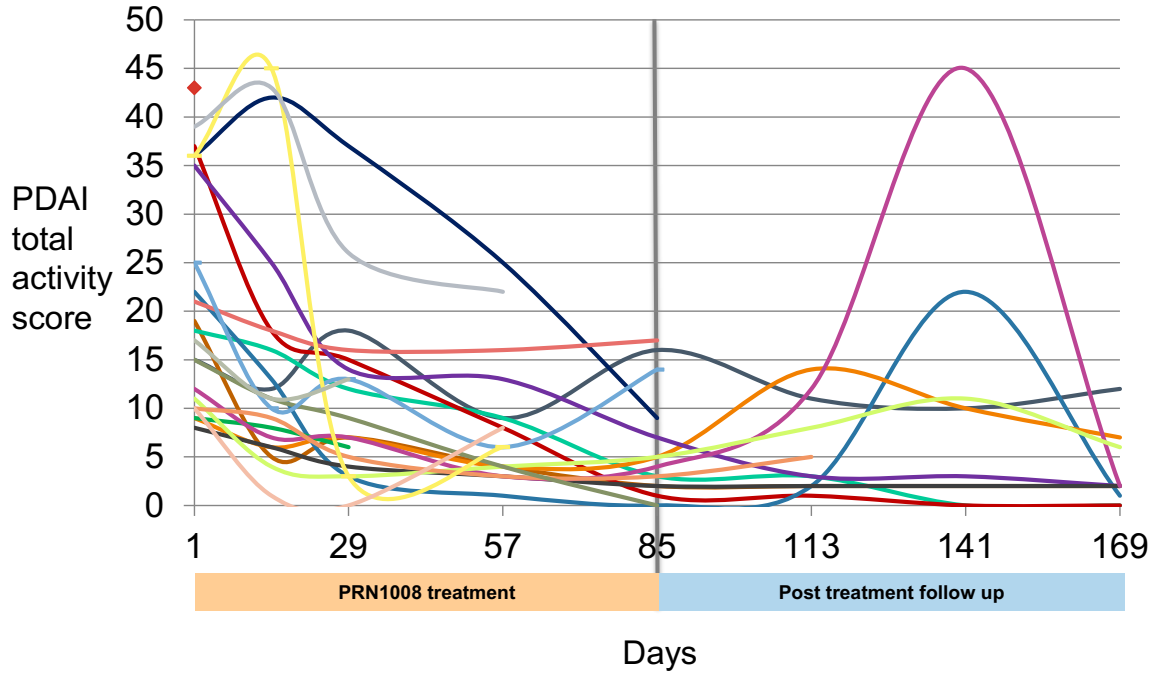


Figure 3 Timing of Individual Clinical Responses (Day 15 to 29 circled) N=21



1.4.2.2 Safety

The following three serious adverse events (SAEs) have been reported in PV patients: a Grade 3 event of cellulitis that led to hospitalization (considered by the investigator to be related to PRN1008), and two events considered unrelated to PRN1008 of 1) a Grade 3 event of "pancreatic pseudocyst – benign" that led to hospitalization and 2) a Grade 5 event of "acute respiratory failure - inflammation of an undiagnosed pulmonary sequestration-congenital" that led to hospitalization after one week of PRN1008 therapy and led to death following lung surgery more than a month after PRN1008 therapy was ceased.

Table 1 shows treatment-emergent adverse events (TEAEs) reported by more than one patient by relatedness and severity. TEAEs reported by more than one patient deemed related to PRN1008 are Grade 1 headache (10%), Grade 1 upper respiratory infection (10%) and Grade 1/2 dry mouth (10%).

Two patients on chronic anticoagulation (warfarin and rivaroxaban) have been treated without bleeding complications.

Table 1 TEAEs Reported by More than One Patient (N=21)

TEAE Term	Related	Grade	Freq. (n, %)
Pemphigus worsening	No	1-2	4 (19%)*
Headache[a]	Yes/No	1	3 (14%)*
Nausea	Yes/No	1	2 (10%)*
Upper respiratory tract infection	Yes	2	2 (10%)
Vomiting	No	1	2 (10%)
Dry mouth	Yes	1-2	2 (10%)*

TEAE = treatment-emergent adverse event
[a] Two of three headaches were deemed related to PRN1008 therapy.
*1 patient was at 500 mg bid, all other patients were at 400 mg bid

Refer to PRN1008 Investigators' Brochure for additional information.

1.5 Clinical Pharmacology of PRN1008

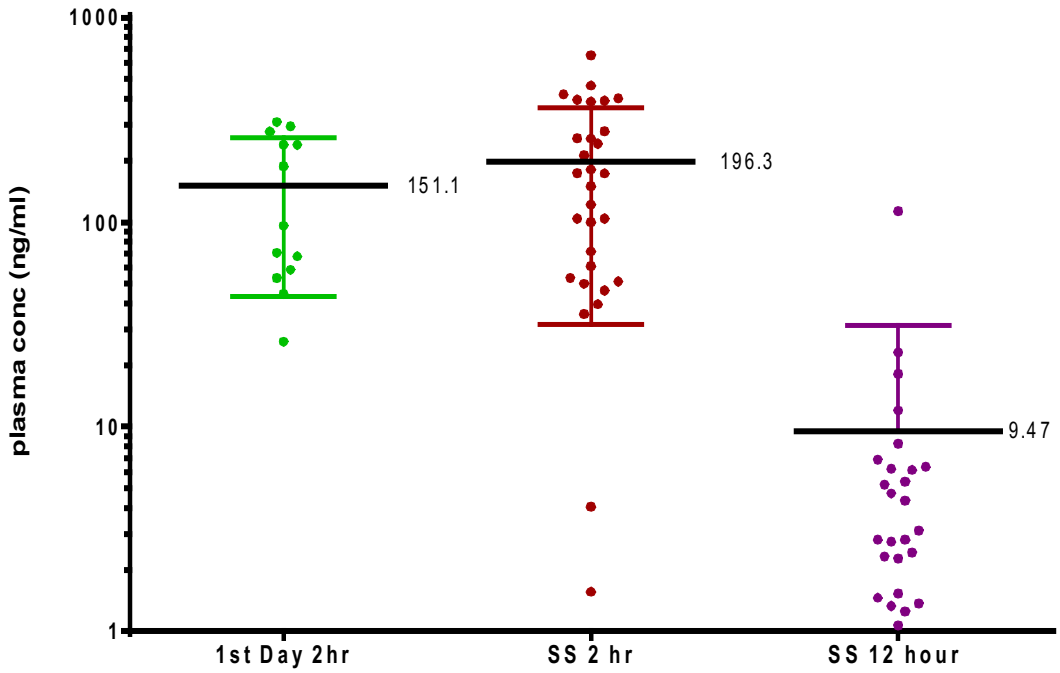
1.5.1 Pharmacokinetics in Healthy Volunteers

With multiple dosing, the terminal half-life of PRN1008 is approximately 3 to 4 hours and the time of maximum concentration (T_{max}) at therapeutic multiple doses of 1.5 to 2.0 hours. With 300 mg *bid* of the liquid formulation, the accumulation ratio was 1.8 after 10 days of dosing. There is no effect of food on the AUC or C_{max} of the tablet formulation although the T_{max} is slightly delayed from 1.5 hours to approximately 2.5 hours. The volume of distribution is high (on the order of 2500 L) and plasma protein binding is 98% (PRN1008 Investigators' Brochure).

1.5.2 Pharmacokinetics and BTK Occupancy in Pemphigus Patients

In this Study PRN1008-005, PK sampling is being conducted in all patients for population PK analysis. Blood samples were drawn pre-dose and at 2 hours following PRN1008 administration on the first day of therapy, pre-dose on the second and seventh day of therapy, and then at random times following dosing at other study visits. Preliminary data suggest that plasma concentrations at 2 hours, steady state 2 hours, and pre-dose were generally consistent to those seen in Phase 1 studies, as corrected for formulation (Figure 4).

Figure 4 Distribution of Plasma Concentrations at BTK Occupancy Timepoints

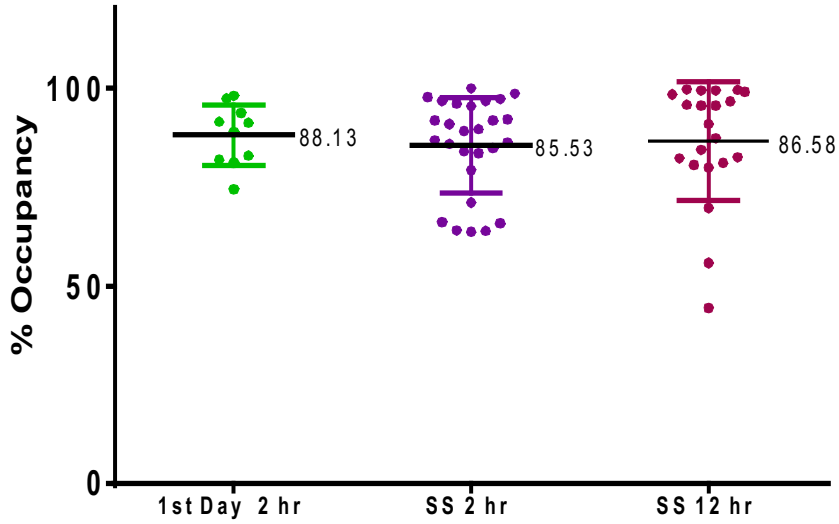


BTK = Bruton's tyrosine kinase; SS = steady state

1.5.3 BTK Occupancy in Patients with Pemphigus

Target occupancies, based on efficacy in animals and the levels reached with a liquid formulation dose of 300 mg *q12h,* were approximately 80% on Day 1, approximately 70% on Day 2 pre-dose (indicated as SS 12 hr), and approximately 90% at SS 2 hr (Figure 5). Thus, target occupancy levels are being reached in nearly all individuals with a 400 mg twice daily dose.

Figure 5 BTK Occupancies (Mean and Standard Deviation) Based on Approximate Timepoints Following Dosing



BTK = Bruton's tyrosine kinase; SS = steady state

2 RATIONALE AND JUSTIFICATION FOR THE STUDY AND THE STUDY DESIGN

2.1 Rationale for the Study Design

This open-label, pilot study is designed to explore the initial efficacy and safety of PRN1008 in PV and to enable the accurate design of pivotal randomized clinical trials which are to follow. An open-label design was chosen for several reasons: PV does not spontaneously remit so there is no placebo effect to account for; clinicians need to know when to use rescue corticosteroids, if necessary, in a timely manner; and lastly, the pilot nature of the investigation itself is best explored in an open-label fashion.

Because of the ability to guide individualized dosing with BTK occupancy measurement, the use of which has been validated in a naturally occurring canine pemphigus study, this assay was used to supplement the clinical response assessments in making dose-adjustments in **Part A**. More than 95% of patients in **Part A** (20/21) had adequate BTK occupancies (mean 86% pre dose at steady-state). In **Part B**, the clinical efficacy of the 400 mg qd dose is being explored to see if lower BTK occupancies will still equate to clinical efficacy. For this reason, clinical response alone, and not BTK occupancies, is recommended to guide dose adjustment in **Part B**.

Given the efficacy seen in this pemphigus study to date at varied clinical severities, and the updated, supporting, chronic, GLP toxicology (Section 1.3), there is clinical equipoise to study PRN1008 monotherapy (or with low dose CS) in patients with mild-to-severe (baseline PDAI 8-60), corticosteroid-naïve or relapsing PV, with close observation and appropriate corticosteroid rescue protocols.

2.2 Selection of the Starting Clinical Dose of PRN1008 in Pemphigus

400 mg bid (Part A): The 400 mg *bid* starting dose is based upon the dose known to produce ~70% BTK occupancy at trough (~85% average occupancy over the day), as adjusted by results of the relative bioavailability study, where the tablet had ~70% of the exposure of the equal dose of the liquid formulation. Adequate BTK occupancies with 400 mg bid dosing of the IR tablet has been confirmed in nearly all of the 21 patients with pemphigus studied to date. To confirm achievement of target, BTK occupancy measurements after the first dose will be expeditiously processed and provided to the treating physician in time for a follow-up visit at Day 15 (**Part A** only). This dose level has adequate safety factors to exposures in chronic toxicology studies (Section 1.3).

400 mg qd (Part B): In some but not all animal studies, a dose-response relationship between pre-dose BTK occupancy and clinical efficacy was observed. As it is unknown whether a once daily PRN1008 dose will provide adequate pharmacodynamics effect, a 400 mg qd dose is being tested in **Part B**, with the option to expeditiously dose-escalate to higher doses at or after the Week 3 visit. This dose level has adequate safety factors to exposures in chronic toxicology studies (Section 1.3).

Please refer to Investigator Brochure, Section 5.5.3, for additional information.

2.3 Overall Risk/Benefit Assessment

Design summary: Study PRN1008-005, is a Phase 2, open-label, cohort study of 12 weeks of PRN1008 therapy, followed by 12 weeks of follow up, using a starting dose in **Part A** of 400 mg twice a day *(bid),* with intra-patient dose-escalation to a maximum dose of 600 mg twice a day. In **Part B** the starting dose is 400 mg once daily (*qd)* with intra-patient dose-escalation to 400 mg bid allowed at or after the week 3 visit based upon insuffcient clinical response (and then again to 600 mg bid if necessary at or after the Week 5 visit).

Safety Profile*:* The one patient with a related SAE of cellulitis and fever observed in a patient with a higher risk of infection underscores the likely, mechanism-based risk of infection during chronic treatment with a BTK inhibitor.

Based on data from 21 patients in this Study PRN1008-005, as of January 18, 2018, PRN1008 has been well tolerated using the IR tablet formulation in doses of up to 400 mg bid (n=19), 500 mg bid (n=1) and 600 mg bid (n=1). No patients have discontinued PRN1008 therapy or dose-reduced due to treatment-related adverse events.

Efficacy*:* High clinical response rates have been observed in the first 21 PV patients in this study, on a background of zero or low dose CS, using a starting dose of 400 mg bid. It is possible that a lower, once daily dose may have a greater benefit-risk relationship, and this is being explored in **Part B**.

Risk/Benefit: Given the encouraging safety and efficacy profile of PRN1008, further exploration of minimally effective dose levels and longer durations of therapy is justified in pemphigus patients. The results of this study will be used to guide PRN1008 use in future patient studies. No risks other than those previously mentioned in the Investigator's Brochure or in the summary of PRN1008 clinical experience described above are known at this time. Refer to PRN1008 Investigators' Brochure, Section 5.6.2, for additional information.

2.4 Drug-Drug Interaction Potential

Based on in vitro data, CYP3A4 appears to be the major CYP isoform responsible for PRN1008 metabolism, including first-pass metabolism through the intestinal wall and liver. Therefore, PRN1008 plasma exposures have the potential to be altered if co-administered with other agents which either inhibit or induce CYP3A, however this potential interaction has not been studied clinically to date. Concomitant use of strong and moderate inducers of CYP3A should be avoided until their effects on PRN1008 exposure have been studied (Appendix 2).

A clinical drug-drug interaction study (PRN1008-002) was conducted to evaluate the effects of the liquid formulation of PRN1008 when administered simultaneously with midazolam, a probe CYP3A substrate. When co-administered with midazolam, midazolam plasma exposures increased approximately 3-fold. PRN1008 is therefore classified as a moderate inhibitor of CYP3A. As a result, sensitive CYP3A substrate drugs, particularly those with a narrow therapeutic index, should be avoided during treatment with PRN1008 (Appendix 2). Additional details are provided in the Investigator Brochure. PRN1008 does not appear to be an inducer of CYP isoenzymes.

Acid reducing drugs may reduce the bioavailability of PRN1008 tablets. Therefore, PRN1008 should be administered 2 hours or more prior to such drugs. Proton pump inhibitors are not permitted during the study (they resulted in a 50% decrease in PRN1008 tablet exposure when administered concomitantly in Study PRN1008-006).

3 OBJECTIVES OF THE STUDY

3.1 Primary Objectives

- To evaluate the clinical safety of PRN1008 in patients with PV over a 12-week (**Part A**) or 24-week (**Part B**) treatment period
- To evaluate the clinical activity of PRN1008 in patients with PV, per criteria in the European Academy of Dermatology and Venereology (EADV) 2014 Pemphigus S2 Guideline (Hertl et al. 2015)*

*As modified to define CR without 2-month durability definition

3.2 Secondary Objective

- To evaluate the pharmacokinetics (PK) and the pharmacodynamics (PD) of PRN1008 in patients with PV

3.3 Exploratory Objective

- To evaluate the relationship of PK and PD to each other and to efficacy and safety in this patient population

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 2, open-label, pilot cohort study.

Part A: Initial PRN1008 dosing will be 400 mg (*bid)*, with intrapatient dose adjustment up to 600 mg (*bid*) based on BTK occupancy and clinical response, and corticosteroid rescue treatment, if indicated. Patients requiring corticosteroid rescue treatment will be treated according to criteria specified in Appendix 7 of the protocol.

Part B: Initial PRN1008 dosing will be 400 mg (*qd)*, with intra-patient dose escalation to 400 mg *bid* allowed at or after Week 3 visit for insufficient clinical response (and then again to 600 mg *bid* if necessary at or after Week 5 visit).

4.2 Number of Participants

This study is planned to enroll up to 50 PV patients, with an interim analysis completed when 6 subjects completed 4 weeks or more of therapy (Study PRN1008-005 Interim Analysis Report).

4.3 Study Duration and Duration of Subject Participation

Part A: Subjects will receive twice-daily PRN1008 treatment for 12 weeks, starting on Day 1 and ending on study Day 85, with a further 12 weeks of follow up (total duration of individual subject participation is approximately 28 weeks).

Part B: Patients will receive once or twice-daily PRN1008 for 24 weeks, starting on Day 1 and ending on study Day 169, with a follow up visit 4 weeks later (a total duration of individual subject participation is approximately 32 weeks).

> *Patients enrolled in a previous version of this protocol who are still in their 12-week active treatment period with PRN1008 are eligible to continue treatment, initially with their current dose level, under this amended protocol for an additional 12 weeks, i.e. 24 weeks total, following review and signature of the EC approved patient's consent see Section 6.1 Inclusion Criteria.*

The expected study duration is approximately 48 months from the first subject treated to the last subject completing Part B in the study.

4.4 End of Study Definition

The end of the study is defined as the date of the final safety follow-up after the LPLV.

4.5 PRN1008 Administration

Part A: Initial PRN1008 dosing will be 400 mg *bid*. The maximum dose in this study, after dose adjustment, will be 600 mg *bid*. Clinical response and tolerability will be assessed at each visit. Dosing may be adjusted according to Section 4.6.

Part B: Initial PRN1008 dosing will be 400 mg *qd*, unless patients previously initiated the study with a 12-week treatment period are on higher doses, in which case they will initially continue with their current dose level. The maximum dose in this study, after dose adjustment will be 600 mg bid. Clinical response and tolerability will be assessed at each visit. Dosing may be adjusted according to Section 4.6.

PRN1008 tablets should be taken with a glass of water and may be taken with or without food, i.e., a period of fasting is not required.

4.5.1 Rationale for PRN1008 Dosage Selection

400 mg bid (Part A): The 400 mg *bid* starting dose is based upon the dose known to produce ~70% BTK occupancy at trough (~85% average occupancy over the day), as adjusted by results of the relative bioavailability study, where the tablet had ~70% of the exposure of the equal dose of the liquid formulation. Adequate BTK occupancies with 400 mg bid dosing of the IR tablet has been confirmed in nearly all of the 21 patients with pemphigus studied to date. To confirm achievement of target, BTK occupancy measurements after the first dose will be expeditiously processed and provided to the treating physician in time for a follow-up visit at Day 15 (**Part A** only). This dose level has adequate safety factors to exposures in chronic toxicology studies (Section 1.3).

400 mg qd (Part B): In some but not all animal studies, a dose-response relationship between pre-dose BTK occupancy and clinical efficacy was observed. As it is unknown whether a once daily PRN1008 dose will provide adequate pharmacodynamic effect, a 400 mg qd dose is being tested in **Part B**, with the option to expeditiously dose-escalate to higher doses at or after the Week 3 visit. This dose level has adequate safety factors to exposures in chronic toxicology studies (Section 1.3).

Maximum dose of 600 mg bid: A dose level 50% higher than the target upper dose level of 400 mg bid was arbitrarily chosen based on previous clinical safety data in healthy volunteers at higher exposures and adequate safety factors to exposure in animal toxicology studies.

4.5.2 Concomitant Medications

- Other immunosuppressive medications are not permitted except for low-dose corticosteroids and when rescue immunotherapy is triggered.
- Inducers and inhibitors of Cytochrome P450 3A (CYP3A) should be avoided as they may reduce or increase the exposure of PRN1008 (Appendix 2) when administered concomitantly.

- PRN1008 is a moderate CYP3A inhibitor and can increase the exposure of drugs metabolized by CYP3A when administered concomitantly. Narrow therapeutic index CYP3A substrate drugs should be avoided (Appendix 3) and care should be taken with other drugs metabolized by the CYP3A.
- Clinically relevant 3A substrate drugs (e.g. "sensitive substrate" listed in Appendix 3) should be managed by administering PRN1008 on a time schedule such that CYP3A substrate drugs can be given 2 hours or more after PRN1008.
- Acid reducing drugs may reduce the bioavailability of PRN1008 tablets. Therefore, PRN1008 should be administered 2 hours or more prior to such drugs. Proton pump inhibitors are not permitted during the study.

4.6 PRN1008 Intrapatient Dose Adjustment

Part A: Initial PRN1008 dosing will be 400 mg *bid*, with intrapatient dose adjustment based on clinical response and tolerability, supplemented by BTK occupancy (Table 2).

Part B: Initial PRN1008 dosing will be 400 mg qd, with intra-patient dose escalation to 400 mg *bid* allowed at or after Week 3 visit for insufficient clinical response (see Table 3) (and then again to 600 mg *bid* if necessary at or after Week 5 visit. Corticosteroid rescue treatment will be initiated, if indicated (Appendix 1).

"Well tolerated" is defined as the absence of Grade 3 or greater gastrointestinal AEs, or Grade 2 non-gastrointestinal AEs, including liver function changes, related to PRN1008 therapy. Investigators should use their judgment of the risk-benefit of continuing therapy by weighing the extent of clinical response, and AEs potentially related to PRN1008 therapy. In general, PRN1008 should be stopped and conventional therapy started when tolerability is poor and clinical response is also suboptimal.

Table 2 (Part A) General Dose Adjustment Guidelines for Dose Selection in the First 4 Weeks

Clinical Response	Trough BTK Occupancy	Tolerability*	Action
Responder 400 mg *bid*	≥ 50%	Well Tolerated	Maintain 400 mg *bid* Taper corticosteroids if used in combination
		Poorly Tolerated	Reduce to 300 mg *bid* Taper corticosteroids if used in combination
	< 50%	Well Tolerated	Maintain 400 mg *bid* Taper corticosteroids if used in combination
		Poorly Tolerated	Reduce to 300 mg *bid* Taper corticosteroids if used in combination
Suboptimal Response 400 mg *bid*	≥ 50%	Well Tolerated	*Follow rescue criteria if triggered*, if not maintain dose at 400 mg *bid*
		Poorly Tolerated	*Follow rescue criteria if triggered*, if not maintain dose at 400 mg *bid* if feasible
	< 50%	Well Tolerated	*Follow rescue criteria if triggered, if not,* increase dose to 600 mg *bid*
		Poorly Tolerated	*Follow rescue criteria if triggered,* if not, increase dose to 600 mg *bid* if tolerability allows.

* "Well tolerated" is defined as the absence of Grade 3 or greater gastrointestinal AEs, or Grade 2 non-gastrointestinal AEs, including liver function changes, related to PRN1008 therapy.

Table 3 (Part B) General Dose Escalation Guidelines

Current Dose	Inadequate Clinical Response* Dose-escalation Rules
400 mg qd	Increase to 400 mg bid (allowed at Week 3 visit or later)**
400 mg bid	Increase to 600 mg bid (allowed at Week 5 visit or later)**
600 mg bid	No dose increase possible. See Appendix 1B for corticosteroid rescue protocol

* Investigator discretion: Generally, clinical response is shown by some improvement seen in first 2 weeks with CDA achieved by the Week 5 visit

** Unless tolerability issues preclude dose-escalation

5 PROTOCOL DEVIATIONS

The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. Principia does not allow intentional or prospective deviations from the protocol unless necessary to eliminate an immediate hazard to study subjects. The Principal Investigator is responsible for immediately (within 24 hours) notifying Principia of a major protocol deviation to permit Principia to determine the impact of the deviation on the subject and/or the study:

Primary Principia Contact:

Secondary Principia Contact:

The Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities, and contract research organization (CRO) Clinical Monitors of all protocol deviations.

6 STUDY POPULATION

The study population is male or female patients with newly diagnosed (i.e., naïve to an effective induction treatment regimen) or relapsing, biopsy-proven, mild to severe PV (PDAI 8-60), for whom an initial period of PRN1008 monotherapy is judged clinically acceptable.

Because patients without mucosal involvement but with a medical history suggestive of PV are allowed into the study, some patients with clinical features suggestive of the pemphigus foliaceus (PF) variant of the disease may be enrolled.

6.1 Inclusion Criteria (Part A and Part B unless noted below)

1. Male or female patients, aged 18 to 80 years old, with biopsy-proven (positive direct immunofluorescence and appearance on H&E microscopy), mild-moderate PV in **Part A** (PDAI 8 to 45) and mild-severe PV in **Part B** (PDAI 8 to 60)
2. Newly diagnosed or relapsing patients for whom an initial period of PRN1008 monotherapy or combination therapy with low-dose corticosteroids (≤0.5 mg/kg of prednis[ol]one or equivalent), is judged clinically acceptable, provided tapering of the corticosteroid treatment regimen is anticipated with good clinical response to PRN1008
3. BMI > 17.5 and < 40 kg/m^2 **Part A only**
4. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥ 1.5 X 10^9/L, Hgb > 9 g/dL, platelet count ≥ 100 X 10^9/L, AST/ALT ≤ 1.5 x ULN, albumin ≥ 3 g/dL, creatinine ≤ ULN **(Part A)** and creatinine ≤ 1.5 x ULN (**Part B**)
5. Female patients who are of reproductive potential must agree for the duration of active treatment in the study to use an effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, condoms or sexual abstinence). Unless surgically sterile, postmenopausal females should have menopause confirmed by FSH testing.
6. Able to provide written informed consent and agreeable to the schedule of assessments.

6.2 Exclusion Criteria

1. Previous use of a BTK inhibitor

   *Patients enrolled in a previous version of this protocol who are still in their 12-week active treatment period with PRN1008 are eligible to continue treatment, initially with their current dose level, under this amended protocol for an additional 12 weeks, i.e. 24 weeks total, following review and signature of the EC approved patient's consent. Patients who completed **Part A** and did not discontinue the study due to a medical condition that might compromise safety assessments or for a PRN1008 related adverse event may be screened for entry under **Part B**.*

2. Pregnant or lactating women

3. ECG findings of QTc > 450 msec (males) or > 470 msec (females), poorly controlled atrial fibrillation (i.e. symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities
4. A history of malignancy of any type, other than surgically excised non-melanoma skin cancers or in situ cervical cancer within 5 years before the day of dosing
5. Use of immunologic response modifiers with the following periods prior to Day 1: as concomitant therapy, other immunologic response modifiers not detailed in this exclusion apart from corticosteroids; *1 week*: cyclophosphamide; *4 weeks*: IVIG, Kinaret (anakinra) and Enbrel (etanercept); *12 weeks*: Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), Orencia (abatercept), Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), plasmapheresis; *6 months*: Rituxan/MabThera (rituximab), ofatumumab, any other anti-CD20 antibody, other long-acting biologics
6. More than 0.5 mg/kg of prednis(ol)one per day ("low dose corticosteroids") within the two weeks prior to Day 1
7. Use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change patient to H2 receptor blocking drugs prior to the first dose of PRN1008)
8. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A (Appendix 2) within 3 days or 5 half-lives (whichever is longer) of study drug dosing
9. Use of CYP3A-sensitive substrate drugs (Appendix 3) with a narrow therapeutic index within 3 days or 5 half-lives (whichever is longer) of study drug dosing including, but not limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or terfenadine
10. Has received any investigational drug (or is currently using an investigational device) within the 30 days before receiving the first dose of study medication, or at least 5 times the respective elimination half-life time (whichever is longer)
11. History of drug abuse within the previous 12 months
12. Alcoholism or excessive alcohol use, defined as regular consumption of more than approximately 3 standard drinks per day
13. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption
14. History of anorexia nervosa or periods of three months or more of low body weight (BMI < 17.5) in the past 5 years
15. Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1
16. History of solid organ transplant
17. History of epilepsy or other forms of seizure in the last 5 years
18. Positive for screening for HIV, hepatitis B (surface and core antibodies unrelated to vaccination), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA)

19. Positive interferon-gamma release assay (IGRA) (e.g., T-spot TB Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus) at Screening. Unless, the patient has latent TB and all of the following 3 conditions are true:
    a. Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease
    b. There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease
    c. Documented receipt of one of the following prophylactic treatment regimens:
        i. Oral daily Isoniazid for 6 months

        or

        ii. Oral daily Rifampin (RIF) for 4 months

        or

        iii. Isoniazid and Rifapentine weekly for 3 months (3HP)

    On a case by case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to 1 of the above tests may be used for eligibility. For example, if a QuantiFERON®-TB Gold, or QuantiFERON-TB Gold Plus (QFT Plus) is positive and a local blood test or T-Spot TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor.

20. History of serious infections requiring intravenous therapy with the potential for recurrence
21. Live vaccine within 28 days prior to baseline or plan to receive one during the study
22. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with subject safety, study evaluations, and/or study procedures

6.3 Prior and Concomitant Therapy

6.3.1 Prior Therapy

Not Permitted:

Use of immunologic response modifiers within the following periods prior to Day 1:

- One week for cyclophosphamide
- Four weeks for Kinaret® (anakinra), intravenous gamma globulin (IVIG), and Enbrel® (etanercept)
- 12 weeks for Remicade® (infliximab), Humira® (adalimumab), Simponi® (golimumab), Orencia® (abatercept), Actemra® (tocilizumab), Cimzia® (certolizumab), Cosentyx™ (secukinumab), plasmapheresis

- 6 months for Rituxan®/MabThera® (rituximab), ofatumumab, any other anti-CD20 antibody, or any other long-acting biologic

6.3.2 Concomitant Therapy

Not Permitted:

- Concomitant use of immunosuppressant medication, other than low-dose corticosteroids, unless rescue criteria (Appendix 1) are triggered.
- Concomitant use of known strong to moderate inducers or inhibitors of CYP3A (Appendix 2) within 14 days or 5 half-lives (whichever is longer) of dosing with PRN1008.
- Use of CYP3A-sensitive substrate drugs (Appendix 3) with a narrow therapeutic index within 14 days or 5 half-lives (whichever is longer) of PRN1008 dosing including, but not limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or terfenadine.
- Proton pump inhibitors are not permitted. Esomeprazole was shown to reduce the exposure of PRN1008 by approximately 50%, presumably due to the effects of a lack of an acidic environment on tablet dissolution. Therefore, subjects who are on proton pump inhibitors should be changed to H2 receptor blocking drugs if possible or not enrolled in the study.

Permitted:

- The use of oral prednis(ol)one may be permitted in some circumstances. For admission to the study, doses of oral prednis(ol)one in the 2 weeks prior to Day 1 may be no higher than 0.5 mg/kg per day (inhaled and mucosal [for symptomatic treatment of oral lesions] corticosteroids are allowed). Where patients enter the study on low-dose corticosteroids, the regimen should be maintained for the initial 2 weeks of PRN1008 therapy. At the Day 15 review, a good clinical response to PRN1008 should allow the tapering of the corticosteroid to commence using the Werth taper (Appendix 7). At all times, the rescue criteria should be followed, as indicated (Appendix 1). In some circumstances, corticosteroids should be added or the dose increased, with or without cessation of PRN1008.
- Clinically relevant 3A substrate drugs (e.g., “sensitive substrate” listed in Appendix 3) should be managed by administering PRN1008 on a time schedule such that CYP 3A substrate drugs can be given 2 hours or more after PRN1008.
- H2 receptor blocking drugs and antacids are permitted provide PRN1008 is given at least 2 hours beforehand.
- Anticoagulation with warfarin should be monitored actively in the first weeks of PRN1008 therapy, as the combination has not been studied previously.

7 LIST OF SCREENING ASSESSMENTS

The Schedule of Assessments is presented in Appendix 4. All participants must sign and date the most current Institutional Review Board (IRB)-approved written informed consent form before any study specific assessments or procedures are performed. An original signed consent form will be retained by the Investigator and the participant will be given a copy of the signed consent form.

Participants must fulfill all entry criteria to be enrolled into the study. Participants who fail to meet the entry criteria may be rescreened once at the discretion of the Investigator. A record of eligibility screening documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria, including screen failures, is to be completed and signed by the Investigator or designee. Ethnicity of participants will be recorded, since this information might be important to evaluate a potential impact of ethnic factors on drug properties [see also ICH Guideline E5 (R1)].

Up to 28 days before enrollment in the study, participants will be required to sign a consent form, after which screening assessments will be carried out. After providing written informed consent, subjects will complete the Screening Assessments within 28 days before the first dose of PRN1008:

- Review of medical history and concomitant medication
- PDAI, ABSIS assessments
- Review of inclusion and exclusion criteria
- Measurement of height and weight
- Physical examination
- 12-Lead ECG
- Vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Clinical laboratory testing (hematology, coagulation, serum chemistry, and urinalysis)
- HIV, hepatitis B (surface antigen and core antigen and antibodies), hepatitis C (anti-HCV antibody confirmed with Hep C RNA)
- TB screen with T-spot TB Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus)
- Serum pregnancy test for females of child bearing potential
- FSH (in postmenopausal women who are not surgically sterile only)
- Skin biopsy if not already performed: lesional for H&E staining, perilesional for direct immunofluorescence

8 LIST OF STUDY ASSESSMENTS

The Schedule of Assessments is presented in Appendix 4.

8.1 Clinical Assessments Part A and B

- Medical history, including evaluation of any on-study AEs and periodic vital signs (body temperature, heart rate, respiratory rate, blood pressure), concomitant medication use, full or abbreviated physical examination
- At screening only: height and weight, full physical examination, and 12-lead electrocardiogram (ECG) (an extra ECG may be taken at additional visits, if indicated)
- Disease activity scores (PDAI, Autoimmune Bullous Skin Disorder Intensity Score [ABSIS]) (Appendix 5)
- Standardized photography of the affected area (Optional)
- Autoimmune Bullous Diseases Quality of Life (ABQOL) and Treatment of Autoimmune Bullous Diseases Quality of Life (TABQOL) assessments (Appendix 5)
- SNAQ appetite questionnaire (Appendix 6)

8.2 Laboratory Assessments Part A and B

Note: Laboratory assessments will be performed at both central and local laboratories, if required.

- **Hematology**: hemoglobin, hematocrit, erythrocyte count (RBCs), thrombocyte count (platelets), leukocyte count (WBCs) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
- **Coagulation**: PT/INR, thrombin time, aPTT, fibrinogen level.
- **Serum Chemistry**: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total, direct, and indirect bilirubin levels, Alkaline phosphatase (ALP), Albumin, Creatinine, Urea, Total Protein, Sodium, Chloride, Calcium, Phosphate, Potassium, Glucose (random), creatine phosphokinase (CPK) and thyroid stimulating hormone (TSH)
- **PK**: Plasma PRN1008 concentration
- **PD:**
  - BTK occupancy in PBMCs at baseline (pre-dose), and 2 and 24 hours after the first dose, then at various times of the day during follow-up visits. For the Day 2 (24 hour) BTK occupancy, PRN1008 should be taken as usual in the evening (only if *bid* dosing) and the PRN1008 morning dose withheld in order to take the blood sample approximately 12 hours after the prior evening dose (for *bid* dosing) or 24 hours after the last dose (for *qd* dosing). Where follow-up is not feasible on Day 2, another day in the first week

of therapy may be used to get trough occupancy instead. For all other visits, occupancy is measured at random times after the usual morning dose.

- Anti-desmoglein-1 and -3 autoantibody titers by enzyme-linked immunosorbent assay (ELISA)

- **Urinalysis**: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocytes measured by dipstick
- **Serology:** HIV, Hepatitis B and Hepatitis C and T-spot TB Test or QuantiFERON® TB testing or QuantiFERON®-TB Gold Plus (QFT Plus) at screening only
- **Pregnancy or FSH**: Serum pregnancy test for women of child bearing potential or serum FSH for post-menopausal females

8.3 Safety and Tolerability Assessments

Specific assessments to evaluate treatment safety include the following: the frequency and type of AEs, clinical laboratory testing, SNAQ appetite questionnaire (Appendix 6) and vital signs. Patients will remain under observation in the clinic for 2 hours after administration of the first PRN1008 dose and until the PK sample is drawn (see also Section 12.1, Safety Monitoring Committee).

9 STUDY TREATMENT

Part A: Initial PRN1008 dosing will be 400 mg *bid*. The maximum dose in this study, after dose adjustment, will be 600 mg *bid*. Subjects will be treated with PRN1008 for a maximum of 12 weeks.

> *Patients enrolled in a previous version of this protocol who are still in their 12-week active treatment period with PRN1008 are eligible to continue treatment, initially with their current dose level, under this amended protocol for an additional 12 weeks, i.e. 24 weeks total, following review and signature of the EC approved patient's consent*.

Part B: Initial PRN1008 dosing will be 400 mg *qd unless patients are eligible to roll from Part A to Part B*. The maximum dose in this study, after dose adjustment, will be 600 mg *bid*. Subjects will be treated with PRN1008 for a maximum of 24 weeks.

PRN1008 tablets should be taken with a glass of water, with or without food, i.e., a period of fasting is not required.

10 IDENTITY OF INVESTIGATIONAL PRODUCT

10.1 Formulation

Each PRN1008 film-coated tablet contains either 100 mg or 300 mg of PRN1008 drug substance. In addition, the tablet contains Microcrystalline Cellulose (filler), Crospovidone (disintegrant), Sodium Stearyl Fumarate (lubricant) and a non-functional film coating.
The 100 mg tablet is a round shape and orange in color. The 300 mg tablet is an oval shape and white in color.

10.2 Packaging

PRN1008 tablets are packaged in white high-density polyethylene (HDPE) bottles with child-resistant induction-sealed caps.

10.3 Storage and Handling

PRN1008 tablets are supplied in white plastic bottles with child-resistant induction-sealed caps or blister packs. The recommended storage condition is 2 to 25°C. Refer to product label for specific instructions.

10.4 Drug Accountability

The Investigator or his/her designated representatives will dispense study drug per the Schedule of Assessments (Appendix 4).

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Investigational Drug Dispensing Log) of the study drug must be maintained. The investigational Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the participant to whom the study drug was dispensed (for example subject identification number, participant initials, and date of birth)
- The date(s), quantity, and lot number(s) of the study drug dispensed to the participant
- The identification of the person who dispensed the study drug

All records and drug supplies must be available for inspection by the Study Monitor at every monitoring visit. When the study is completed, the Investigator will return any used and unused study drug (e.g., empty, partially used, and unused containers), occluded labels (or the equivalent) to the Sponsor as requested. The completed Drug Dispensing Log and Drug Return Record(s) will be returned to the Local Sponsor. The Investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to the Sponsor.

10.5 Destruction of Investigational Product

Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study center staff to destroy dispensed investigational product before a monitoring inspection, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed, and provided that adequate storage and integrity of drug has been confirmed. Written authorization must be obtained from the Sponsor or Sponsor designee after final accountability prior to destruction.

Unused study drug from the site that has not been stored properly should not be destroyed until the final report has been approved.

Written documentation of destruction must contain the following:

- Identity of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed the investigational products

Investigational sites that do not have a procedure for destruction and appropriate disposal of investigational product, or cannot dispose of investigational product locally may request assistance and documentation for return to the Sponsor, or assignment to a local qualified vendor for destruction and disposal.

11 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1 Primary Outcome Measures

11.1.1 Safety

The incidence of treatment-emergent AEs (TEAEs), including clinically significant changes in physical examination, laboratory tests, and vital signs.

11.1.2 Efficacy

The proportion of subjects who are able to achieve control of disease activity (CDA) within 4 weeks of starting PRN1008 treatment without the need for doses of prednis(ol)one > 0.5 mg/kg.

11.2 Secondary Outcome Measures

The following clinical activity endpoints* will be assessed:

- Proportion of subjects able to achieve CDA without corticosteroids within 4 weeks
- Proportion of subjects able to achieve a complete response (CR) without corticosteroids within 12 weeks (and 24 weeks in **Part B**)
- Proportion of subjects able to achieve CR without the need for doses of prednis(ol)one of greater than 0.5mg/kg within 12 weeks (and 24 weeks in **Part B**)
- Time to CDA
- Time to CR
- Time to end of consolidation phase
- Time to relapse after PRN1008 treatment discontinuation
- Cumulative corticosteroid usage over the first 12 weeks (and 24 weeks in **Part B**)
- Change from baseline in Pemphigus Disease Area Index (PDAI) and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) scores at each follow-up visit
- Change from baseline in Autoimmune Bullous Diseases Quality of Life (ABQOL) and Treatment of Autoimmune Bullous Diseases Quality of Life (TABQOL) scores at each follow-up visit
- Change from baseline in appetite (SNAQ score) at each follow-up visit

*Clinical activity endpoints as defined by the EADV 2014 pemphigus S2 guideline (Hertl et al. 2015) with the exception that CR is defined as CR at a single point in time rather than present for ≥2 months

11.3 PK/PD Outcome Measures

11.3.1 PK Outcome Measures

- Plasma concentrations of PRN1008 at approximately the time of maximum concentration on Day 1 and at various subsequent times during outpatient dosing

11.3.2 PD Outcome Measures

- Percentage BTK occupancy for individuals in peripheral blood mononuclear cells (PBMCs) at 2 & 24 hours after the first PRN1008 dose and at varied subsequent times during outpatient dosing
- Change from baseline in anti-dsg1-3 autoantibody levels by ELISA at various time points

11.3.3 Exploratory PK/PD Analysis

Exploratory PK/PD analysis will examine the effects, if any, of covariates on PK and/or PD, and the relationship between PK, PD, and efficacy in this population.

11.4 Determination of Sample Size

Sample size for this pilot study was determined pragmatically by the number of subjects required to determine a preliminary safety profile and a point estimate for the primary endpoint of efficacy. If the clinical response rate is 50%, 25 subjects in each Part will result in an 80% CI of ± 13%. Results from this pilot study will be used to design confirmatory clinical trials.

11.5 Analysis Populations

Four study populations will be defined: Screening Population, Safety Population, Efficacy Population, and Pharmacokinetic Population.

11.5.1 Screening Population

All participants who provide informed consent and have screening assessments evaluated for study participation are included in the Screening Population.

11.5.2 Safety Analysis Population

All participants who have received at least one dose of PRN1008 will be included in the safety analysis. The Safety Analysis Population will be defined for all safety analyses.

11.5.3 Efficacy Analysis Population

All patients who have received at least one dose of PRN1008 will be included in the efficacy analysis. Subject response and disease progression will be determined using PDAI, ABSIS, ABQOL, and TABQOL scores. Efficacy data will be presented in listings by subject and tabulated for each efficacy endpoint. Data may be combined where appropriate for Parts A

and B. Additional sub-group analyses (e.g. disease severity, dose group) may be performed as appropriate.

11.5.4 Pharmacokinetic Analysis Population

A pharmacokinetic population will be defined for participants who provide adequate plasma concentration data to allow for PK analysis. Participants may be excluded from the PK population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete, all of which may influence the analysis. Excluded cases will be documented together with the reason for exclusion in the Clinical Study Report.

11.6 Randomization and Blinding Procedures

Not applicable; the study is open-label.

11.7 Subject Numbers and Treatment Assignments

As they are enrolled in the study, subjects will be assigned a unique consecutive number. The site, in conjunction with the Sponsor, will be responsible for assignment of all unique subject numbers and dose assignments.

11.8 Subject Disposition, Subject Replacement, and Demographics and Baseline Characteristics

11.8.1 Disposition

The numbers of subjects enrolled, completing, and withdrawing, along with reasons for withdrawal, will be tabulated. The number of subjects in each analysis population will be reported overall.

11.8.2 Replacement of Subjects

Participants prematurely discontinued from the study for non-safety reasons may be replaced at the discretion of the Sponsor, to ensure adequate numbers of evaluable participants. A patient is considered "evaluable" if they took one or more doses of the study drug. Each patient who provides informed consent will be assigned a unique subject identifier (USUBJID). Participants recruited to be replacement patients will be assigned the next available subject identifier.

11.8.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics (pemphigus type, age, sex, race, ethnicity, weight, height, and body mass index) will be summarized for the Safety Population using descriptive statistics. No formal statistical analyses will be performed, and no inferential statistics reported.

Prior and concomitant medications will be summarized overall, by dose level, and by the number and percentage of subjects taking each medication, classified using World Health Organization. Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms (WHODD).

Disposition, baseline demographics and subject characteristics will be summarized for the Safety Population.

11.9 Efficacy Analysis

11.9.1 Subject Response and Disease Progression

Subject response and disease progression will be determined using PDAI, ABSIS, ABQOL, and TABQOL scores. Efficacy data will be presented in listings, by subject, and tabulated overall. Data may be combined where appropriate for Parts A and B. Additional sub-group analyses (e.g. disease severity, dose group) may be performed as appropriate.

The PDAI, ABSIS, ABQOL, and TABQOL questionnaires are located in Appendix 5.

11.10 Safety Analysis

Quantitative safety data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum) by dose level. Summaries will also be presented for the change from baseline, when appropriate. All safety analyses will be based on the Safety Analysis Population. As appropriate, listings, summary tables and graphs (individual plots and/or mean plots) by period will be provided to the Investigator and to the SMC for safety and tolerability assessment.

11.10.1 Adverse Events

The original verbatim AE terms recorded on the participant's case report form (CRF) by the Investigator will be standardized by the Local Sponsor by assigning preferred terms and system organ classes from the most recent available version of the Medical Dictionary for Drug Regulatory Affairs (MedDRA).

AEs will be described by individual listings and frequency tables by preferred terms and body system. The NCI CTCAE, version 4.0 will be used for grading AEs.

11.10.2 Clinical Laboratory Tests

All clinical laboratory data will be stored in the database in the units in which they were reported. Normal ranges for the local laboratory parameters must be provided to Principia/designee before the study starts. Participant listings and summary statistics at each assessment time, including change from baseline, will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before analysis.

Clinical laboratory results will be summarized descriptively for baseline and each time point. The numerical change from baseline to each time point will be computed. In addition, laboratory shift tables will be provided for all laboratory parameters where low/normal/high or abnormal/ normal status can be ascertained for shift from baseline to each time point. Listings of individual laboratory parameters by visit with normal ranges and abnormality assessments will also be completed by subject.

Scatter plots of the baseline value (x-axis) and end of study (y-axis) will be completed for each continuous clinical laboratory parameter. In addition, individual and group mean laboratory values over time (i.e., by visit) will also be completed to evaluate changes and trends in laboratory safety. Reference ranges will be highlighted on the plots to identify laboratory assessment out of range. Other graphical displays may be created as appropriate.

11.10.3 Vital Signs

Vital signs data will be presented by individual listings. Systolic blood pressure values < 90 or > 140 mmHg and diastolic blood pressure values < 60 or > 80 mmHg will be flagged as outside the normal range. Resting heart rate < 40 or > 100 beats per minute will be flagged as abnormal. Descriptive statistics of values and changes from baseline (mean, median, standard deviation) will be reported for quantitative variables separately for each period. In addition, tabular and graphical summaries will be used, as appropriate.

11.10.4 Concomitant Medications

The original terms recorded on the participants' CRF by the Investigator for concomitant medications will be standardized by the Local Sponsor by assigning preferred terms from the WHODD (World Health Organization Drug Dictionary) drug terms dictionary for treatments or coded via generic name of the concomitant medication.

Concomitant medications will be presented in summary tables and listings.

11.11 Pharmacokinetics/Pharmacodynamics Analyses

Individual and group PK and PD data will be summarized, displayed graphically, and by descriptive statistics for each visit where measured. Data will be summarized by descriptive statistics and related to clinical responses for each patient and as a group. PD and PD data will be pooled with data from other studies, and analyzed and reported separately.

11.11.1 Missing PK/PD Values

The methodology of handling missing PK/PD values in the analysis will be determined.

11.12 Statistical and Analytical Methods

11.12.1 Descriptive Summaries and Inference

Descriptive summary statistics will be provided for the safety, PK, and PD variables.
For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation, median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category. Descriptive summaries will be completed by study part, cohort, and dose.

Due to the small sample sizes, all p-values derived from inferential analyses will be considered informative. In general, all significant testing will be two-sided at significance level 0.05.
All tests will be made without adjustment for multiplicity or multiple comparisons.

11.12.2 Exploratory Analyses

Exploratory analyses not specified in the protocol or statistical analysis plans may be performed to further explore study results.

11.12.3 Interim Analysis

An interim analysis to evaluate safety, and to reevaluate sample size and other aspects of study design, was conducted for this study when 6 patients completed 4 weeks or more of PRN1008 therapy (Part A only) (Study PRN1008-005 Interim Analysis Report).

12 SAFETY AND TOXICITY MANAGEMENT

This section provides detailed information on reporting requirements and interpretation of safety assessments for AEs and reporting requirements for serious SAEs. Guidance and reporting requirements for pregnancy are also provided.

12.1 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will review the emerging safety data (TEAEs, safety labs), and efficacy, PD, and dose modification data approximately every 3 months within the first 6 months following the first subject enrolled in the study, and then with a frequency determined as appropriate by the SMC. The SMC members will include the Sponsor's Medical Monitor, a Principal Investigator, and a pemphigus clinical expert who is not an investigator in the study. The trial statistician will also participate in safety reviews. Documentation of the patient data reviewed at each meeting, including the individual SMC member's confirmation of data review and the findings and actions of the SMC, will be included in the Trial Master File. SMC findings that impact the safety of patients in this study will be immediately reported to the local Competent Authority (CA) and Ethics Committee (EC).

An SMC Charter outlining the SMC composition and responsibilities will be in place prior to the first scheduled meeting.

12.2 Adverse Event Collection Period

The AE Collection Period begins at the time of the first screening/eligibility assessment and ends at the end of the study for each patient.

12.3 Clinical Adverse Events

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product. All AEs encountered during the clinical study will be reported in detail in the source documents and documented in the CRF, from the date of participant consent throughout the follow-up visit.

Pre-existing conditions that worsen during a study are to be reported as AEs, with the exception of the disease under study as it is expected that there may be variation in pemphigus disease activity, and this is captured in other measurements.

The below guidelines should be followed when recording AEs:

Medical terms: Whenever possible, use recognized medical terms when recording AEs on the AE CRF. Do not use colloquialisms or abbreviations.

Diagnosis: If known or suspected, record the diagnosis rather than component signs and symptoms on the AE CRF and SAE form (e.g., if a diagnosis is made of congestive heart failure, record congestive heart failure rather than the symptoms of dyspnea, rales, cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the AE CRF or SAE form.

Death: Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the AE CRF and SAE form (except for sudden, unexplained death.)

Surgical or diagnostic procedures: For medical or surgical procedures (e.g., colonoscopy, biopsy), the medical condition that led to the procedure is an AE. Elective procedures (e.g., vasectomy), planned hospitalizations, and procedures for treatment of conditions noted in the patient's medical history that have not worsened (e.g., planned cataract surgery, hernia repair) are not considered AEs.

Chronic disease: In the case of disease (excluding disease under study) that is progressing by episodes (chronic disease), if the disease is known when the participant enters the trial, only worsening (increased frequency or intensity of the episodes or attacks) will be documented as an AE. If the disease is detected during the trial, and if repeated episodes enable diagnosis of a chronic disease, the episodes will be entered with the diagnosis and start/stop dates grouped together, and clearly described in the source documents.

Disease under study (Pemphigus): Unexpected progression, signs, or symptoms of the disease under study are not AEs and are not to be recorded on the AE page of the CRFs unless the event meets the definition of an SAE or is not consistent with the typical clinical course of the patient's disease as established by the patient's medical history. Worsening of the disease under study or other disease-related symptoms should be recorded as an AE only if the event meets the definition of an SAE or is not consistent with the typical clinical course of the disease.

Laboratory Out of Range Values: An isolated, out-of-range laboratory result in the absence of any associated, clinical finding may or may not be considered an AE; the Investigator's evaluation should be based on a consideration of the overall clinical context. An out-of-range laboratory result will be considered clinically significant and recorded as an AE when it is part of a clinical abnormality requiring specific medical intervention or follow-up. The test will be repeated and the patient will be followed-up until the test value has returned to the normal range or baseline, or the Investigator has determined that the abnormality is chronic or stable. The Investigator will exercise medical judgment in deciding whether out-of-range values are clinically significant and document the assessment in the source records.

12.4 Adverse Event Intensity Grading

All clinical AEs encountered during the clinical study will be reported on the AE page of the CRF. Intensity of AEs will be graded based on the NCI CTCAE, Version 4.0 or higher and reported in detail as indicated on the CRF. For any AEs not found in the CTCAE, a description of intensity grading can be found below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

12.5 Adverse Event Relationship to Study Drug

Investigators should use their knowledge of the study participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly.

The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (if applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the study participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

12.6 Treatment and Follow-Up of Adverse Events

SAEs for which the relationship to the study drug is “related”, should be followed up until they have returned to baseline status or stabilized.

If after follow-up, return to baseline status or stabilization cannot be established an explanation should be recorded on the CRF.

12.7 Laboratory and ECG Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the CRF, or appear on electronically produced laboratory reports, if applicable.

Any treatment-emergent abnormal laboratory or ECG result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE page in the CRF:

- Accompanied by clinical symptoms
- Leading to a change in study drug (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Note: Any laboratory or ECG result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an AE in the CRF.

12.7.1 Follow-Up of Abnormal Laboratory Test Values

In the event of unexplained clinically significant abnormal laboratory test values, the tests should be repeated as soon as possible and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the CRF.

12.8 Serious Adverse Event (SAE) Reporting

12.8.1 SAE Definitions

An SAE is any experience (clinical AE or abnormal laboratory test) that suggests a significant hazard, contraindication, side effect, or precaution. An SAE must fulfill at least one of the following criteria at any dose level:

- is fatal (results in the outcome death)*
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

Note that the term "sudden death" should only be used when the cause is of a cardiac origin as per standard *definition. The terms "death" and "sudden death" are clearly distinct and must not be used interchangeably.*

12.8.2 SAE Reporting

Any clinical adverse event or abnormal laboratory test value that is serious and which occurs during the course of the study (as defined above), occurring from the enrollment visit (start of study screening procedures), including long term follow-up must be reported to:

- The Local Sponsor (or designee) and monitor within 24 hours of the Investigator becoming aware of the event (expedited reporting).
- The investigational site's IRB by the investigator in accordance with their regulations.

Initial notification of an SAE must be confirmed in24 hours from the time the investigational team first become aware of the event using the PPD RAVE system, if possible. Paper SAE report forms should only to be used when the PPD RAVE system is not accessible, and SAEs should be transferred into RAVE once the system is available.

If PPD RAVE is not accessible, a written, narrative description of any SAE must be scanned and emailed to 1008005SAE@principiabio.com within 24 hours of awareness of the event.

If paper SAE forms are used, copies of the initial and follow-up SAE report forms must be made and the originals retained of all information faxed to PPD in the Investigator Site File.

As further information regarding the SAE becomes available, such follow-up information should be documented as an update in the RAVE system, or if RAVE is not accessible, on a new SAE report form, marked as a follow-up report and emailed to 1008005SAE@principiabio.com.

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention must be reported within 24 hours (e.g., SAEs related to invasive screening procedures such as biopsies, medication washout, or no treatment run-in). After first study medication, all SAEs must be reported within 24 hours.

SAEs identified after a subject has exited the study, that the Investigator deems related to PRN1008 exposure, should be reported to the Sponsor as noted above.

Unrelated SAEs must be collected and reported during the study and for up to 30 days after the last dose of study medication.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to Investigators at each site and associated IRB when the following conditions occur:

- The event is a SAE
- There is a reasonable possibility that the event is an adverse reaction caused by the administered drug

- The adverse reaction is unexpected, that is to say, not foreseen in the Investigator's Brochure
- When all participants at a particular site are off treatment, as defined by the protocol, individual SUSAR reports will be forwarded to the site and its associated IRB on an expedited basis.

Individual SUSARs considered to be a significant safety issue and/or which result in a change to the informed consent form will be reported in an expedited manner to all Investigators and IRBs.

Reporting of any SAEs to applicable regulatory authorities will be the responsibility of the Local Sponsor in compliance with local regulations.

12.8.3 Other Safety Findings Requiring Expedited Reporting

Significant safety findings will be reported to the Investigator by Principia or designee as obtained. The Investigator is responsible for reporting to the investigational site's IRB in accordance with their regulations. Reporting to applicable regulatory authorities will be the responsibility of Principia (or designee) in compliance with local regulations.

12.9 Pregnancy

Pregnancy in a Female Clinical Trial Participant: If a female clinical trial participant becomes pregnant during the study, she must be instructed to stop taking the study drug and immediately inform the Investigator. Pregnancies occurring up to 90 days after the completion of the study drug must also be reported to the Investigator. The participant should be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until the outcome of the pregnancy is known. The Investigator should report all pregnancies in clinical trial participants to the Sponsor within 24 hours of becoming aware of them, using the Clinical Trial Pregnancy Reporting Form.

Pregnancy in the Partner of a Male Clinical Trial Participant: If the Investigator becomes aware of a pregnancy occurring in the partner of a participant participating in the study, the pregnancy should be reported to the Sponsor within 24 hours working day of obtaining written consent from the pregnant partner. The Investigator will make arrangements for the pregnant partner to be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant partner should continue until the outcome of the pregnancy is known.

Note: The Pregnancy Reporting Form should only be completed by the Investigator if the pregnant partner has signed an Informed Consent Form "Information to Pregnant Partner of Participant."

13 DATA QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data, including data collection and management, will be described in the Data Management Plan.

Accurate and reliable data collection will be assured by verification and cross–check of the CRF against the Investigator's records by the study monitor (source document verification), and the maintenance of a study drug–dispensing log by the Investigator.

Data for this study will be recorded in the study Electronic Data Capture (EDC) CRFs. The data will be entered by the study center from the source documents into the CRF or will be loaded from electronic files (e.g., safety lab data). In no case is the CRF to be considered as source data for this study.

A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the Investigator. All discrepant data will be resolved in the EDC database and all data entered in the database will be independently compared with the original Investigator's records.

13.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned to the original terms recorded on the CRF, using the most up to date version of the MedDRA for AEs, diseases and surgical and medical procedures, and the WHODD for drug and herbal treatments.

14 ETHICAL ASPECTS

This section provides information for the Investigator on the ethics requirements for the study, including subject informed consent, IRB/EC review of the study and study materials, and conditions for modifying or terminating the study. Requirements for financial disclosure for the Investigator are also described.

14.1 Local Regulations/Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in current "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the participant.

14.2 Subject Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator [if acceptable by local regulations], to obtain signed and dated informed consent from each participant prior to participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. The Investigator or designee must also explain that the participants are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The CRFs for this study contain a field for documenting informed participant consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All participants should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

14.3 Institutional Review Board Review

This protocol and any accompanying material provided to the participant (such as participant information sheets or descriptions of the study used to obtain informed consent), as well as any advertising or compensation given to the participant, will be submitted by principal Investigator or coordinating Investigator to the relevant institutional IRB responsible for the investigational study.

An approval letter or certificate (specifying the protocol number and title) from the IRB must be obtained before starting the study (initiation). The approval letter to the Investigator should specify the date on which the committee met and granted the approval. The Local Sponsor must also obtain relevant regulatory authority approvals before starting the study.

Any modifications made to the protocol after receipt of the IRB approval must also be submitted by the principal Investigator or coordinating Investigator to the IRB in accordance with local procedures and regulatory requirements. The Local Sponsor must also obtain relevant regulatory

approval for protocol modifications according to the local regulations. The Local Sponsor will assist the Investigator in submitting the protocol to an appropriate IRB.

14.4 Conditions for Modifying the Protocol

Any protocol modifications must be prepared and approved by a representative of The Sponsor.

All protocol modifications must be submitted to the appropriate IRB for information and/or approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study participants, or when the change(s) involves only logistical or administrative aspects of the study [e.g., change in monitor(s), change of telephone number(s)].

14.5 Conditions for Terminating the Study

The Sponsor, the Investigator and the IRB responsible for the study reserve the right to terminate the study at any time. Should this be necessary, the parties will consult and arrange the termination procedures on an individual study basis. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the participant's interests. The appropriate IRB and Regulatory Agencies should be informed accordingly.

14.6 Financial Disclosure

The Investigator(s) will provide the Sponsor with sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The Investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last participant, last visit).

15 STUDY DOCUMENTATION, MONITORING, CASE REPORT FORMS, AND RECORD RETENTION REQUIREMENTS

15.1 Investigator's File/Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) participant clinical source documents.

The Investigator's Study File will contain the protocol/amendments, CRF data and Discrepancies, IRB and regulatory authority approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

Participant clinical source documents independent of the CRF would include participant hospital/clinic records, physician's and nurse's notes, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and participant screening and enrollment logs.

To comply with international regulations, the records should be retained by the investigator for 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 application in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. However, the investigator may need to retain these documents for a longer period if require by the local regulatory requirements or by agreement with the Sponsor.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the participant, appropriate copies should be made for storing outside of the site.

15.2 Source Documents and Background Data

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that participant confidentiality is protected.

15.3 Audits and Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Sponsor or its designees, or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

15.4 Case Report Forms

The data collected in the source documents for this study will be entered into the study EDC CRF. An audit trail will maintain a record of initial entries and changes made; time and date of entry; and name of person making entry or change. For each participant enrolled, a CRF must be completed and signed by the Principal Investigator or authorized delegate from the study staff. If a participant withdraws from the study, the reason must be noted in the CRF. If a participant is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

15.5 Study Monitoring

It is understood that the responsible Sponsor study monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (CRFs and other pertinent data) provided that participant confidentiality is maintained in accordance with local requirements.

It will be the monitor's responsibility to inspect the EDC CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the participant received the assigned dose. The monitor should have access to laboratory test reports and other participant records needed to verify the entries in the EDC CRF. The Investigator (or deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15.6 Confidentiality of Clinical Trial Documents and Participants' Medical Records

The Investigator must assure that participants’ anonymity will be maintained and that their identities are protected from unauthorized parties. In the EDC CRF or other documents submitted to the Sponsor, participants should not be identified by their names, but by an identification code.

The Sponsor already maintains rigorous confidentiality standards for clinical studies by “coding” (i.e. assigning a unique participant identification (ID) number at the Investigator site) all participants enrolled in Sponsor clinical studies. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

15.7 Clinical Study Report

A Clinical Study Report will be written and submitted to relevant IRB/HREC/EC and regulatory authorities in accordance with local requirements.

15.8 Publication of Data and Protection of Trade Secrets

It is anticipated that the results of this study may be published or presented at scientific meetings. Investigators cannot publish without prior written permission of the Sponsor. Authors must allow a reasonable period for manuscript review of at least 30 days. The Sponsor may delay publication for commercial reasons for up to 6 months.

16 STUDY ADMINISTRATIVE PROCEDURES

This section provides additional information on study-related administrative procedures, definitions, requirements, and record-keeping activities related to the study assessments described in Section 8.

16.1 Subject Recruitment Procedures

Participants will be identified for potential recruitment by the Investigator using recruitment plan agreed upon with Principia, possibly including, but not limited to, a listing from study center, volunteer database, newspaper/radio/internet advertisement, or mailing list.

16.2 Subject Enrollment Procedures

Participants cannot commence enrollment procedures until all entry criteria have been fulfilled. Where the clinical significance of an abnormal screening test result (lab or any other tests) is considered uncertain, the test may be repeated.

The Investigator or designee will enter data for each enrolled participant in the study CRF and enter the corresponding number for allocation to the treatment groups in the appropriate place on each participant's CRF. A participant enrollment and Identification Code List must be maintained by the Investigator or Pharmacist, or designee.

Under no circumstances will participants who enroll in this study and complete treatment as specified be permitted to re-enroll in the study.

16.3 Patient Premature Withdrawal – Definition

A patient who withdraws from the study before taking one or more doses of study drug is considered to have withdrawn from the study early.

16.4 Procedures for Patients Who Withdraw from the Study

Participants have the right to withdraw from the study at any time for any reason. In the event that a participant decides to discontinue from the study, he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF.

When applicable, participants should be informed of circumstances under which their participation may be terminated by the Investigator without the participant's consent. The Investigator may withdraw participants from the study in the event of intercurrent illness, AEs, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures or any other reasons where the Investigator feels it is in the best interest of the participant to be terminated from the study.

Reasons for withdrawal must be documented and explained to the participant. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible, particularly the follow-up examinations.

The Investigator should contact the participant or a responsible relative either by telephone (followed by registered mail) or through a personal visit to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the participant's withdrawal should be made, with an explanation of why the participant is withdrawing from the study. If the reason for removal of a participant from the study is an AE, the principal specific event must be recorded on the CRF. The participant should be followed until the AE is resolved, if possible.

16.5 Treatment Compliance

Accountability and participant compliance will be assessed by maintaining adequate study drug dispensing records and medication counts. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. See Section 10.4 for instructions on Drug Accountability procedures.

16.6 Recording of AEs on the CRF

All AEs encountered during the clinical study will be reported in detail in the source documents and documented in the CRF, from the date of participant consent throughout the follow-up visit. SAEs for which the relationship to test drug is considered "related", should be followed up until they have returned to the baseline status or stabilized. If the cause of the AE is established, it should be described in detail, including supporting information, in the source documents and on the CRF.

16.7 Physical Examination Procedures

At screening and follow-up visits, a complete physical examination will consist of checking the normality or abnormality of the following body systems: general appearance, skin, eyes, ears, nose, throat, heart, chest/breast, abdomen, neurological system, lymph nodes, spine and extremities (skeletal).

An abbreviated physical examination will consist of checking the normality or abnormality of the following body systems: general appearance, abdomen, and cardiorespiratory examination.

The results of the physical examination will be summarized as normal/abnormal. In case of abnormality, details will be recorded in the participant notes and in the CRF.

Height will be recorded at screening only.

16.8 Vital Signs Procedures

Blood pressure (BP), pulse rate, body temperature and respiratory rate will be recorded at the time points specified in the Schedule of Assessments (Appendix 4).

16.9 Body Weight

Body weight should be measured on the same digital clinic scale, after checking for accurate zero calibration each time. Weight is recorded in kg to one decimal place.

16.10 ECG Procedures

Single 12-lead ECG assessments will be obtained as specified in the Schedule of Assessments (Appendix 4) to confirm eligibility and to ensure real time safety evaluation of the participants in the study, as specified in the Schedule of Assessments. Unscheduled ECGs may be performed as clinically indicated and recorded in the eCRF.

Participants should be in a resting position for at least 10 minutes prior to any measurement. Body position should also be consistently maintained for each ECG evaluation. In particular, changes in heart rate should be avoided. There should be no environmental distractions (TV, radio, conversation) during the pre-ECG rest and the ECG recording time.

Heart rate (HR), QRS duration and respiratory rate (RR), and QT intervals will be recorded. Changes of the T-wave and U-wave morphology and overall ECG interpretation will be documented.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements.

For safety monitoring purposes, the Investigator must review, sign and date all ECG tracings. Paper copies will be kept at the study center with the participant's clinical file as part of the permanent record. The ECG intervals and interpretation will be recorded on the CRF.

16.11 Laboratory Test Procedures

The laboratory assessments will be performed at a central laboratory, with the provision for occasional local laboratory testing, if required. Laboratory safety tests shall be collected at time points specified in the Schedule of Assessments (Appendix 4).

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range, are considered to be clinically stable, and/or an adequate explanation of the abnormality is found.

16.11.1 Recording of Laboratory Test Results on the CRF

Results of clinical laboratory testing will be recorded on the CRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory, if applicable.

The procedures for the collection, handling and shipping of laboratory samples will be specified in the Sample Collection, Handling and Logistics Manual.

16.12 Recording of Concomitant Medications on the CRF

All medications (prescription and over-the-counter [OTC]) taken within 28 days prior to study screening (reference Exclusion Criteria, Item #5) will be recorded in the CRF.

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APPENDIX 1A CORTICOSTEROID RESCUE CRITERIA AND TREATMENT PROTOCOL (PART A)

Systemic corticosteroids will be avoided during PRN1008 monotherapy unless these rescue criteria are triggered, as described below, or if patients enter the study on low doses (≤ 0.5 mg/kg mg per day). In each rescue scenario, the recommended method of corticosteroid taper is shown in Appendix 7.

Rescue Criteria #1: Flare which, in the mind of investigator, is potentially life threatening

- Commence conventional immunosuppressive therapy and discontinue PRN1008

Rescue Criteria #2: Development of severe but not life-threatening PV (defined as PDAI score ≥ 45) at any time during PRN1008 therapy:

- If most recent BTK trough occupancy was 50% or more, commence conventional immunosuppressive therapy and discontinue PRN1008
- If most recent BTK trough occupancy was < 50% and PRN1008 dose has not been increased since last BTK assay, commence, or increase dose to, full-dose prednis(ol)one (1.0 mg/kg) orally and increase dose of PRN1008 by an amount agreed to with the Sponsor's Medical Monitor. At next review:
  - If not responding, commence conventional immunosuppressive therapy and discontinue PRN1008
  - If responding, maintain or taper corticosteroids as clinically appropriate while maintaining PRN1008 treatment
- If no BTK trough occupancy is available to guide therapy, maintain PRN1008, and commence, or increase to, full-dose prednis(ol)one (1.0 mg/kg) orally. Seek to expedite latest BTK trough occupancy test result or arrange for a new blood draw to measure BTK trough occupancy. At next review:
  - If not responding, commence conventional immunosuppressive therapy and discontinue PRN1008
  - If responding, maintain or taper corticosteroids as clinically appropriate while maintaining PRN1008 treatment (including adjust dose upwards if BTK trough occupancy < 50% in consultation with the Sponsor Medical Monitor)

Rescue Criteria #3: Patients with non-severe PV but who fail to achieve "Control of Disease Activity (CDA*)" by 4 weeks

- If most recent BTK trough occupancy was 50% or more, commence, or increase dose to, low dose prednis(ol)one (0.5 mg/kg) orally. Review after another ~2 weeks:
  - If not responding, commence conventional immunosuppressive therapy and discontinue PRN1008
  - If responding, maintain or taper corticosteroids as clinically appropriate while maintaining PRN1008 treatment
- If most recent BTK trough occupancy was < 50% and PRN1008 dose has not been increased since last BTK assay, increase dose of PRN1008 by an amount agreed to with the Sponsor's Medical Monitor. At review after another ~2 weeks:
  - If not responding, commence, or increase dose to, low-dose prednis(ol)one (0.5 mg/kg) orally and maintain PRN1008 treatment. If a dose of ≥ 0.5 mg/kg is already in use, or if after further review the patient is still not responding, commence conventional immunosuppressive therapy and discontinue PRN1008.
  - If responding, maintain PRN1008 treatment and consider tapering of prednis(ol)one

In each rescue scenario, the recommended method of corticosteroid taper is shown in Appendix 7.

When patients enter the study on corticosteroids, the dose should be maintained for the initial 2 weeks of PRN1008 therapy if possible in order to evaluate the additive effects of PRN1008. During this time and subsequently, the rescue criteria should be followed if indicated. In other words, in some circumstances the corticosteroid dose should be increased, with or without cessation of PRN1008. If patients respond well to PRN1008 without increasing the corticosteroid dose, the Werth taper (Appendix 7) should be commenced after four weeks of PRN1008 therapy.

*As defined by the EADV 2014 Pemphigus S2 Guideline (Hertl et al. 2015)

APPENDIX 1B CORTICOSTEROID RESCUE CRITERIA AND TREATMENT PROTOCOL (PART B)

Systemic corticosteroids will be avoided during PRN1008 monotherapy unless these rescue criteria are triggered, as described below, or if patients enter the study on low doses (≤ 0.5 mg/kg mg per day). In each rescue scenario, the recommended method of corticosteroid taper is shown in Appendix 7.

Rescue Criteria #1: Flare which, in the mind of investigator, is potentially life threatening

- Commence conventional immunosuppressive therapy and discontinue PRN1008

Rescue Criteria #2: Development of severe (defined as PDAI score ≥ 45) but not life-threatening PV or clinically significant worsening of already severe PV during PRN1008 therapy:

- Commence, or increase dose to, full-dose prednis(ol)one (1.0 mg/kg) orally and increase dose of PRN1008 by an amount agreed to with the Sponsor's Medical Monitor to a maximum of 600 mg bid. At next review:
  - If not responding, commence conventional immunosuppressive therapy and discontinue PRN1008
  - If responding, maintain or taper corticosteroids as clinically appropriate while maintaining PRN1008 treatment.

Rescue Criteria #3: Patients with non-severe PV but who fail to achieve "Control of Disease Activity (CDA*)" by 4 weeks

- If partially responding, increase dose of PRN1008 if not already maximal (Table 4), review in 1-2 weeks, and then consider additional CS up to a dose of 0.5 mg/kg. If subsequently responding, maintain PRN1008 treatment and taper prednis(ol)one.
- If not responding, increase dose of PRN1008 if not already maximal (Table 4), review in 1-2 weeks, and then consider additional CS up to a dose of 1.0 mg/kg. If subsequently responding, maintain PRN1008 treatment and taper prednis(ol)one.

Table 4 Dose Escalation Rules Part B

Current Dose	Inadequate Clinical Response[1] Dose-Escalation Rules
400 mg qd	Increase to 400 mg bid (allowed at Week 3 visit or later)[2]
400 mg bid	Increase to 600 mg bid (allowed at Week 5 visit or later)[2]
600 mg bid	No dose increase possible.

1. Investigator discretion: Generally, clinical response is shown by some improvement seen in first 2 weeks with CDA achieved by the Week 5 visit
2. Unless tolerability issues preclude dose-escalation

In each rescue scenario, the recommended method of corticosteroid taper is shown in Appendix 7.

When patients enter the study on corticosteroids, the dose should be maintained for the initial 2 weeks of PRN1008 therapy if possible in order to evaluate the additive effects of PRN1008. During this time and subsequently, the rescue criteria should be followed if indicated. In other words, in some circumstances the corticosteroid dose should be increased, with or without cessation of PRN1008. If patients respond well to PRN1008 without increasing the corticosteroid dose, the Werth taper (Appendix 7) should be commenced after four weeks of PRN1008 therapy.

* As defined by the EADV 2014 Pemphigus S2 Guideline (Hertl et al. 2015)

APPENDIX 2 STRONG AND MODERATE CYP3A INHIBITORS AND INDUCERS

	Strong	**Moderate**
3A Inducers	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin
3A Inhibitors	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, Seville orange juice, grapefruit juice, imatinib, verapamil

From: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. U.S. Food and Drug Administration.

APPENDIX 3 SENSITIVE CYP3A SUBSTRATES INCLUDING THOSE WITH NARROW THERAPEUTIC INDEX

3A Sensitive Substrate	Subset with Narrow Therapeutic Index
Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

From: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. U.S. Food and Drug Administration.

APPENDIX 4 SCHEDULE OF ASSESSMENTS

PART A: 12-WEEK TREATMENT/ 12-WEEK FOLLOW-UP:

	Screen	Day 1, Week 1 Pre-dose	Day 1 Week 1 Post-dose[g]	Day 2, Week 1[a]	Day 15, Week 3 +/- 3 days	Day 29, Week 5 +/- 3 days	Day 57, Week 9 +/- 7 days	Day 85, Week 13 +/- 7 days	Day 113, Week 17 +/- 7 days	Day 141, Week 21 +/- 7 days	Day 169, Week 25 +/- 7 days	Unscheduled Visit
Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Height	X											
Weight	X	X			X	X	X	X	X	X	X	X
Physical exam./med. History, PDAI and ABSIS	X											
Abbreviated physical exam, PDAI, ABSIS		X			X	X	X	X	X	X	X	X
ECG (12-lead)	X											(X)[b]
Vital Signs	X	X		X	X	X	X	X	X	X	X	X
Urinalysis	X											
Hep B & C, HIV, T-spot TB Test, QuantiFERON®-TB Gold, QuantiFERON®-TB Gold Plus (QFT Plus)	X											
Pregnancy test[c]	X	X				X	X	X			X	
Skin biopsy[d]	X											
Hem, Coag, Chem	X[e]	X			X	X	X	X				X
FSH[f]	X											
BTK occupancy sample		X[g]	X[h]	X	X	X	X	X				(X)[b]
PK sample		X	X[h]	X	X	X	X	X				(X)[b]
Anti-DSG antibodies		X				X	X	X	X	X	X	
Photography (Optional)[i]		X			X	X	X	X	X	X	X	X
ABQOL & TABQOL		X			X	X	X	X	X	X	X	X
SNAQ questionnaire		X			X	X	X	X	X	X	X	X
AEs		X		X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X
Drug dispensed		X				X	X					
Drug reconciliation					X	X	X	X				

Schedule of Assessments Footnotes:

a. Withhold PRN1008 on morning of Day 2 until PK/PD measurement has been taken as close to 12 hours after second dose as possible. Where follow-up on Day 2 is not possible, PK/PD samples may be taken on another day in the first week of treatment. On all other days, instruct patient to take PRN1008 in the morning as usual prior to clinic and take note of the time taken. Extra PK/PD sample intended for 1 to 5 days after dose adjustment or to replace missing samples–not required for other extra visits.

b. Only if clinically indicated.

c. For women of childbearing potential only. Serum pregnancy test done at screening, urine dip test done at other time points.

d. Performed only if no suitable prior biopsy.

e. TSH and CPK taken as part of chemistry panel.

f. To confirm postmenopausal status for women who are not surgically sterile only.

g. Two-8mL pre-dose blood tubes to be collected at baseline to ensure sufficient samples for later time point assay calculations.

h. 2 hours post-dose (+/- 15 mins)

i. Photography is used to document skin disease changes; ideally in most patients. Strict masking of patient identity is required.

PART B: SCHEDULE OF ASSESSMENTS (24-weeks Treatment/ 4-weeks Follow Up)

	Screen	Day 1, Week 1 Pre-dose	Day 1 Week 1 Post-dose[a]	Day 2, Week 1[g]	Day 15, Week 3 +/-3 days	Day 29, Week 5 +/-3 days	Day 57, Week 9 +/-7 days	Day 85, Week 13 +/-7 days	Day 113, Week 17 +/-7 days	Day 141, Week 21 +/-7 days	Day 169, Week 25 +/-7 days	Day 197, Week 29 +/-7 days	Unscheduled Visit
Informed Consent[k]	X												
Inclusion/Exclusion Criteria	X	X											
Height	X												
Weight	X	X			X	X	X	X	X	X	X	X	X
Physical exam/med.History PDAI, ABSIS	X												
Abbreviated physical exam., PDAI, ABSIS		X			X	X	X	X	X	X	X	X	X
ECG (12-lead)	X												(X)[b]
Vital Signs[j]	X	X		X	X	X	X	X	X	X	X	X	X
Urinalysis	X												
Hep B &C, HIV, T-spot TB Test, QuantiFERON®-TB Gold, QuantiFERON®-TB Gold Plus (QFT Plus)	X												
Pregnancy test[c]	X	X				X	X	X	X	X	X	X	
Skin biopsy[d]	X												
Hem, Coag, Chem	X[e]	X			X	X	X	X	X	X	X	X	X
FSH[f]	X												
BTK occupancy sample		X[g]	X[h]	X	X	X	X	X	X	X	X		(X) [b]
PK sample		X	X[h]	X[a]	X	X	X	X	X	X	X		(X) [b]
Anti-DSG antibodies		X				X	X	X	X	X	X	X	
Photography (Optional)[i]		X			X	X	X	X	X	X	X	X	X
ABQOL & TABQOL		X			X	X	X	X	X	X	X	X	X
SNAQ questionnaire		X			X	X	X	X	X	X	X	X	X
AEs		X		X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X	X
Drug dispensed		X				X	X	X	X	X			
Drug reconciliation					X	X	X	X	X	X	X	X	

Schedule of Assessments Footnotes:

a. Withhold PRN1008 on morning of Day 2 until PK/PD measurement has been taken as close to 12 hours (when *bid* dosing) or 24 hours (when q*d* dosing) after the prior dose as possible. Where follow-up on Day 2 is not possible, PK/PD samples may be taken on another day in the first week of treatment. On all other days, instruct patient to take PRN1008 in the morning as usual prior to clinic and take note of the time taken. Extra PK/PD sample intended for 1 to 5 days after dose adjustment or to replace missing samples–not required for other extra visits.

b. Only if clinically indicated.

c. For women of childbearing potential only. Serum pregnancy test done at screening, urine dip test done at other time points.

d. Performed only if no suitable prior biopsy.

e. TSH and CPK taken as part of chemistry panel.

f. To confirm postmenopausal status for women who are not surgically sterile only.

g. Two-8mL pre-dose blood tubes to be collected at baseline to ensure sufficient samples for later time point assay calculations.

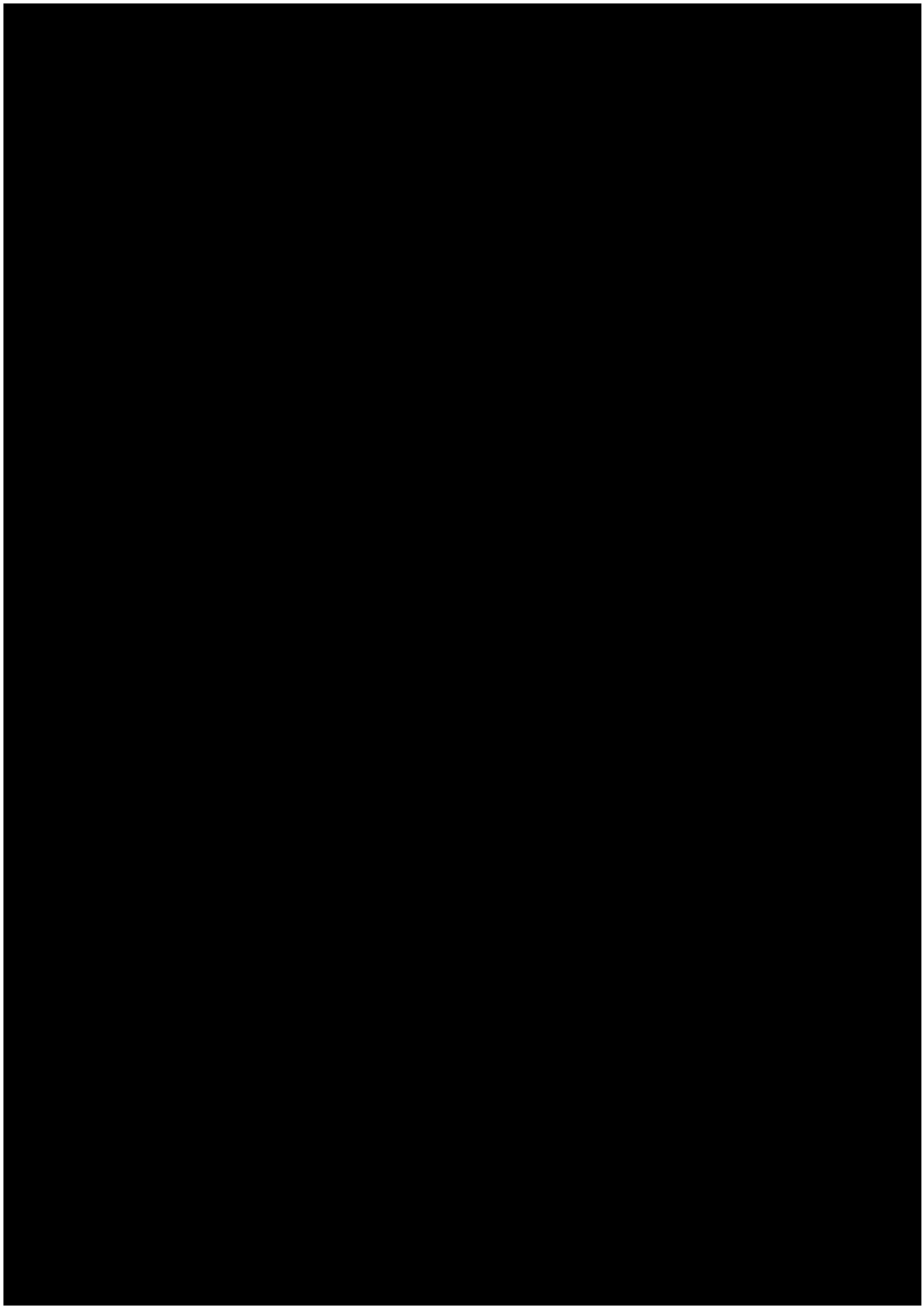
h. 2 hours post-dose (+/- 15 mins)

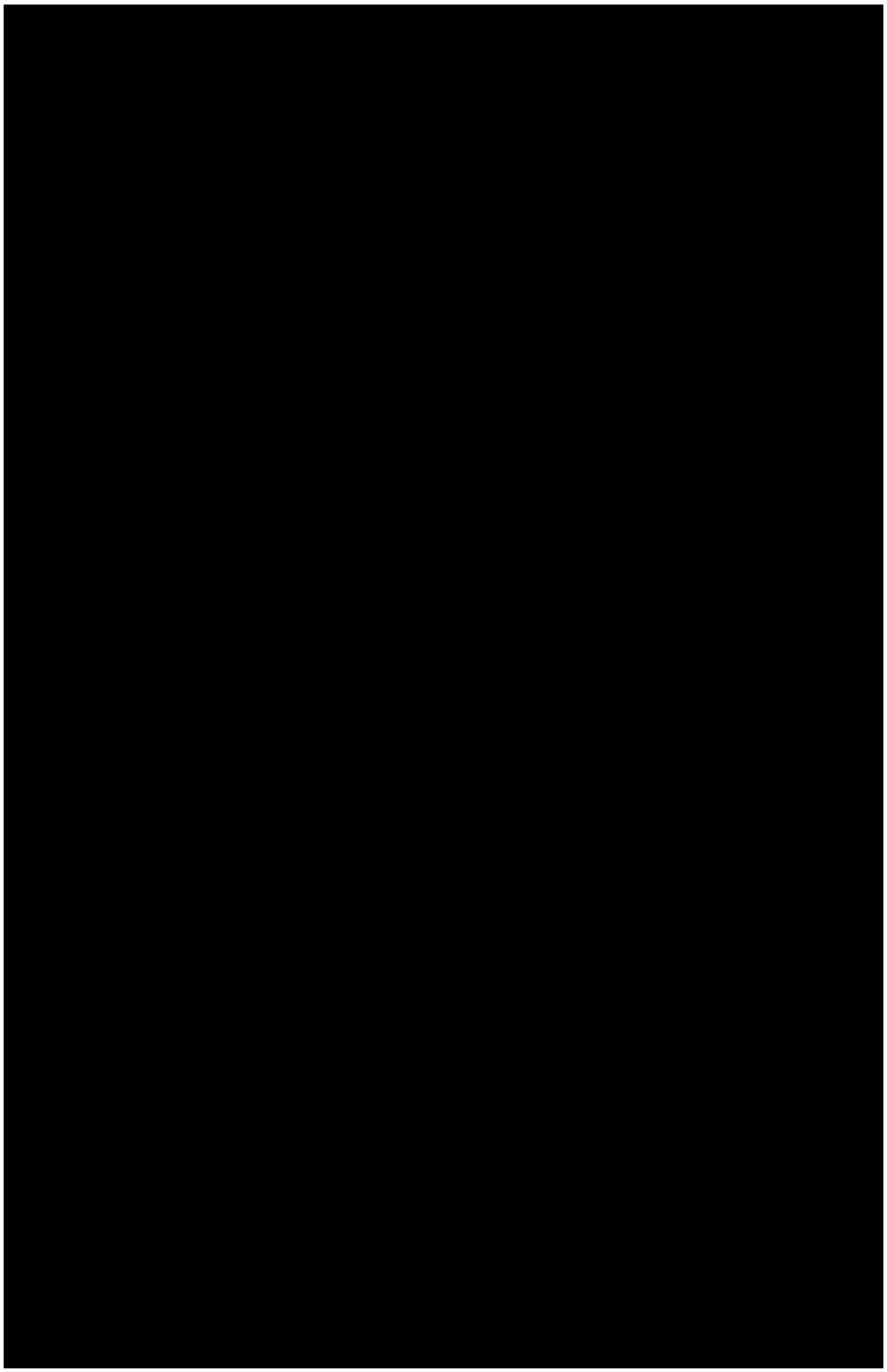
i. Photography is used to document skin disease changes; ideally in most patients. Strict masking of patient identity is required.

j. Vital sign include blood pressure (BP), pulse rate, body temperature and respiratory rate and are recorded at the time points specified

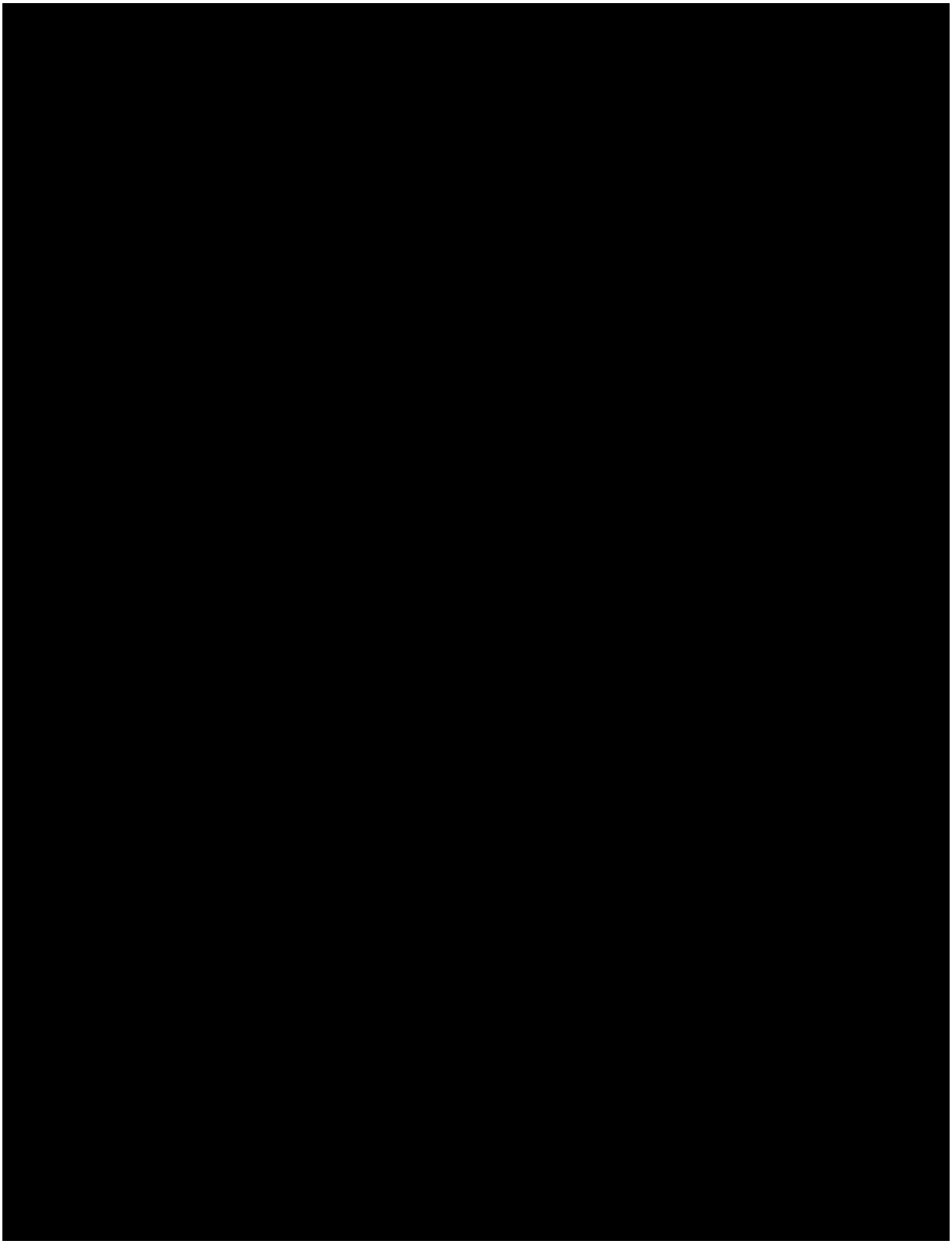
k. The Schedule of Assessments has been revised to be consistent with the 24 week treatment duration and 4 week safety follow up assessments described in this protocol Version 5, Part B. Patients enrolled in an earlier protocol version (Part A) who are in the active12-week treatment period are eligible to continue treatment, initially at their current dose, for up to a total of 24 weeks active treatment upon review and signature of the Part B EC approved Patient Informed Consent Form, with procedures and tests per this Schedule. Patients that have completed **Part A** of the trial are also eligible to be screened as a **Part B** patient, upon review and signature of the *Part B* EC-approved Patient Informed Consent Form.

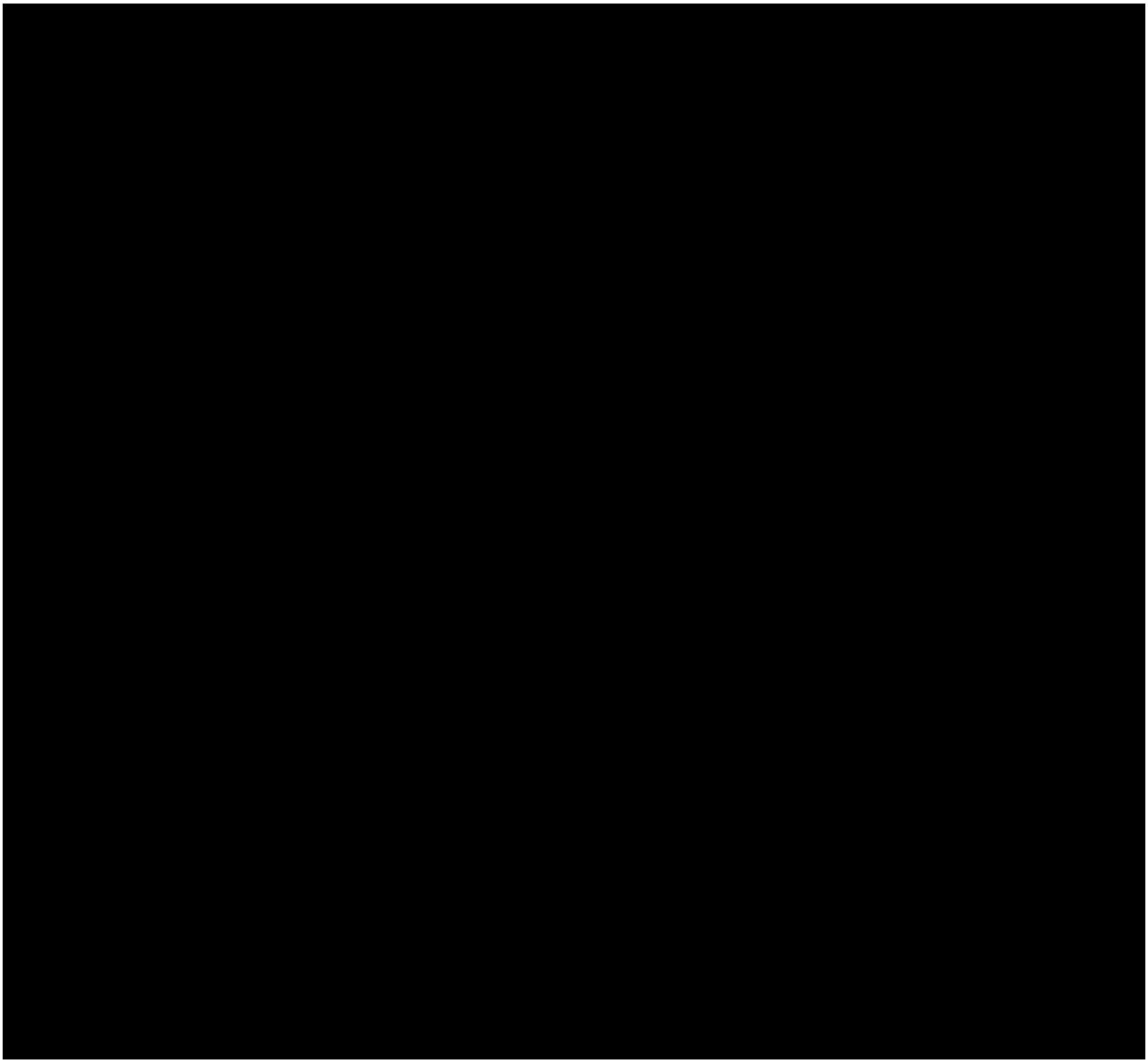
APPENDIX 5 PEMPHIGUS DISEASE ACTIVITY AND QUALITY OF LIFE EVALUATION INSTRUMENTS: ABQOL, TABQOL, PDAI, ABSIS





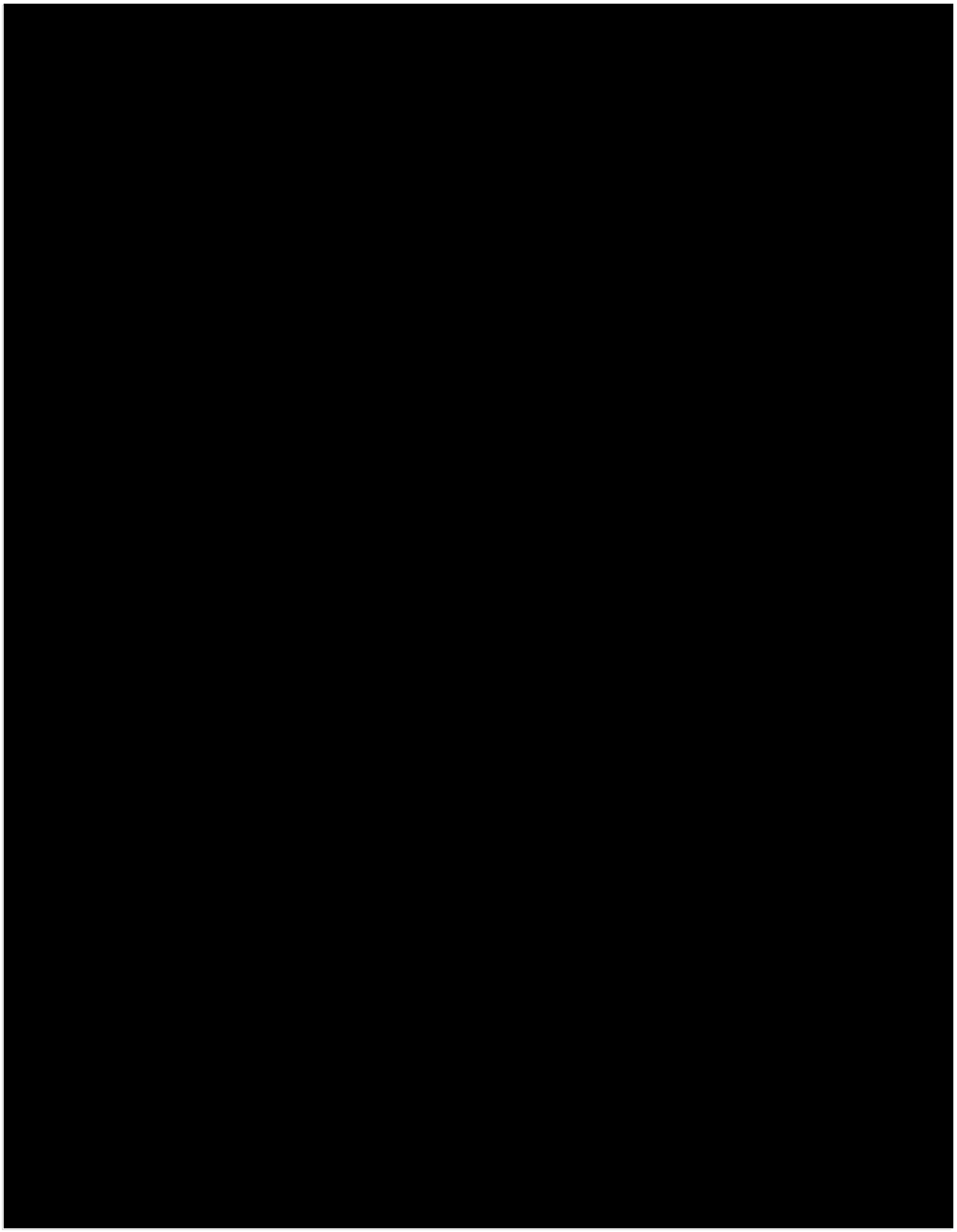
Treatment of Autoimmune Bullous Diseases Quality of Life Assessment (TABQOL)



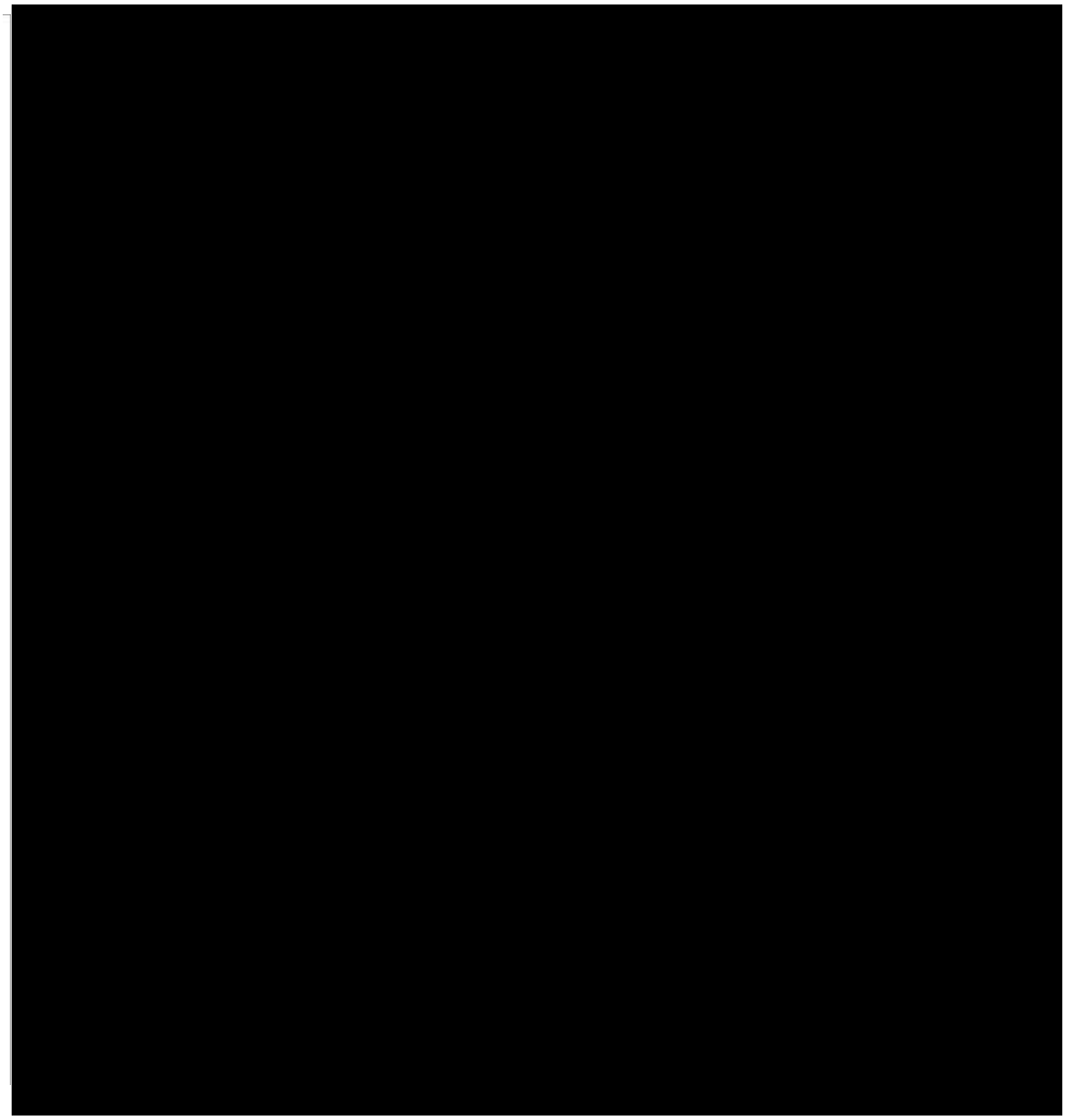


From: Tjokrowidjaja et al. 2013

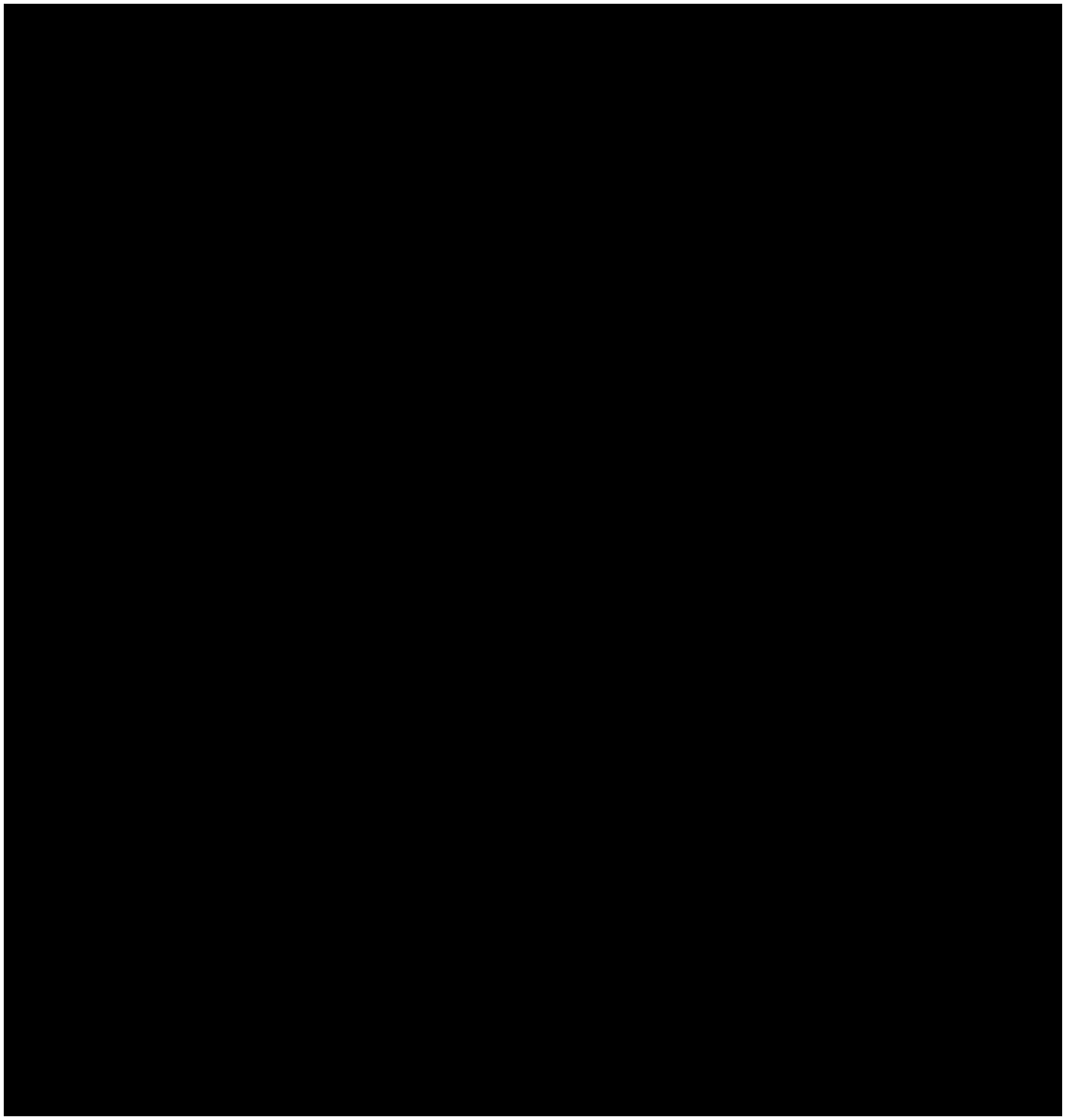
Pemphigus Disease Activity Index (PDAI) (Murrell et al. 2008)



Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) (Rosenbach et al. 2009)



APPENDIX 6 SIMPLE NUTRITIONAL APPETITE QUESTIONNAIRE (SNAQ)



From Wilson et al., 2005

APPENDIX 7 CORTICOSTEROID TAPER PROTOCOL

Maintain corticosteroid dose for 2 weeks after disease control has been achieved.

Subsequently, reduce the corticosteroid dose by 15% every three weeks.

-OR-

Table 1. Glucocorticoid Taper Schedules

Prednisone Dosage, mg/d × 7 d		
40	17.5	5
35	15	4
30	12.5	3
25	10	2
20	7.5	1
Prednisone, mg Every Other Day × 8 d[a]		
40-35	40-5	12.5-1
40-30	40-4	12.5-0
40-25	40-3	10-0
40-20	35-3	7.5-0
40-18	30-3	6-0
40-15	30-2	5-0
40-15	25-2	4-0
40-13	20-2	3-0
40-10	17.5-2	2-0
40-7.5	17.5-1	1-0
40-6	15-1	0

From: Werth et al. 2008