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
Sponsor:	Principia Biopharma Australia Pty Ltd Principia Biopharma Inc.

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GLOSSARY OF ABBREVIATIONS AND TERMS

ABBREVIATION OR TERM	DEFINITION
ABQOL	Autoimmune Bullous Diseases Quality of Life (assessment)
AE	Adverse event
Ae	Amount excreted unchanged in the urine
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
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
CDA	Control of disease activity
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
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for AEs
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
GLP	Good Laboratory Practice
H&E	Haematoxylin & eosin
H2	Histamine two (receptor)
HBsAg	Hepatitis B surface antigen
Hgb	hemoglobin
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
IMP	Investigational medicinal product

ABBREVIATION OR TERM	DEFINITION
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
MedDRA	Medical Dictionary for Regulatory Activities
N	Sample Size
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
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
QD	Once a day
QTc	QT interval corrected for heart rate
RBC	Red blood cell
RNA	Ribonucleic acid
RR	Resting Rate
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard Deviation
SI	Système international d'unités (International system of units)
SMC	Safety Monitoring Committee
SNAQ	Simplified Nutritional Appetite Questionnaire
SSR	Six-Month SUSAR Report
SUSAR	Suspected Unexpected Serious Adverse Reaction
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
ULN	Upper limit of normal
WBC	White blood cell
WHODD	World Health Organisation Drug Dictionary
XLA	X-linked agammaglobulinemia

1 OBJECTIVES OF THE STUDY

1.1 Primary Objectives

- To evaluate the clinical safety of PRN1008 in patients with PV over a 12-week 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

1.2 Secondary Objective

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

2 INVESTIGATIONAL PLAN

2.1 Overall Study Design and Plan

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

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 by Werth et al. 2008.

2.2 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).

2.3 Study Duration and Duration of Subject Participation

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).

2.4 End of Study Definition

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

2.5 PRN1008 Administration

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 2.6.

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.

2.5.1 Rationale for PRN1008 Dosage Selection

400 mg bid: 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. This dose level has adequate safety factors to exposures in chronic toxicology studies.

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.

2.5.2 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 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 and care should be taken with other drugs metabolized by the CYP3A.
- Clinically relevant 3A substrate drugs (e.g. "sensitive substrate") 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.

2.6 PRN1008 Intrapatient Dose Adjustment

Initial PRN1008 dosing will be 400 mg *bid*, with intrapatient dose adjustment based on clinical response and tolerability, supplemented by BTK occupancy (**Error! Reference source not found.**).

"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 1. 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.

3 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:

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.

4 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.

4.1 Inclusion Criteria

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 (PDAI 8 to 45) and mild-severe PV (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
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
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.

4.2 Exclusion Criteria

1. Previous use of a BTK inhibitor
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 within 3 days or 5 half-lives (whichever is longer) of study drug dosing
9. Use of CYP3A-sensitive substrate drugs 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

4.3 Prior and Concomitant Therapy

4.3.1 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

4.3.2 Concomitant Therapy

Not Permitted:

- Concomitant use of immunosuppressant medication, other than low-dose corticosteroids, unless rescue criteria are triggered.
- Concomitant use of known strong to moderate inducers or inhibitors of CYP3A within 14 days or 5 half-lives (whichever is longer) of dosing with PRN1008.

- Use of CYP3A-sensitive substrate drugs 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 (Werth et al. 2008). At all times, the rescue criteria should be followed, as indicated by Werth et al. 2008. 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”) 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.

5 LIST OF SCREENING ASSESSMENTS

The Schedule of Assessments is presented in Appendix 1. 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 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

6 LIST OF STUDY ASSESSMENTS

The Schedule of Assessments is presented in Appendix 1.

6.1 Clinical Assessments

- 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) (Murrell et al. 2008)
- Standardized photography of the affected area (Optional)
- Autoimmune Bullous Diseases Quality of Life (ABQOL) assessments
- SNAQ appetite questionnaire (Wilson et al. 2005)

6.2 Laboratory Assessments

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

6.3 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 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.

7 STUDY TREATMENT

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.

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

8 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.1 Primary Outcome Measures

8.1.1 Safety

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

8.1.2 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.

8.2 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
- 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
- Time to CDA
- Time to CR
- Time to relapse after PRN1008 treatment discontinuation
- Cumulative corticosteroid usage over the first 12 weeks
- Change from baseline in Pemphigus Disease Area Index (PDAI) scores at each follow-up visit
- Change from baseline in Autoimmune Bullous Diseases Quality of Life (ABQOL) 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

8.3 PK/PD Outcome Measures

8.3.1 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

8.3.2 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

8.4 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 will result in an 80% CI of ± 13%. Results from this pilot study will be used to design confirmatory clinical trials.

8.5 Analysis Populations

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

8.5.1 Screening Population

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

8.5.2 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.

8.5.3 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 and ABQOL, scores. Efficacy data will be presented in listings by subject and tabulated for each efficacy endpoint. Additional sub-group analyses (e.g. disease severity, dose group) may be performed as appropriate.

8.5.4 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.

8.6 Randomization and Blinding Procedures

Not applicable; the study is open-label.

8.7 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.

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

8.8.1 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.

8.8.2 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.

8.8.3 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.

8.9 Efficacy Analysis

8.9.1 Subject Response and Disease Progression

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

8.10 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.

8.10.1 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.

8.10.2 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.

8.10.3 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.

8.10.4 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.

8.11 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.

8.11.1 Missing PK/PD Values

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

8.12 Statistical and Analytical Methods

8.12.1 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.

8.12.2 Exploratory Analyses

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

8.12.3 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 (Study PRN1008-005 Interim Analysis Report).

9 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.

9.1 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.

9.2 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.

9.3 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.

9.4 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.

9.5 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

9.6 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.

9.7 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.

9.7.1 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.

9.8 Serious Adverse Event (SAE) Reporting

9.8.1 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.*

9.8.2 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.

9.8.3 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.

9.9 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."

10 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.

10.1 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.

10.2 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.

10.3 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.

10.4 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)].

10.5 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.

11 REFERENCES

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APPENDIX 1 SCHEDULE OF ASSESSMENTS

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.