NCT03762265

PRINCIPIA BIOPHARMA
A SANOFI COMPANY

# AMENDED CLINICAL TRIAL PROTOCOL 07

| | |
|---|---|
| **Protocol title:** | **A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial to Evaluate the Efficacy and Safety of Oral BTK Inhibitor Rilzabrutinib (PRN1008) in Moderate to Severe Pemphigus** |
| **Protocol number:** | **PRN1008-012** |
| **Amendment number:** | **07** |
| **Compound number (INN/Trademark):** | **PRN1008 (rilzabrutinib)** |
| **Brief title:** | **PEGASUS Pivotal Study** |
| **Study Phase:** | **3** |
| **Sponsor name:** | **Principia Biopharma Inc.** |
| **Legal registered address:** | **220 E Grand Avenue South San Francisco CA 94080, USA** |
| **Monitoring team's representative name and contact information:** | |

**Regulatory agency identifier number(s):**

| | |
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| Other | Not applicable |

Date: 30-Aug-2021 Total number of pages: 267

**PROTOCOL AMENDMENT SUMMARY OF CHANGES**

# DOCUMENT HISTORY

| Document | Country/Countries impacted by amendment | Date, version |
|---|---|---|
| Amended Clinical Trial Protocol 07 | All | [30 Aug 2021], version 1 (electronic 4.0) |
| Amended Clinical Trial Protocol 06 | All | [06 May 2021], version 2 (electronic 3.0) |
| Amended Clinical Trial Protocol 06 | All | [01 April 2021], version 1 (electronic 2.0) |
| Clinical Study Protocol Version 5.2 | UK only | [21 December 2020] |
| Clinical Study Protocol Version 5.2 | Germany only | [30 November 2020] |
| Clinical Study Protocol Version 5.1 | UK only | [22 June 2020] |
| Clinical Study Protocol Version 5.1 | Germany only | [19 May 2020] |
| Clinical Study Protocol Version 5 | All | [22 January 2020] |
| Clinical Study Protocol Version 4.1 | US only | [04 December 2019] |
| Clinical Study Protocol Version 4.1 | Germany only | [30 September 2019] |
| Clinical Study Protocol Version 4 | All | [29 August 2019] |
| Clinical Study Protocol Version 3.2 | Germany only | [22 May 2019] |
| Clinical Study Protocol Version 3.1 | Germany only | [01 May 2019] |
| Clinical Study Protocol Version 3.1 | Canada only | [24 April 2019] |
| Clinical Study Protocol Version 3 | All | [9 October 2018)] |
| Clinical Study Protocol Version 2 | US only | [12 September 2018] |
| Clinical Study Protocol Version 1 (original) | All | [04 June 2018] |

Note: The name and numbering of the protocol is based on a new numbering system followed by the Sponsor.

**Amended Clinical Trial Protocol 07 (30 Aug 2021)**

This is a global amendment to Amended Clinical Trial Protocol 06 and is considered to be substantial. No changes to protocol procedures are included in this global amendment.

# OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment to Protocol PRN1008-012 are:

- Change corticosteroid dose criterion to ≤10 mg/day and modify key secondary endpoints to align with FDA comments
- Address statistical analysis of clinical assessments impacted by the COVID-19 pandemic including those performed remotely

**Protocol amendment summary of changes table**

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 1.1 Synopsis: Outcome Measures, Section 1.2 Schema Figure 1: Study Design Flow Chart, Section 3 Objectives and Endpoints, Section 9.1 Sample Size Determinatinon, Section 9.3.5 Efficacy analysis (mITT Population) | CS dose criterion for primary efficacy endpoint changed from ≤5 mg/day to ≤10 mg/day | Align with recommendations from FDA |
| Section 1.1 Synopsis: Outcome Measures, Section 3 Objectives and Endpoints, Section 9.1 Sample Size Determinatinon, Section 9.3.6 Key Secondary Efficacy Sequential Testing | Changed the following endpoints from Key Secondary Endpoints to Other Secondary Endpoints:<br>• Proportion of patients with at least one disease relapse/flare from initial control of disease activity (CDA) to Week 37<br>• Cumulative duration of CR with a CS dose ≤10 mg/day, from Week 37 to Week 61<br>• Cumulative duration of CR with a CS dose = 0 mg/day, from Week 37 to Week 61 | Align with comments from FDA |
| Section 1.1 Synopsis: Outcome Measures, Section 3 Objectives and Endpoints | Changed CS dose criterion for proportion of patients who are in CR from Week 29 to Week 37 from ≤10 mg/day to ≤5 mg/day. | Align with change to CS dose criterion for the primary efficacy endpoint |
| Section 9.2 Populations for Analyses | Removes statement that the ITT Population will be used for sensitivity analyses | Correction |
| Section 9.3.5 Efficacy Analysis (mITT population) | Clarified handling of clinical efficacy data collected in-person or remotely in analysis | Align with recommendations from FDA |
| Section 9.3.5 Efficacy Analysis (mITT population) | Deleted the last sentence in the following paragraph: Patients who drop out of the trial, withdraw, or who receive a rituximab dose prior to Week 37 will count as non-responders in the analysis. ~~Additional sensitivity analyses, including adjusting for severity, will be described in the SAP.~~ | Correction |
| Section 9.3.5 Efficacy Analysis (mITT population) and Section 9.3.6 Key Secondary Efficacy Sequential Testing | Moved statement regarding proportion of patients with at least one disease relapse/flare from initial CDA to Week 37 from Key Secondary to Other Secondary | Align with changes to Key Secondary and Other Secondary endpoints |
| Section 9.3.5 Efficacy Analysis (mITT population) | Deleted timepoints from the cumulative duration of CR analysis: Cumulative duration of CR with CS dose ≤ 10mg/day from Baseline to Week 37~~, from Week 37 to Week 61, and cumulative duration of CR with CS dose = 0 mg/day from Week 37 to Week 61~~ will be analyzed using a zero-inflated negative binomial model with terms for treatment group and disease history. | To align with the SAP |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 9.3.6 Key Secondary Efficacy Sequential Testing | Replaced the leading sentence to: After testing the primary endpoint in the PV mITT population and the mITT population (i.e. PV+PF population), key secondary efficacy endpoints will be tested sequentially, first on the PV mITT population in the order specified below, and then on the mITT population in the same order:<br>The following sentence was revised to: The proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤10 mg/day of CS at any time will be **compared using the same method as the primary endpoint**. | Revised for clarity/accuracy |
| Section 9.3.9 Long Term Extension Analysis | Deleted the following sentence: The number of received doses and treatment duration will be described. | To align with the SAP |
| Section 9.3.10 | First sentence was revised to: Missing data will not be imputed except for the situations described in the SAP. ~~As a general strategy, missing data will not be imputed in this trial.~~ Details on the handling of missing data**, including missing data due to the COVID-19 pandemic,** will be described in the SAP. | To align with the SAP |

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# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

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| **Protocol Title**<br>A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial to Evaluate the Efficacy and Safety of Oral BTK Inhibitor Rilzabrutinib (PRN1008) in Moderate to Severe Pemphigus |
| **Protocol Number**<br>PRN1008-012 |
| **Sponsor**<br>Principia Biopharma Inc. |
| **Trial Medication**<br>The investigational drug product is PRN1008 (Rilzabrutinib) in combination with tapering doses of oral corticosteroid (CS, [prednisone or prednisolone]). |
| **Phase**<br>This is a Phase 3 pivotal study. |
| **Study Population**<br>Approximately 120 male or female patients with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]) will be enrolled with a targeted minimum of 90 patients with PV, and a target maximum of 22 patients with PF. |
| **Duration of Trial Participation**<br>For each patient, the trial will last approximately 68 weeks including Screening Period (up to 4 weeks), the Blinded Treatment Period (Week 1 through Week 37), the Open-Label Extension Period (Week 37 to Week 61), and a 4-week end of treatment follow-up (up to Week 65).<br>Long Term Extension Period<br>Study duration for the patients who enter the Long Term Extension Period will be determined by the criteria described in the Study Design of the Study Synopsis. |
| **Number of Study Sites**<br>Approximately 100 sites worldwide. |

**Outcome Assessment Definitions (Consensus Guidelines)** (1)

***Control of Disease Activity (CDA):***

Control of disease activity (disease control) is defined as the visit at which new lesions cease to form and established lesions begin to heal. This is also considered the beginning of the consolidation phase. The expected interval of time to reach the control of disease activity is on the order of weeks, although it may be shorter.

***End of Consolidation Phase (ECP):***

The end of the consolidation phase is defined as the visit at which no new lesions have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions have healed. Therefore, in order to achieve ECP, CDA must be confirmed at a visit ≥2 weeks later and 80% of the lesions seen previously must have healed.

***Complete Remission (CR):***

Complete remission is defined as the absence of new and established lesions and is intended to mean "no disease activity". Various qualifying statements are added to this definition for endpoints in this protocol.

***Relapse/Flare:***

A relapse of disease and a flare of disease are synonymous. They are defined by the appearance of 3 or more new lesions after CDA and within a month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved CDA.

**Objectives**

**Efficacy Objectives**

- To evaluate the efficacy of rilzabrutinib in achieving durable CR on low to zero doses of oral corticosteroid (CS) and on the timecourse of quantitative disease activity scores
- To assess the ability of rilzabrutinib to reduce CS exposure and the adverse effects of CS
- To evaluate the time to specified clinical endpoints
- To assess the longer term durability of CR

**Safety Objectives**

- To evaluate the safety of rilzabrutinib
- To evaluate differences in potentially CS-related adverse events

**PK/PD Objectives**

- To evaluate the pharmacokinetics (PK) of rilzabrutinib
- To evaluate pharmacodynamic (PD) effects of rilzabrutinib on anti-desmoglein (anti-dsg) autoantibody titers (anti-dsg1 and anti-dsg3)

**Exploratory Objectives**

- To evaluate the PK of rilzabrutinib metabolites
- To examine the effects of rilzabrutinib if any, of the baseline covariates on PK and/or PD, and the relationship between PK, PD, and efficacy
- To explore association of vaccine response with rilzabrutinib
- To examine the effect of rilzabrutinib on the costs of hospitalizations, outpatient medical visits, adverse events, concomitant medication use, and other relevant health economic outcomes
- To examine the temporal relationship of change from baseline in Pemphigus Disease Area Index (PDAI) total activity score and quality of life and health economic measures

**Long Term Extension Objective**

- To evaluate the long-term safety and efficacy of rilzabrutinib.

## Investigational Plan

### Study Design

This is a randomized, parallel-group, double-blind, placebo-controlled trial with 36 weeks of treatment during a Blinded Treatment Period followed by an Open-Label Extension Period of 24 weeks. After completing the Open-Label Extension Period, eligible patients may continue in the Long Term Extension Period of 48 weeks. Patients will continue to have a 4 week follow-up visit after the patient's last dose of rilzabrutinib as detailed in the End of Trial (Follow-up Period, 4 Weeks after last Trial Dose) Section below.

### Blinded Treatment Period (Weeks 1 to 37):

**Table 1: Definitions of Moderate to Severe Population and Starting CS doses**

| | PDAI entry criteria | Required CS dose starting at Screening[a] |
|---|---|---|
| Newly diagnosed (diagnosed ≤ 6 months prior to Screening) | PDAI ≥ 15 | ≥ 0.5 mg/kg/day |
| Relapsing, chronic (diagnosed > 6 months prior to Screening) | PDAI ≥ 9 | ≥ 0.2 mg/kg/day |

*a* Doses shown above are minimum requirements. Actual doses will be determined by Investigator judgment.

After informed consent is obtained, patients with moderate to severe pemphigus (PV and PF) will be screened and if eligible will be randomized in a 1:1 allocation ratio to receive either rilzabrutinib 400 mg twice daily (bid) (n ~ 60) or placebo bid (n ~ 60) during the Blinded Treatment Period (Week 1 to Week 37).

At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, shown in Table 1 above, and as required to adequately treat the disease. CS doses may be adjusted per Investigator discretion during the Screening period (Appendix 1 Section 12.1) but the dose should not be reduced below the required minimum initial dose levels (Table 1) (2, 3). CS taper below the required minimum dose level should not begin until ECP has been achieved.

Rilzabrutinib (400 mg tablet) or placebo will be taken twice daily by mouth starting on Day 1. Tablets may be taken with or without food.

If a patient achieves CDA (no new lesions and established lesions begin to heal), a follow-up visit ≥2 weeks later must confirm the finding of no new lesions prior to declaring ECP and tapering CS. ECP is achieved with the confirmation of CDA (no new lesions for ≥2 weeks) with approximately 80% of the established lesions epithelialized (healed). If needed, confirmation of CDA and achievement of ECP may be documented at an Unscheduled Visit, prior to the next scheduled study visit. See Table 2 for all required assessments for an Unscheduled Visit, which also includes Efficacy Outcome Assessment and PDAI.

While continuing on rilzabrutinib or placebo, following the achievement of ECP, patients will undergo a moderately rapid CS taper regimen as recommended by recently published consensus guidelines (1) with the goal to reduce the CS dose to 5 mg/day by no later than

Study Week 29, with CS dose-adjustment as clinically indicated to control disease (CS and Rituximab Management protocol, Appendix 1 Section 12.1).

CS taper should not begin until ECP has been achieved.

If the first documentation of CDA coincides with no disease activity (PDAI = 0), a follow-up visit ≥2 weeks later must still confirm that no new lesions are seen and PDAI = 0. At this time the patient is deemed to have confirmed CDA, ECP, and CR and therefore CS tapering can begin. If new lesion(s) are seen, the patient is no longer in CDA and therefore CS tapering should not begin. If a patient has not achieved CDA or new lesions emerge or existing lesions worsen but do not meet definition of relapse/flare, refer to Appendix 1 Section 12.1 regarding increasing steroid dosage.

Throughout the Blinded Treatment Period, patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1 Section 12.1) until CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The Principal Investigator (PI) should consult with the Medical Monitor in such cases.

Efficacy Outcome Assessment should be performed per the Efficacy Outcome Assessment Flowchart, Appendix 8 Section 12.8.

Once patients achieve CR on a dose of 5 mg/day of CS, that dose should be maintained (not tapered further) until Study Week 37 (time of primary endpoint).

Rituximab treatment may be administered during the Blinded Treatment Period at or after the Week 5 Visit, only after a second “qualifying relapse/flare” occurs, unless contraindicated (Appendix 1 Section 12.1).

If rituximab is administered, patients should continue to take rilzabrutinib/placebo, remain on trial and blinded to treatment assignment. After completing the Blinded Treatment Period, patients will enter the Open-Label Extension Period to receive active treatment with rilzabrutinib described below. A patient in the Blinded Treatment Period requiring an additional “top up” dose of rituximab after their initial rituximab course of treatment must be discontinued from the trial.

**Open-Label Extension Period (Weeks 37 to 61):**

From Week 37, all patients will receive active drug in the Open-Label Extension Period for 24 weeks per Table 3. Patients who received placebo will thus receive active treatment with rilzabrutinib 400 mg bid. Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse/flare during this period, must be discontinued from the study. If a patient has a qualifying relapse/flare during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period, the patient may continue in the trial.

Patients that received rituximab during the Blinded Treatment Period and are continuing in the study, will complete TBNK testing (T and B and Natural Killer Lymphocyte Panel) at their Week 37 Visit.

From Week 37 (time of primary endpoint), further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated. Patients who fail to respond to treatment or experience worsening of disease should have their CS dose increased per CS management guidelines (Appendix 1 Section 12.1) until CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor in such cases.

**Long Term Extension (LTE) Period (Week 61 to Week 109):**

After completing the Open-Label Extension Period, patients who are responding to rilzabrutinib treatment will be eligible to enter the Long Term Extension Period and will continue to receive open-label rilzabrutinib 400 mg bid for 48 weeks per Table 4.

Patients are eligible to participate in the LTE if:

a) they have achieved and/or maintained an ECP with ≤10 mg/day CS at any time between 37 and 61 weeks in the study.

Patients are not eligible to participate in the LTE if:

a) they have more than one relapse/flare following ECP requiring treatment with >10 mg/day CS (excluding CS taken short-term for dental work or surgery), or
b) have failed to adequately recover after a relapse/flare despite maximal tolerated CS dose.

Failure to adequately recover is defined as: <25% decrease from peak PDAI despite treatment with maximal steroid doses (minimum of 1.5 mg/kg/day unless there is a specific documented medical contraindication) for at least 2 weeks.

CS doses above refer to doses of prednisone or its equivalent.

Patients may continue in the LTE until:

a) they have had more than one relapse/flare following ECP that requires >10 mg/day CS (excluding CS taken short-term for dental work or surgery) or have failed to adequately recover after a relapse/flare despite maximal tolerated CS dose (per definition of failure to adequately recover above);
b) the drug is no longer being developed by the Sponsor for this indication;
c) the program is stopped for safety reasons.

Patients who have previously completed the Open-Label Extension Period prior to this amendment and were responders per the LTE requirement may enroll into the LTE.

Patients entering the LTE will receive Sponsor-provided CS, following CS Management Guidelines (Appendix 1 Section 12.1).

Patients requiring rituximab during the Long Term Extension Period will be discontinued from the trial.

**End of Trial (Follow-up Period, 4 Weeks after last Trial Dose):**

End of Trial (EOT) for the overall clinical trial is defined as the point at which the last patient has completed the last visit of the study.

For patients eligible for the Long Term Extension, the EOT is defined as the point at which the patient has completed their Week 113 Visit (4 weeks after the patient's last dose of rilzabrutinib).

For patients that are not eligible for the Long Term Extension, the EOT is defined as the point at which the patient has completed their Week 65 Visit (4 weeks after the patient's last dose of rilzabrutinib).

Patients who are not able to complete the Blinded Treatment Period, Open-Label Extension Period or Long Term Extension Period as planned and discontinue the study early should be encouraged to come back for an Early Termination (ET) Visit as soon as possible. Patients that discontinue early will have the ET assessments completed as outlined in the Schedule of Assessments based upon from which phase treatment they are terminating, Table 2 (Blinded Treatment Period), Table 3 (Open-Label Extension Period), or Table 4 (Long-Term Extension Period).

In addition to the ET Visit, patients should return for the EOT Visit 4 weeks following their last dose of rilzabrutinib/placebo or rilzabrutinib.

In the event the ET Visit occurs ≥4 weeks after their last dose of rilzabrutinib/placebo or rilzabrutinib, this will be recorded as the ET Visit and there is no need for the 4-week safety follow-up (EOT) Visit.

**Urgent Safety Measures Initiated Due to Coronavirus disease 2019 (COVID-19) Pandemic:**

Each participating site, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and drug regulatory authority was informed of urgent safety measures implemented to ensure continued supply of study medication and safety monitoring for patients. These measures are described in the "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits Due to Travel Restrictions and Any Foreseeable Impacts of COVID-19" (Appendix 9 Section 12.9). When the COVID-19 pandemic resolves, the measures will be repealed back to the previous state as government rules and benefit/risk assessment allow.

**Study Assessments Overview:**

See Schema in Section 1.2.

Figure 1 for a diagram of the study design and the Schedules of Assessments (Table 2, Table 3, and Table 4) and for description of the assessments.

**Corticosteroid Management** (Appendix 1 Section 12.1)

**Corticosteroid Starting Doses and Management During Screening and at Day 1**

Required initial doses of CS for the duration of Screening are ≥0.2 mg/kg/day of CS for patients with relapsing disease (diagnosed >6 months prior to Screening) and ≥0.5 mg/kg/day for patients with newly diagnosed disease (diagnosed ≤6 months prior to Screening).
At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, and as required to adequately treat the disease during the Screening period. CS doses may be adjusted per Investigator discretion during the Screening period (Appendix 1 Section 12.1) but the dose should not be reduced below the required minimum initial dose levels (Table 1). CS taper below the required minimum dose level should not begin until ECP has been achieved.

If disease significantly (Investigator judgment) worsens during the Screening period, up-titration of CS dose by 50-100% should occur, as often as every 5-7 days if needed (4).

**Corticosteroid Management during Blinded Treatment Period, Open-Label Extension Period, and Long Term Extension Period**

**Corticosteroid-Tapering (Consensus Guidelines)** (1)

CS will be tapered from ECP towards a goal of 5 mg/day by ≤Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. From Week 37, further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated. At Investigator discretion, the CS may be switched to equivalent doses of oral hydrocortisone instead of prednisone or prednisolone when tapering from 5 mg to 0 mg CS.

CS tapering should follow the modified dosing guidelines below (1):

Adjustment of the dosing guideline protocol by investigators is permitted for safety reasons, based on assessment and documentation of clinical need.

- Start tapering CS as soon as ECP is confirmed.
- Decrease CS by 25% every two weeks, until 20 mg per day
- Once at 20 mg per day, decrease CS by 2.5 mg per week
- Once at 10 mg/day, decrease CS by 1 mg per week

Note, because 1 mg will be the smallest CS dosage provided and tablet splitting is not allowed, the Investigator must round up or down to the nearest whole milligram for CS dose after calculation of the new dose level.

**Corticosteroid-Up-Titration** (4)

Patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1 Section 12.1 ) until CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor in such cases.

For full details of up-titration see Appendix 1 Section 12.1.

**Concomitant Medications**

Strong to Moderate Inducers or Inhibitors of cytochrome P450 (CYP)3A, and "Sensitive" CYP3A Substrate Drugs with a narrow therapeutic index are not permitted (Appendix 7 Section 12.7).

Other "Sensitive" CYP3A drugs should be used cautiously by administering them only if the benefit/risk is favorable, using staggered administration at least 2 hours after rilzabrutinib or placebo.

Patients on proton pump inhibitor drugs should have their medication changed to histamine 2 (H2) blockers during Screening and at least 3 days before Day 1. H2 blockers should be administered at least 2 hours after rilzabrutinib or placebo.

**Inclusion Criteria**

Patients may be included in the study if ALL of the following criteria are met:

**Type of participant and disease characteristics**

I01. Male or female patients, aged 18 to 80 years old with moderate to severe, newly diagnosed or relapsing PV or PF, with a clinical presentation and histopathology consistent with PV or PF (see Section 8.4.3).

I02. Positive circulating anti-dsg1 or 3 autoantibody titer.

I03. At Screening, PDAI score of at least 9 points for relapsing patients (diagnosed >6 months prior to Screening) or at least 15 points for newly diagnosed patients (diagnosed ≤6 months prior to Screening).

I04. Adequate hematologic, hepatic, and renal function (including but not limited to absolute neutrophil count $\geq 1.5 \times 10^9$/L, hemoglobin [Hgb] >9 g/dL, platelet count $\geq 100 \times 10^9$/L, aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] ≤1.5 × upper limit of normal [ULN], albumin ≥3 g/dL, creatinine ≤1.5 × ULN).

**Sex, contraceptive/barrier method and pregnancy testing requirements**

I05. Female patients who are of reproductive potential must agree for the duration of the study to use an effective means of contraception (eg, hormonal contraception methods that inhibit ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or condoms).

For females considered not to have reproductive potential:

Any woman of age ≥55 years with amenorrhea for >1 year, will be considered as having confirmed menopause and follicle-stimulating hormone (FSH) or pregnancy testing will not be needed. Postmenopausal females <55 years of age (defined as amenorrhea >1 year) must have menopause confirmed by elevated

FSH levels at screening. Surgically sterile females do not require any further confirmation of menopause and will not be considered to have reproductive potential.

For participants in Germany, please see specific instructions in Appendix 10 Section 12.10.

**Informed Consent**

I06. Able to provide written informed consent and agreeable to the schedule of assessments.

**Exclusion Criteria**

Patients will be excluded from the trial if any of the following criteria are met:

**Medical conditions**

E01. Suspected paraneoplastic pemphigus and other forms of pemphigus that are not pemphigus vulgaris or pemphigus foliaceus.

E02. Previous use of a Bruton tyrosine kinase (BTK) inhibitor.

E03. Pregnant or lactating women.

E04. Electrocardiogram (ECG) findings of QT corrected for heart rate (QTc) >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities.

E05. A history of malignancy of any type within 5 years before Day 1, other than surgically excised non-melanoma skin cancers or in situ cervical cancer.

**Prior/concomitant therapy**

E06. Use of immunologic response modifiers as concomitant medication and with the following washout periods: A) stop ***at least 2 weeks prior to Screening***: mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, intravenous immunoglobulin (IVIG), Kinaret (anakinra), Enbrel (etanercept), or any other immunosuppressant not mentioned in this exclusion criterion; B) ***12 weeks prior to Screening***: Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), Orencia (abatercept), Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), plasmapheresis; C) ***6 months prior to Screening (or shorter if there is documented B cell reconstitution for anti-CD20 drugs):*** anti-CD20 drugs such as rituximab, ofatumumab, other long-acting biologics.

E07. Use of proton pump inhibitor drugs such as omeprazole and esomeprazole within 3 days of Day 1 (it is acceptable to change patient to H2 receptor blocking drugs prior to Day 1).

E08. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A within 3 days or 5 half-lives (whichever is longer) of Day 1 (Appendix 7 Section 12.7).

E09. Use of CYP3A-sensitive substrate drugs with a narrow therapeutic index within 3 days or 5 half-lives (whichever is longer) of Day 1 and for the remainder of the trial including, but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus (topical and oral), or terfenadine.

E010. Has received any investigational drug (or is currently using an investigational device) within the 30 days before Day 1, or at least 5 times the respective elimination half-life time (whichever is longer).

E011. History of drug abuse within the previous 12 months.

E012. Alcoholism or excessive alcohol use, defined as regular consumption of more than approximately 3 standard drinks per day.

**Other exclusions**

E013. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate rilzabrutinib/placebo absorption.

E014. Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1.

E015. History of solid organ transplant.

E016. Positive at Screening for human immunodeficiency virus (HIV), hepatitis B (surface antigen and/or core antibodies), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA).

E017. Positive interferon-gamma release assay (IGRA) (eg, T-spot TB Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus), at Screening. Unless, the patient has latent tuberculosis (TB) and all of the following 3 conditions are true:

a) Chest X-ray does not show evidence suggestive of active 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 indeterminate for any reason 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.

E18. History of serious infections requiring intravenous therapy with the potential for recurrence or currently active moderate to severe infection at Screening (Grade 2 or higher).

E19. Live vaccine within 28 days prior to Day 1 or plan to receive one during the trial.

E20. Any other clinically significant disease, condition [including contraindication to CS and/or inability to follow CS dosing as outlined in the protocol (see Table 1 for more details)], or medical history that, in the opinion of the Investigator, would interfere with patient safety, trial evaluations, and/or trial procedures. In areas endemic for Chagas disease, screening is recommended prior to enrollment.

For participants in Germany, please see specific instructions in Appendix 10 Section 12.10.

**Outcome Measures**

**Primary Efficacy Endpoint**

- The proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤10 mg/day.

**Key Secondary Efficacy Endpoints**

- Cumulative CS dose from Baseline to Week 37
- Cumulative duration of CR with a CS dose ≤10 mg/day, from Baseline to Week 37
- Time to first CR with a CS dose ≤10 mg/day, from Baseline to Week 37

**Other Secondary Endpoints**

- The proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤5 mg/day
- The proportion of patients who have a PDAI score <3 from Week 29 to Week 37 with a CS dose ≤10 mg/day
- Cumulative duration of CR with a CS dose ≤10 mg/day from Baseline to Weeks 61 and 109
- Cumulative duration of CR with a CS dose = 0 mg/day from Baseline to Weeks 61 and 109
- GTI score at Week 37
- Change in PDAI score from Baseline to Weeks 5, 13, 25, 37, 61, and 109
- Change in Autoimmune Bullous Disease Quality of Life (ABQOL) score from Baseline to Weeks 5, 13, 25, 37, 61, and 109
- Proportion of patients with ABQOL Score of zero at Weeks 5, 13, 25, 37, 61, and 109

- Change in EuroQOL-5 Dimension 5 Level (EQ-5D-5L) results (visual analog scale [VAS] results and individual dimension) scores from Baseline to Weeks 5, 13, 25, 37, 61, and 109
- Time to first CR with a CS dose ≤10 mg/day, from Baseline to Weeks 61 and 109
- Total number of disease relapses/flares from initial CDA to Week 37
- Time to initial relapse/flare from initial CDA to Week 37
- Proportion of patients with 3 or more new lesions within 1 month that do not heal spontaneously within 1 week, or with extension of established lesions, from Baseline to Week 37
- Proportion of patients with at least one disease relapse/flare from initial control of disease activity (CDA) to Week 37
- Cumulative duration of CR with a CS dose ≤10 mg/day, from Week 37 to Week 61
- Cumulative duration of CR with a CS dose = 0 mg/day, from Week 37 to Week 61

**Safety Endpoints**

- Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects.
- Change from Baseline in vital signs and clinical laboratory test results (including complete blood count and blood chemistry).

**Pharmacokinetic Endpoints**

- Plasma concentrations of rilzabrutinib at approximately the time of maximum concentration at Day 1 and at varied subsequent timepoints (refer to Table 2 and Table 3).

**Pharmacodynamic Endpoints**

- Change from Baseline in anti-dsg1 and anti-dsg3 autoantibody levels by enzyme-linked immunosorbent assay (ELISA) at Weeks 13, 25, 37, 49, 61, and 109.

**Exploratory Endpoints**

- Plasma concentrations of rilzabrutinib metabolites
- 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
- Cost utilities based on the number and type of hospitalizations, outpatient medical visits, concomitant medication use, adverse events and other relevant outcomes
- Change from Baseline in PDAI by visit and the temporal relationship to changes in quality of life and health economic variables
- Proportion of patients with relapse/flare after achievement of CR between Baseline and Weeks 61 and 109

- Proportion of patients initially randomized to rilzabrutinib that are in CR with a zero CS dose, from Week 53 to Week 61 (no randomized treatment comparison)
- Proportion of patients initially randomized to placebo that are in CR with a zero CS dose, from Week 53 to Week 61 (no randomized treatment comparison)
- Change in Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) score from Baseline to Weeks 5, 13, 25, 37, 61, and 109
- Total number of disease relapses/flares from Week 37 to Weeks 61 and 109
- (Optional) Blood samples for exploratory analysis of vaccine IgG response during treatment.

**Long Term Extension Endpoints**

- Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects during the LTE from Week 61 to Week 113
- Average daily dose of CS from Week 61 to Week 113
- Time to initial relapse/flare from initial CDA to Week 109.

**Safety Assessments**

The safety of the drug will be evaluated by multiple assessments of patient vital signs, physical exams, and laboratory tests. Concomitant medications and adverse events (AEs) will be monitored and tracked.

An independent Data Safety Monitoring Board (DSMB) will regularly review unblinded safety data.

Please refer to Schedule of Assessments (Table 2, Table 3 and Table 4) and Section 8.6.

**Pharmacokinetic and Pharmacodynamic**

Individual and group PK (rilzabrutinib and metabolites as applicable) and PD (anti-desmoglein-1 and -3) data will be summarized, displayed graphically, and by descriptive statistics for each visit, where measured. Please refer to the Statistical Section 9.3.7.

**Sample Size**

See Section 9.1.

**Randomization**

Patients will be randomized at Day 1, in a 1:1 allocation, using a stratification by PV/PF disease type, and by newly diagnosed disease (diagnosed ≤6 months prior to Screening) or by relapsing disease (diagnosed >6 months prior to Screening.)

**Other Statistical Considerations**

The primary efficacy analysis will be conducted when all patients have completed the Study Week 37 Visit (ie, completed the Blinded Treatment Period).

A formal Statistical Analysis Plan (SAP) will be developed prior to database lock and unblinding. The SAP will contain a more detailed and/or comprehensive presentation of statistical methods or procedures, attention to any changes of substance to planned analysis procedures relative to those indicated in the protocol, and will be the final authority for all statistical analyses.

Descriptive summaries of variables by treatment will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation (SD), minimum, and maximum will be tabulated by treatment and where appropriate by study day and study timepoint.

Summaries will also be presented for the change from baseline, when appropriate. For categorical variables, the counts and proportions of each value will be tabulated by treatment and where appropriate by study day and study timepoint. For time to event variables, point estimates ($25^{th}$, $50^{th}$, and $75^{th}$ percentiles) along with 95% confidence intervals will be tabulated by treatment. Survival estimates will also be shown graphically for each treatment.

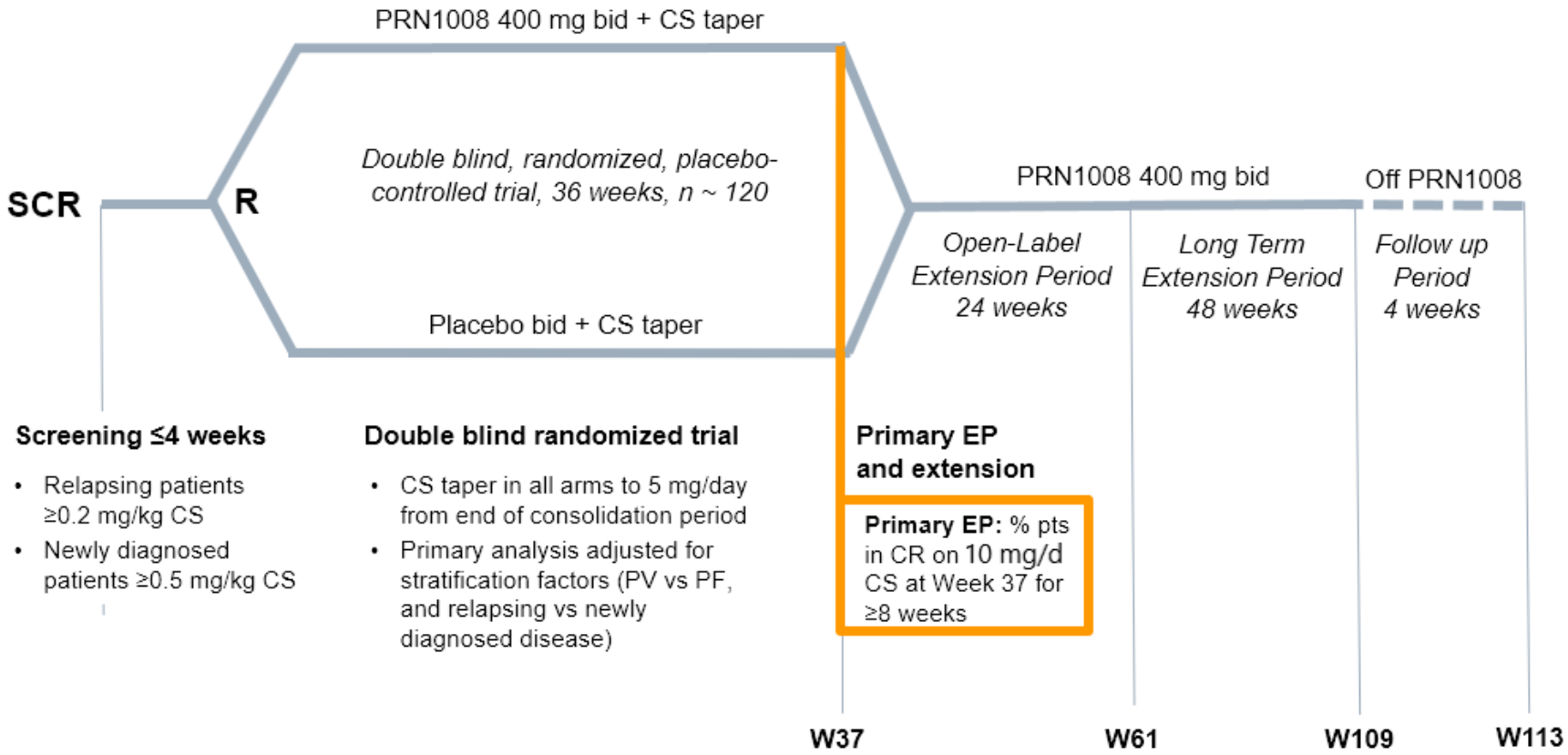
All statistical tests will be two-sided unless otherwise noted.

An independent DSMB will regularly review unblinded safety data. Full details of DSMB functioning will be included in a Charter.

Please refer to Statistical Section 9.

## 1.2 SCHEMA

**Figure 1: Study Design Flow Chart**




Abbreviations: bid = twice daily; CR = complete remission; CS = corticosteroids; EP = endpoint; PF = pemphigus foliaceus; PV = pemphigus vulgaris; R = randomization; SCR = Screening Period; W = week.

## 1.3 SCHEDULE OF ACTIVITIES (SOA)

**Table 2: Schedule of Assessments - Blinded Treatment Period**

| | Screening | Blinded Treatment Period | | | | | | | | | | | Early Termination (ET) | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -29)[n,o] WK (-4) | Day 1 Week 1 Pre-dose | Day 1 Week 1 Post-dose | WK 3 | WK 5 | WK 9 | WK 13 | WK 17 | WK 21 | WK 25 | WK 29 | WK 33 | WK 37 | |
| **Visit Window** | | | | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | |
| Informed Consent | X | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X[o] | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | |
| Weight | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Full physical examination | X | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | |
| Abbreviated physical examination | | X | | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | | | | | | | | | | X | (X)[a] |
| Vital Signs | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis[b] | X | | | | | | | | | | | | X | (X)[a] |
| Hep B and C, HIV, & QuantiFERON-TB Gold or Quantiferon-TB Gold Plus or TB-Spot | X | | | | | | | | | | | | | |
| Pregnancy test[c] | X | X | | | X | X | X | X | X | X | X | X | X | X |
| Skin biopsy[d] | X | | | | | | | | | | | | | |
| Hematology, coagulation, and serum chemistry[e] | X | X | | X | X | X | X | | | X | | | X | X | (X)[a] |
| HbA1c and LDL[e] (fasting) | | X | | | | | X | | | X | | | X | X | |
| FSH[f] | X | | | | | | | | | | | | | |
| PK sample | | X | X[g] | X[h] | X[h] | X[h] | X[h] | | | X[h] | | | X[h] | X[h] | (X)[a] |
| PD: anti-desmoglein-1 and -3 autoantibody titers by ELISA | X | X | | | | | X | | | X | | | X | X | (X)[a] |
| PDAI | X | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| ABQOL, TABQOL | X | X | | X | X | | X | | | X | | | X | X | X |

| | Screening | Blinded Treatment Period | | | | | | | | | | | | Early Termination (ET) | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -29)[n, o] WK (-4) | Day 1 Week 1 Pre-dose | Day 1 Week 1 Post-dose | WK 3 | WK 5 | WK 9 | WK 13 | WK 17 | WK 21 | WK 25 | WK 29 | WK 33 | WK 37 | | |
| **Visit Window** | | | | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | | |
| EQ-5D-5L | X | X | | X | X | | X | | | X | | | X | X | X |
| GTI Index | | X | | | | | X | | | X | | | X | X | |
| Efficacy Outcome Assessment[i] | X | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| AEs[m] | X | X | X | X | 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 | X | X |
| Rilzabrutinib or placebo dispensed[p] | | X | | | X | X | X | X | X | X | X | X | | | X |
| CS daily dosing[j] | See Appendix 1 | | | | | | | | | | | | | X | X |
| Rituximab infusion[k] | | | | | See Appendix 1 | | | | | | | | | | |
| Photography[l] | X | X | | X | X | X | X | X | X | X | X | X | X | X | |
| Drug reconciliation[q] (Rilzabrutinib or placebo /CS Dosing Documentation) | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Vaccine IgG | X[r] | | | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] | X[s] |
| SARS-CoV-2 (for participants in Germany only, see specific instructions in Appendix 10) | X | | | | | | | | | | | | | X | X |

ABQOL = Autoimmune Bullous Disease Quality of Life; AE = adverse event; CDA = control of disease activity; CS = corticosteroids; CR = complete remission; ECG = electrocardiogram; ECP = end of consolidation phase; ELISA = enzyme-linked immunosorbent assay; EOT = End of Trial; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; FSH = follicle-stimulating hormone; GTI = Glucocorticoid Toxicity Index; Hep = hepatitis; HIV = human immunodeficiency virus; LDL = low-density lipoprotein; PD = pharmacodynamics; PDAI = Pemphigus Disease Area Index; PF = pemphigus foliaceus; PK = pharmacokinetic(s); PV = pemphigus vulgaris; TABQOL = Treatment of Autoimmune Bullous Disease Quality of Life; TB = tuberculosis, Wk = Week.

*a* Only if clinically indicated.

*b* Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes, and reflex microscopy.

*c* For women of childbearing potential only. Serum pregnancy test must be performed at Screening; a urine pregnancy test should be performed at all other trial timepoints.

*d* A new biopsy is not required if there is a prior and available biopsy report documenting histopathologic findings diagnostic for PV or PF. A new biopsy should be performed if an archival biopsy report is not available. Refer to Section 8.4.3.

*e* Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Serum chemistry will include the following: 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; and glucose (random). Creatine phosphokinase (CPK) is to be performed at Screening only. Coagulation will include: PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Screening, Day 1 Week 1 Pre-dose, and Weeks 3, 5, 9, 13, 25, & 37. HbA1c and LDL level (fasting) will be collected every 3 months with GTI assessment.

*f* Any woman of age ≥55 years with amenorrhea for >1 year, will be considered as having confirmed menopause and will not need FSH or pregnancy testing.
Postmenopausal females <55 years of age (defined as amenorrhea >1 year) should have menopause confirmed by follicle-stimulating hormone (FSH) and serum pregnancy testing at screening. Surgically sterile females do not require any further confirmation of menopause and will not be considered to have reproductive potential.

*g* Two hours post-dose (±15 minutes).

*h* PK sample should be taken at random timepoints during the patient visits with as much variation in time since last dose as practicable. Time of draw will be captured as well as time of the last two rilzabrutinib or placebo doses, and time of the patient's last meal.

*i* Pemphigus Clinical Response Definitions for CDA, CR, ECP, relapse/flare (refer to protocol Section 3).

*j* For CS management, refer to Appendix 1. At any point if CS needs to be adjusted between required visits, the patient may return for an unscheduled visit and additional CS may be dispensed via IWRS if required. CS doses taken will be recorded by the patient on a dosing diary. Patients should bring their diary and used and unused CS containers with them at every visit.

*k* Rituximab may be administered intravenously during the Blinded Treatment Period, unless contraindicated, after a second "qualifying relapse/flare" occurs at or after Day 29 Visit. See Appendix 1. Any rituximab dispensed will undergo drug accountability.

*l* Photography of lesions allowed at selected centers at the discretion of the Investigator and as per local regulations.

*m* AEs occurring after Screening and before baseline dosing are recorded as treatment AEs unrelated to rilzabrutinib or placebo.

*n* As described in Section 8.3.1, laboratory assessments delayed due to logistic considerations may be performed with an extended Screening window (up to 7 additional business days), upon Sponsor review and approval. Patients may be re-screened once. Any labs completed in prior Screening, within 2 weeks of re-screening will remain valid and should not be repeated. Labs performed for a previous screening within 6 weeks, may be considered for determination of eligibility on approval of the Medical Monitor. In the specific cases of QuantiFERON-TB, anti desmoglein antibodies and hepatitis/HIV testing, tests may be considered for determination of eligibility if performed in a previous screen within the last 12 weeks, with the approval of the Medical Monitor. However, pregnancy tests should be repeated at re-screening.

*o* To determine a patient's eligibility, Screening laboratory results will be used, not Day 1.

*p* The last rilzabrutinib/placebo blinded dose should be taken on the morning of the Week 37 Visit. At the Week 37 Visit, open-label rilzabrutinib will be dispensed and used for the Week 37 evening dose.

*q* Subjects are required to bring all used and unused study drug supplies with them to every clinic visit.

*r* Patients will be encouraged to provide vaccination plans for any vaccines which are in line with the participants'age-appropriate local medical practice or guidelines (live attenuated vaccines are excluded) during the study. Participants planning to receive any vaccines during the study may optionally consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine dose regimen.

*s* Vaccination data will be reported when possible (see Section 12.11, Appendix 11). Additionally, optional collection of blood for assay of vaccine IgG in serum for each vaccine: the first sample should be collected within 6 weeks prior to each vaccine dose regimen, and the second should be collected within approximately 3 to 6 weeks after the vaccine regimen is complete. Vaccinations should preferably occur after completion of at least 6 weeks of any treatment of rilzabrutinib/placebo (Blinded Treatment Period) or rilzabrutinib (OLE or LTE), while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits.

**Table 3: Schedule of Assessments - Open-Label Extension Period**

| | | Open-Label Extension Period | | | | | | | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 37[k] | Week 39 | Week 41 | Week 45 | Week 49 | Week 53 | Week 57 | Week 61[l] | EOT/ Week 65 4 wk FU Visit | Early Termination (ET) [a] | Unscheduled Visit |
| **Visit Windows** | ±3 days | ±3 days | ±5 days | ±5 days | ±5 days | ±5 days | ±5 days | ±5 days | ±5 days | | |
| Weight | X | X | X | X | X | X | X | X | X | X | X |
| Abbreviated physical examination | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | | | | | X | | (X)[b] | (X)[b] |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis[c] | X | | | | | | | X | X | X | (X)[b] |
| Urine pregnancy test[d] | X | | X | X | X | X | X | X | X | X | |
| Hematology, coagulation, and serum chemistry[c] | X | X | | | X | | | X | X | X | (X)[b] |
| HbA1c and LDL[c] (fasting) | X | | | | | | | | | | |
| PK Sample[e] | X | X | | | X | | | X | | X | (X)[b] |
| PD: anti-desmoglein-1 and -3 autoantibody titers by ELISA | X | | | | X | | | X | | X | (X)[b] |
| PDAI | X | X | X | X | X | X | X | X | X | X | X |
| ABQOL and TABQOL | X | X | | | X | | | X | X | X | X |
| EQ-5D-5L | X | X | | | X | | | X | X | X | X |
| GTI Index | X | | | | | | | | | | |
| Efficacy Outcome Assessment[f] | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X |
| Photography[g] | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X |
| Rilzabrutinib dispensed | X[j] | | X | X | X | X | X | X[l] | | | |
| TBNK Panel | X[m] | | | | | | | | | | |
| Drug reconciliation[h] (rilzabrutinib/CS Dosing Documentation) | X | X | X | X | X | X | X | X | X | X | X |
| CS Daily Dosing[i] | | X (See Appendix 1) | | | | | | | | | X |
| Vaccine IgG | X[n] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] | X[o] |
| SARS-CoV-2 (for participants in Germany only, see specific instructions in Appendix 10) | X | | | | | | | | | | X |

ABQOL = Autoimmune Bullous Disease Quality of Life; CDA = control of disease activity; CR = complete remission; CS = corticosteroids; ECG = electrocardiogram; ECP = End of consolidation phase; ELISA = enzyme-linked immunosorbent assay; EOT = End of Trial; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; FU = follow-up; HgbA1c = hemoglobin A1c; LDL = low-density lipoprotein; PD = pharmacodynamics; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetic(s); TABQOL = Treatment of Autoimmune Bullous Disease Quality of Life; wk = week.

*a* The early termination (ET) Visit should be performed for patients who are not able to complete the Open Label Extension period including Week 65 Visit and discontinue from the trial early.

*b* Only if clinically indicated.

*c* Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Serum chemistry will include the following: 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; and glucose (random). Creatine phosphokinase (CPK) is to be performed at Screening only. Coagulation will include: PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Weeks 39, 49, 61, ET, and EOT (if applicable). Urinalysis will include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes and reflex microscopy. At Week 37, the HbA1c and LDL level (fasting) will be collected with GTI assessment.

*d* For women of childbearing potential only.

*e* PK sample should be taken at random timepoints during the patient visits with as much variation in time since last dose as practicable. Time of draw will be captured as well as time of the last two rilzabrutinib doses, and time since the patient's last meal.

*f* Pemphigus Clinical Response Definitions for CDA, CR, ECP, relapse/flare (refer to protocol Section 3).

*g* Photography of lesions allowed at selected centers at the discretion of the Investigator and as per local regulations.

*h* Subjects are required to bring all used and unused study drug supplies with them to every clinic visit.

*i* For CS management, refer to Appendix 1. At any point if CS needs to be adjusted between required visits, the patient may return for an unscheduled visit and additional CS may be dispensed via IWRS if required. CS doses taken will be recorded by the patient on a dosing diary. Patients should bring their diary and used and unused CS containers with them at every visit. Patients entering the LTE will receive Sponsor-provided CS, following CS Management Guidelines (Appendix 1).

*j* The last rilzabrutinib/placebo blinded dose should be taken on the morning of the Week 37 visit. At the Week 37 visit, open-label rilzabrutinib will be dispensed and used for the Week 37 evening dose.

*k* Assessments performed at the Week 37 Visit of the Blinded Treatment Period should not be repeated at this visit.

*l* If patient is eligible for the Long Term Extension Period at Week 61 they will continue to receive rilzabrutinib per Table 4. If the patient is not eligible for the Long Term Extension Period at Week 61 they will discontinue rilzabrutinib and complete the EOT visit at Week 65.

*m* Patients that received rituximab during the Blinded Treatment Period and are continuing in the study, TBNK panel will be drawn at their Week 37 visit.

*n* Patients will be encouraged to provide vaccination plans for any vaccines which are in line with the participants'age-appropriate local medical practice or guidelines (live attenuated vaccines are excluded) during the study. Participants planning to receive any vaccines during the study may optionally consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine dose regimen.

*o* Vaccination data will be reported when possible (see Section 12.11, Appendix 11 ). Additionally, optional collection of blood for assay of vaccine IgG in serum for each vaccine: the first sample should be collected within 6 weeks prior to each vaccine dose regimen, and the second should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Vaccinations should preferably occur after completion of at least 6 weeks of any treatment of rilzabrutinib/placebo (Blinded Treatment Period) or rilzabrutinib (OLE or LTE), while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits.

**Table 4: Schedule of Assessments - Long Term Extension Period**

| Visit Windows | Long Term Extension Period | | | | | | | | Early Termination (ET)[a] | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 61[j] | Week 65 | Week 69 | Week 73 | Week 85 | Week 97 | Week 109 | EOT/Week 113 4 wk FU Visit | | |
| | ±5 days | ±5 days | ±5 days | ±5 days | ±10 days | ±10 days | ±10 days | ±5 days | | |
| Weight | X | X | X | X | X | X | X | X | X | X |
| Abbreviated physical examination | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | | | | X | | (X)[b] | (X)[b] |
| Vital Signs | X | X | X | X | X | X | X | X | X | X |
| Urinalysis[c] | X | | | | | | X | X | X | (X)[b] |
| Urine pregnancy test[d] | X | X | X | X | X | X | X | X | X | |
| Hematology, coagulation, and serum chemistry[c] | X | | | | X | X | X | X | X | (X)[b] |
| PK Sample[e] | X | | | | | | | | | (X)[b] |
| PD: anti-desmoglein-1 and -3 autoantibody titers by ELISA | X | | | X | X | X | X | | X | (X)[b] |
| PDAI | X | | | | | | X | | X | |
| ABQOL and TABQOL | X | | | | | | X | | X | |
| EQ-5D-5L | X | | | | | | X | | X | |
| Efficacy Outcome Assessment[f] | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X |
| Photography[g] | X | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Rilzabrutinib dispensed | X | X | X | X | X | X | | | | |
| Drug reconciliation[h] (rilzabrutinib/CS Dosing Documentation) | X | X | X | X | X | X | X | X | X | X |
| CS Daily Dosing[i] | | | | | X | See Appendix 1 | | | | X |
| Vaccine IgG | X[k] | X[l] | X[l] | X[l] | X[l] | X[l] | X[l] | X[l] | X[l] | X[l] |
| SARS-CoV-2 (for participants in Germany only, see specific instructions in Appendix 10) | | | | | | X | | | | X |

ABQOL = Autoimmune Bullous Disease Quality of Life; CDA = control of disease activity; CR = complete remission; CS = corticosteroids; ECG = electrocardiogram; ECP = End of consolidation phase; ELISA = enzyme-linked immunosorbent assay; EOT = End of Trial; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; FU = follow-up;
HgbA1c = hemoglobin A1c; LDL = low-density lipoprotein; PD = pharmacodynamics; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetic(s); TABQOL = Treatment of Autoimmune Bullous Disease Quality of Life; wk = week

*a* The early termination (ET) Visit should also be performed for patients who are not able to complete the Long-Term Extension period including Week 113 Visit and discontinue from the trial early.

*b* Only if clinically indicated.

*c* Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Serum chemistry will include the following: 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; and glucose (random). Coagulation will include: PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Weeks 61, 85, 97, 109, ET, and EOT. Urinalysis will include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes and reflex microscopy.

*d* For women of childbearing potential only. May be performed monthly between Week 73 and Week 113 if required by local regulations.

*e* PK sample required at Week 61; and after Week 61 only if the patient experiences relapse/flare. Time of draw will be captured as well as time of the last two rilzabrutinib doses, and time since the patient's last meal.

*f* Pemphigus Clinical Response Definitions for CDA, CR, ECP, relapse/flare (refer to protocol Section 3).

*g* Any photos should be taken and stored in accordance with local regulations (Week 61 only).

*h* Subjects are required to bring all used and unused rilzabrutinib study drug supplies with them to every clinic visit.

*i* For CS management, refer to Appendix 1. Patients entering the LTE will receive Sponsor-provided CS. At any point if CS needs to be adjusted between required visits, the patient may return for an unscheduled visit and additional CS may be dispensed.

*j* Assessments performed at the Week 61 Visit of the Open-Label Period should not be repeated at this visit.

*k* Patients will be encouraged to provide vaccination plans for any vaccines which are in line with the participants'age-appropriate local medical practice or guidelines (live attenuated vaccines are excluded) during the study. Participants planning to receive any vaccines during the study may optionally consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine dose regimen.

*l* Vaccination data will be reported when possible (see Section 12.11, Appendix 11). Additionally, optional collection of blood for assay of vaccine IgG in serum for each vaccine: the first sample should be collected within 6 weeks prior to each vaccine dose regimen, and the second should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Vaccinations should preferably occur after completion of at least 6 weeks of any treatment of rilzabrutinib/placebo (Blinded Treatment Period) or rilzabrutinib (OLE or LTE), while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits.

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

Study PRN1008-012 is a randomized, parallel-group, double-blind, placebo-controlled trial over 36 weeks (Blinded Treatment Period) followed by an Open-Label Extension Period of 24 weeks, Long Term Extension Period of 48 weeks, and a Follow-up Period of 4 weeks, which is intended to evaluate the efficacy and safety of oral PRN1008 (Rilzabrutinib) in moderate to severe pemphigus.

The primary purpose of the 24-week, Open-Label Extension Period (OLE) is to allow access to study drug who were on placebo medication as well as to evaluate durability of clinical response and accrue additional long term data on the safety and efficacy of rilzabrutinib.

The primary purpose of the 48-week, Long Term Extension Period (LTE) is to provide extended access to rilzabrutinib for patients who are receiving clinical benefit and to accrue additional long-term data on the safety and efficacy of rilzabrutinib.

## 2.2 BACKGROUND

### 2.2.1 Overview of pemphigus

Pemphigus is a group of rare autoimmune diseases that causes painful blistering of the skin and mucous membranes (mouth, nose, throat, eyes, and genitals). Pemphigus is associated with autoantibodies to the epithelial protein, desmoglein, in about 90% of cases. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the main subtypes of pemphigus with PV being the most common in most parts of the world (5, 6). Pemphigus can occur at any age, but often strikes people in middle or older age. Studies have shown that some populations may be at greater risk for certain types of pemphigus. For instance, people of Jewish descent and those from India, Southeast Europe, and the Middle East are at greater risk for PV, while PF is common in South America.

PV typically begins with blisters (bullae) in the mouth, which are often mistaken for aphthous ulcers. The blisters are flaccid and are easily broken, leading to often-painful lesions or erosions. Blistering can also affect the esophagus, rectum, nose, or the lining of the eyelids. Skin lesions appear several weeks or months after the onset of mucosal erosions. PV is associated with circulating antibodies to desmoglein 3 in most cases.

PF affects the skin only, without mucosal involvement. Antibodies to desmoglein 1 are commonly detected. The natural history is chronic, and treatment is identical to that for PV.

In both types of pemphigus, Nikolsky's sign (shear force displacement of skin) can appear on perilesional skin or, in some cases, even on healthy skin. The diagnosis can be confirmed by

standard histopathological analysis and direct immunofluorescence test on affected skin. The presence of elevated anti-desmoglein antibodies is confirmatory.

Presently, there are few effective treatment options for pemphigus. Current treatments include corticosteroids (CS) to reduce inflammation and antibiotics to treat associated infections. Agents such as mycofenolate mofetil are often used and rituximab has been reported to be effective. Mycofenolate mofetil has not been approved for this indication in any country and rituximab to treat pemphigus vulgaris has not been globally approved. The beneficial effects of these 2 products take weeks to months. Current day practice guidelines recommend first-line therapy with relatively high doses of CS initially (0.5 to 1.5 mg/kg/day of prednisone or equivalent CS), with rituximab also for consideration as first line therapy in combination with CS (1). The long-term use of CS has many adverse effects including serious infections, osteoporosis, decreased bone density, hypertension, and iatrogenic Cushing's syndrome. Therefore, there is a significant unmet medical need for new therapeutics that can rapidly achieve and maintain disease remission while obviating or minimizing the need for CS therapy.

### 2.2.2 BTK inhibitor (rilzabrutinib)

Bruton tyrosine kinase (BTK) is expressed in cells of the B-cell lineage, including marrow-derived hematopoietic stem cells, common lymphoid progenitor cells and developing B and myeloid lineages. Bruton tyrosine kinase is also expressed in other cells of hematopoietic lineage with the exception of T cells, natural killer cells and plasma cells (7).

A BTK inhibitor such as rilzabrutinib has the potential to target multiple pathways and cell types involved in inflammation and autoimmunity. These include: B cell receptor (BCR)-mediated B cell pathways, FcγR-induced cytokine release from monocytes and macrophages, FcεR-induced mast cell degranulation and granulocyte migration and mediator release.

### 2.2.3 Nonclinical experience

Rilzabrutinib has been evaluated in various pharmacology, pharmacokinetic, and toxicology studies in mice, rats, and dogs primarily by the intended oral route of administration. Rilzabrutinib demonstrated blockade of the rat arthus reaction, full disease reversal of a rat collagen-induced arthritis model, and reduction in platelet loss in a mouse model of immune thrombocytopenia. The therapeutic effects of rilzabrutinib in pemphigus was studied in dogs with newly diagnosed, naturally occurring PF in an outpatient clinical trial. The drug safely controlled disease without the need for CS in 4 of 4 cases.

Please refer to the Investigator Brochure (IB) for more details.

### 2.2.4 Clinical experience

In clinical studies to date, Rilzabrutinib has been administered to more than 200 people, including healthy volunteers and patients with pemphigus and idiopathic thrombocytopenia. Twenty-seven patients with PV in a Phase 2 study (NCT02704429) used a starting dose of 400 mg BID which was shown to produce adequate BTK occupancies in all but one patient. One patient dose-escalated

to 500 mg BID and two to 600 mg BID, with all other patients using the 400 mg BID dose. The primary endpoint of the study, “control of disease activity by the Week 5 Visit on ≤0.5 mg/kg/day of prednisone (or equivalent CS)” was met by 54% (14/26) of patients. Complete remission (CR) on ≤0.5 mg/kg/day of CS was achieved by 25% (5/20) of patients completing 12 weeks treatment.

Treatment-emergent adverse events (TEAEs) in the pemphigus study related to rilzabrutinib in ≥10% of patients were nausea (15%), abdominal pain (11%) and headache (11%). One serious adverse event (AE) of Grade 3 “cellulitis” considered related to rilzabrutinib therapy occurred, resulting in a three day interruption of rilzabrutinib therapy. This patient continued therapy for two further months without recurrence of the event.

Overall, results from Phase 1 and Phase 2 studies demonstrate that rilzabrutinib has an acceptable safety profile and is well tolerated in healthy subjects and patients with pemphigus. Please refer to the IB, for more details.

## 2.3 BENEFIT/RISK ASSESSMENT

Phase 1 and Phase 2 studies have demonstrated an encouraging safety profile and a clinically meaningful treatment effect with Rilzabrutinib in mild to moderate pemphigus. In particular, the ability of rilzabrutinib to rapidly induce control of disease on doses of CS between 0 and 30 mg per day suggests that the drug may have a major CS-sparing effect. No risks other than those previously mentioned in the IB or in the summary of rilzabrutinib clinical experience, or in the rituximab and CS prescribing information are known at this time. Given this profile, there is equipoise in the proposed randomized, controlled trial of rilzabrutinib versus placebo on a background of usual care with CS. The risks of combination of rituximab and rilzabrutinib, should this occur, are justified as the combination will only be used in a multiple relapse/flare setting which requires more intensive immunosuppression. Furthermore, a similar rate of TEAEs has been reported in a randomized trial comparing the combination of rituximab and ibrutinib, a BTK/ interleukin-2-inducible T-cell kinase (ITK)/ epidermal growth factor receptor (EGFR) inhibitor to ibrutinib alone (8).

# 3 OBJECTIVES AND ENDPOINTS

**Table 5: Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Efficacy** | |
| • To evaluate the efficacy of rilzabrutinib in achieving durable CR on low to zero doses of oral corticosteroid (CS) and on the timecourse of quantitative disease activity scores<br>• To assess the ability of rilzabrutinib to reduce CS exposure and the adverse effects of CS<br>• To evaluate the time to specified clinical endpoints<br>• To assess the longer term durability of CR | **Primary Efficacy Endpoint**<br>• The proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤10 mg/day<br>**Key Secondary Efficacy Endpoints**<br>• Cumulative CS dose from Baseline to Week 37<br>• Cumulative duration of CR with a CS dose ≤10 mg/day, from Baseline to Week 37<br>• Time to first CR with a CS dose ≤10 mg/day, from Baseline to Week 37<br>**Other Secondary Endpoints**<br>• The proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤5 mg/day<br>• The proportion of patients who have a PDAI score <3 from Week 29 to Week 37 with a CS dose ≤10 mg/day<br>• Cumulative duration of CR with a CS dose ≤10 mg/day from Baseline to Weeks 61 and 109<br>• Cumulative duration of CR with a CS dose = 0 mg/day from Baseline to Weeks 61 and 109<br>• GTI score at Week 37<br>• Change in PDAI score from Baseline to Weeks 5, 13, 25, 37, 61, and 109<br>• Change in Autoimmune Bullous Disease Quality of Life (ABQOL) score from Baseline to Weeks 5, 13, 25, 37, 61, and 109<br>• Proportion of patients with ABQOL Score of zero at Weeks 5, 13, 25, 37, 61, and 109<br>• Change in EuroQOL-5 Dimension 5 Level (EQ-5D-5L) results (visual analog scale [VAS] results and individual dimension) scores from Baseline to Weeks 5, 13, 25, 37, 61, and 109<br>• Time to first CR with a CS dose ≤10 mg/day, from Baseline to Weeks 61 and 109<br>• Total number of disease relapses/flares from initial CDA to Week 37<br>• Time to initial relapse/flare from initial CDA to Week 37<br>• Proportion of patients with 3 or more new lesions within 1 month that do not heal spontaneously within 1 week, or with extension of established lesions, from Baseline to Week 37<br>• Proportion of patients with at least one disease relapse/flare from initial control of disease activity (CDA) to Week 37 |

| Objectives | Endpoints |
|---|---|
| | • Cumulative duration of CR with a CS dose ≤10 mg/day, from Week 37 to Week 61<br>• Cumulative duration of CR with a CS dose = 0 mg/day, from Week 37 to Week 61 |
| **Safety**<br>• To evaluate the safety of rilzabrutinib<br>• To evaluate differences in potentially CS-related adverse events | • Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects<br>• Change from Baseline in vital signs and clinical laboratory test results (including complete blood count and blood chemistry) |
| **PK/PD Objectives**<br>• To evaluate the pharmacokinetics (PK) of rilzabrutinib<br>• To evaluate pharmacodynamic (PD) effects of rilzabrutinib on anti-desmoglein (anti-dsg) autoantibody titers (anti-dsg1 and anti-dsg3) | **Pharmacokinetic Endpoints**<br>• Plasma concentrations of rilzabrutinib at approximately the time of maximum concentration at Day 1 and at varied subsequent timepoints (refer to Table 2 and Table 3)<br>**Pharmacodynamic Endpoints**<br>• Change from Baseline in anti-dsg1 and anti-dsg3 autoantibody levels by enzyme-linked immunosorbent assay (ELISA) at Weeks 13, 25, 37, 49, 61, and 109 |
| **Exploratory Objectives**<br>• To evaluate the PK of rilzabrutinib metabolites<br>• To examine the effects of rilzabrutinib if any, of the baseline covariates on PK and/or PD, and the relationship between PK, PD, and efficacy<br>• To explore association of vaccine response with rilzabrutinib<br>• To examine the effect of rilzabrutinib on the costs of hospitalizations, outpatient medical visits, adverse events, concomitant medication use, and other relevant health economic outcomes<br>• To examine the temporal relationship of change from baseline in Pemphigus Disease Area Index (PDAI) total activity score and quality of life and health economic measures | **Exploratory Endpoints**<br>• Plasma concentrations of rilzabrutinib metabolites<br>• 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<br>• Cost utilities based on the number and type of hospitalizations, outpatient medical visits, concomitant medication use, adverse events and other relevant outcomes<br>• Change from Baseline in PDAI by visit and the temporal relationship to changes in quality of life and health economic variables<br>• Proportion of patients with relapse/flare after achievement of CR between Baseline and Weeks 61 and 109<br>• Proportion of patients initially randomized to rilzabrutinib that are in CR with a zero CS dose, from Week 53 to Week 61 (no randomized treatment comparison)<br>• Proportion of patients initially randomized to placebo that are in CR with a zero CS dose, from Week 53 to Week 61 (no randomized treatment comparison)<br>• Change in Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) score from Baseline to Weeks 5, 13, 25, 37, 61, and 109<br>• Total number of disease relapses/flares from Week 37 to Weeks 61 and 109 |

| Objectives | Endpoints |
|---|---|
| | • (Optional) Blood samples for exploratory analysis of vaccine IgG response during treatment. |
| **Long Term Extension Objective**<br>• To evaluate the long-term safety and efficacy of rilzabrutinib | **Long Term Extension Endpoints**<br>• Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects during the LTE from Week 61 to Week 113<br>• Average daily dose of CS from Week 61 to Week 113<br>• Time to initial relapse/flare from initial CDA to Week 109. |

## 3.1 APPROPRIATENESS OF MEASUREMENTS

**Outcome Assessment Definitions**

***Control of Disease Activity (CDA):***

Control of disease activity (disease control) is defined as the visit at which new lesions cease to form and established lesions begin to heal. This is also considered the beginning of the consolidation phase. The expected interval of time to reach the control of disease activity is on the order of weeks, although it may be shorter.

***End of Consolidation Phase (ECP):***

The end of the consolidation phase is defined as the visit at which no new lesions have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions have healed. Therefore, in order to achieve ECP, CDA must be confirmed at a visit ≥2 weeks later and 80% of the lesions seen previously must have healed.

***Complete Remission (CR):***

Complete remission is defined as the absence of new and established lesions and is intended to mean “no disease activity”. Various qualifying statements are added to this definition for endpoints in this protocol.

***Relapse/Flare:***

A relapse of disease and a flare of disease are synonymous. They are defined by the appearance of 3 or more new lesions after CDA and within a month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved CDA.

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

This is a randomized, phase 3, parallel-group, double-blind, placebo-controlled trial with 36 weeks of treatment during a Blinded Treatment Period followed by an Open-Label Extension Period of 24 weeks. After completing the Open-Label Extension Period, eligible patients may continue in the Long Term Extension Period of 48 weeks. Patients will continue to have a 4 week follow-up visit after the patient's last dose of rilzabrutinib as detailed in the Figure 1. This study will be conducted at approximately 100 global sites.

**Duration of Trial Participation**

For each patient, the trial will last approximately 68 weeks including Screening Period (up to 4 weeks), the Blinded Treatment Period (Week 1 through Week 37), the Open-Label Extension Period (Week 37 to Week 61), and a 4-week end of treatment follow-up (up to Week 65).

**Blinded Treatment Period (Weeks 1 to 37)**

After informed consent is obtained, patients with moderate to severe pemphigus (PV and PF) will be screened and if eligible will be randomized in a 1:1 allocation ratio to receive either rilzabrutinib 400 mg twice daily (bid) (n ~ 60) or placebo bid (n ~ 60) during the Blinded Treatment Period (Week 1 to Week 37).

At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, shown in Table 1, and as required to adequately treat the disease. CS doses may be adjusted per Investigator discretion during the Screening period (Appendix 1 Section 12.1) but the dose should not be reduced below the required minimum initial dose levels (Table 1). CS taper below the required minimum dose level should not begin until ECP has been achieved.

Rilzabrutinib (400 mg tablet) or placebo will be taken twice daily by mouth starting on Day 1. Tablets may be taken with or without food.

If a patient achieves CDA (no new lesions and established lesions begin to heal), a follow-up visit ≥2 weeks later must confirm the finding of no new lesions prior to declaring ECP and tapering CS. ECP is achieved with the confirmation of CDA (no new lesions for ≥2 weeks) with approximately 80% of the established lesions epithelialized (healed). If needed, confirmation of CDA and achievement of ECP may be documented at an Unscheduled Visit, prior to the next scheduled study visit. See Table 2 for all required assessments for an Unscheduled Visit, which also includes Efficacy Outcome Assessment and PDAI.

While continuing on rilzabrutinib or placebo, following the achievement of ECP, patients will undergo a moderately rapid CS taper regimen as recommended by recently published consensus guidelines (1) with the goal to reduce the CS dose to 5 mg/day by no later than Study Week 29, with CS dose-adjustment as clinically indicated to control disease (CS and Rituximab Management protocol, Appendix 1 Section 12.1).

CS taper should not begin until ECP has been achieved.

If the first documentation of CDA coincides with no disease activity (PDAI = 0), a follow-up visit ≥2 weeks later must still confirm that no new lesions are seen and PDAI = 0. At this time the patient is deemed to have confirmed CDA, ECP, and CR and therefore CS tapering can begin. If new lesion(s) are seen, the patient is no longer in CDA and therefore CS tapering should not begin. If a patient has not achieved CDA or new lesions emerge or existing lesions worsen but do not meet definition of relapse/flare, refer to Appendix 1 Section 12.1 regarding increasing steroid dosage.

Throughout the Blinded Treatment Period, patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1 Section 12.1) until CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The Principal Investigator (PI) should consult with the Medical Monitor in such cases.

Efficacy Outcome Assessment should be performed per the Efficacy Outcome Assessment Flowchart, Appendix 8 Section 12.8.

Once patients achieve CR on a dose of 5 mg/day of CS, that dose should be maintained (not tapered further) until Study Week 37 (time of primary endpoint).

Rituximab treatment may be administered during the Blinded Treatment Period at or after the Week 5 Visit, only after a second “qualifying relapse/flare” occurs, unless contraindicated (Appendix 1 Section 12.1).

If rituximab is administered, patients should continue to take rilzabrutinib/placebo, remain on trial and blinded to treatment assignment. After completing the Blinded Treatment Period, patients will enter the Open-Label Extension Period to receive active treatment with rilzabrutinib described below. A patient in the Blinded Treatment Period requiring an additional “top up” dose of rituximab after their initial rituximab course of treatment must be discontinued from the trial.

**Open-Label Extension Period (Weeks 37 to 61)**

From Week 37, all patients will receive active drug in the Open-Label Extension Period for 24 weeks per Table 3. Patients who received placebo will thus receive active treatment with rilzabrutinib 400 mg bid. Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse/flare during this period, must be discontinued from the study. If a patient has a qualifying relapse/flare during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period, the patient may continue in the trial.

Patients that received rituximab during the Blinded Treatment Period and are continuing in the study, will complete TBNK testing (T and B and Natural Killer Lymphocyte Panel) at their Week 37 Visit.

From Week 37 (time of primary endpoint), further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated. Patients who fail to respond to treatment or experience worsening of disease should have their CS dose increased per CS management guidelines (Appendix 1 Section 12.1) until CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor in such cases.

**Long Term Extension (LTE) Period (Week 61 to Week 109):**

After completing the Open-Label Extension Period, patients who are responding to rilzabrutinib treatment will be eligible to enter the Long Term Extension Period and will continue to receive open-label rilzabrutinib 400 mg bid for 48 weeks per Table 4.

Patients are eligible to participate in the LTE if:

a) they have achieved and/or maintained an ECP with ≤10 mg/day CS at any time between 37 and 61 weeks in the study.

Patients are not eligible to participate in the LTE if:

a) they have more than one relapse/flare following ECP requiring treatment with >10 mg/day CS (excluding CS taken short-term for dental work or surgery), or

b) have failed to adequately recover after a relapse/flare despite maximal tolerated CS dose.

Failure to adequately recover is defined as: <25% decrease from peak PDAI despite treatment with maximal steroid doses (minimum of 1.5 mg/kg/day unless there is a specific documented medical contraindication) for at least 2 weeks.

CS doses above refer to doses of prednisone or its equivalent.

Patients may continue in the LTE until:

a) they have had more than one relapse/flare following ECP that requires >10 mg/day CS (excluding CS taken short-term for dental work or surgery) or have failed to adequately recover after a relapse/flare despite maximal tolerated CS dose (per definition of failure to adequately recover above);

b) the drug is no longer being developed by the Sponsor for this indication;

c) the program is stopped for safety reasons.

Patients who have previously completed the Open-Label Extension Period prior to this amendment and were responders per the LTE requirement may enroll into the LTE.

Patients entering the LTE will receive Sponsor-provided CS, following CS Management Guidelines (Appendix 1 Section 12.1).

Patients requiring rituximab during the Long Term Extension Period will be discontinued from the trial.

**Study Population**

Approximately 120 male or female patients with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]) will be enrolled with a targeted minimum of 90 patients with PV, and a target maximum of 22 patients with PF.

**Study Assessments Overview**

See Figure 1 for a diagram of the study design and the Schedules of Assessments (Table 2, Table 3, and Table 4) and for description of the assessments.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Study PRN1008-012 is a randomized, parallel-group, double-blind, placebo-controlled trial over 36 weeks (Blinded Treatment Period) followed by an Open-Label Extension Period of 24 weeks, Long Term Extension Period of 48 weeks, and a Follow-up Period of 4 weeks, which is intended to evaluate the efficacy and safety of oral PRN1008 (Rilzabrutinib) in moderate to severe pemphigus.

Placebo has been selected as the comparator to rilzabrutinib, as there are no globally approved medicinal products, other than CS (approved in European Union [EU] but not US) that could serve as a suitably rapid-acting and active comparator. While azathioprine is approved in the EU for pemphigus, it is regarded as minimally effective by expert dermatologists (6) and takes 9 months to demonstrate any CS-sparing effects (9); therefore, it is not a suitable comparator to a fast acting agent like rilzabrutinib. Use of placebo is ethical in this context, since all patients in the trial will receive concomitant flexible dosing of CS therapy in accordance with standard of care, and rituximab rescue therapy may be used after a second “qualifying relapse/flare” (defined in Appendix 1 Section 12.1).

All patients will undergo a standard CS taper as soon as possible, commencing at the ECP, with the goal of achieving a reduction of CS dose to 5 mg/day by no later than Week 29, so that the “durable CR” primary endpoint at Week 37 can be met. From Week 37, further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated. Please refer to Appendix 1 Section 12.1 (Corticosteroid and Rituximab Management) and Section 3 (Response Definitions). A CS dose of 5 mg/day has been recommended by a European task force of experts as the level for long-term use associated with a low risk of harm (10).

The marketed tyrosine kinase (BTK) inhibitor, ibrutinib, has been studied in combination with rituximab in the treatment of chronic lymphocytic leukemia without evidence of increased drug-related adverse events (8). There is no a priori drug interaction potential between anti-CD20 biologic drugs and the small molecule rilzabrutinib apart from the theoretic on-target effects of combined immunosuppression.

The primary purpose of the 24-week, Open-Label Extension Period (OLE) is to allow access to study drug who were on placebo medication as well as to evaluate durability of clinical response and accrue additional long term data on the safety and efficacy of rilzabrutinib.

The primary purpose of the 48-week, Long Term Extension Period (LTE) is to provide extended access to rilzabrutinib for patients who are receiving clinical benefit and to accrue additional long-term data on the safety and efficacy of rilzabrutinib.

During the Coronavirus disease 2019 (COVID-19) pandemic, measures to ensure continued drug supply and safety monitoring for patients are described in the "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits Due to Travel Restrictions and Any Foreseeable Impacts of COVID-19" (Appendix 9 Section 12.9). These measures include remote study visits, enrollment procedures, direct to patient delivery of study medication and approved urine pregnancy tests, and handling of protocol deviations.

## 4.3 JUSTIFICATION FOR DOSE

Based on dose-ranging in the Phase 1 program using the BTK occupancy of rilzabrutinib in circulating white blood cells, a 400 mg bid dosing regimen with the tablet formulation was selected because this dose was predicted to produce >70% BTK occupancy predose (or >85% average occupancy over the day). BTK occupancy data from Study PRN1008-005 of patients with pemphigus confirms adequacy of this dose with an average Day 1 2-hour and Day 2 predose BTK occupancy of approximately 85%. Twice a day dosing has been more efficacious in both the rat collagen induced arthritis model and naturally occurring PF in dogs, and was confirmed to have a promising efficacy and safety profile in Study PRN1008-005.

The exposures from a 400 mg bid dose in humans have adequate safety factors to exposures in chronic rat and dog Good Laboratory Practices (GLP) safety toxicology studies. Please refer to the IB for more details.

**Rituximab and Possible Combination with rilzabrutinib**

Rituximab is a chimeric anti-CD20 antibody authorized for the treatment of rheumatoid arthritis, non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (granulomatosis with polyangiitis [GPA] also known as Wegener's granulomatosis) and microscopic polyangiitis (MPA) in combination with CS. An open-label, randomized study comparing rituximab with 0.5 to 1 mg/kg/day of prednisone with 1 to 1.5 mg/kg/day of prednisone found a CR rate of 89% could be achieved by two years compared with 34% for CS alone. The study used a regimen of treatment at Month 0 of two 1 g infusions, two weeks apart, and 500 mg each at Month 12 and 18 (11). Although it is approved for the treatment of pemphigus only in the US at this time, it is recommended as a possible first-line therapy in combination with CS in newly updated consensus guidelines (1).

RITUXAN, MabThera or other approved, biosimilar agents may be used in this clinical trial per protocol. Instructions for administration of the intravenous infusion will be provided in the Pharmacy Manual. For detailed safety information on rituximab or other biosimilar agents investigators should refer to the current, locally applicable, approved product information.

## 4.4 END OF STUDY DEFINITION

**End of Trial (Follow-up Period, 4 Weeks after last Trial Dose):**

End of Trial (EOT) for the overall clinical trial is defined as the point at which the last patient has completed the last visit of the study.

For patients eligible for the Long Term Extension, the EOT is defined as the point at which the patient has completed their Week 113 Visit (4 weeks after the patient's last dose of rilzabrutinib).

For patients that are not eligible for the Long Term Extension, the EOT is defined as the point at which the patient has completed their Week 65 Visit (4 weeks after the patient's last dose of rilzabrutinib).

Patients who are not able to complete the Blinded Treatment Period, Open-Label Extension Period or Long Term Extension Period as planned and discontinue the study early should be encouraged to come back for an Early Termination (ET) Visit as soon as possible. Patients that discontinue early will have the ET assessments completed as outlined in the Schedule of Assessments based upon from which phase treatment they are terminating, Table 2 (Blinded Treatment Period), Table 3 (Open-Label Extension Period), or Table 4 (Long-Term Extension Period).

In addition to the ET Visit, patients should return for the EOT Visit 4 weeks following their last dose of rilzabrutinib/placebo or rilzabrutinib.

In the event the ET Visit occurs ≥4 weeks after their last dose of rilzabrutinib/placebo or rilzabrutinib, this will be recorded as the ET Visit and there is no need for the 4-week safety follow-up (EOT) visit.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 INCLUSION CRITERIA

Patients may be included in the study if ALL of the following criteria are met:

**Type of participant and disease characteristics**

I 01. Male or female patients, aged 18 to 80 years old with moderate to severe, newly diagnosed or relapsing PV or PF, with a clinical presentation and histopathology consistent with PV or PF (see Section 8.4.3).

I 02. Positive circulating anti-dsg1 or 3 autoantibody titer.

I 03. At Screening, PDAI score of at least 9 points for relapsing patients (diagnosed >6 months prior to Screening) or at least 15 points for newly diagnosed patients (diagnosed ≤6 months prior to Screening).

I 04. Adequate hematologic, hepatic, and renal function (including but not limited to absolute neutrophil count ≥1.5 × $10^9$/L, hemoglobin [Hgb] >9 g/dL, platelet count ≥100 × $10^9$/L, aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] ≤1.5 × upper limit of normal [ULN], albumin ≥3 g/dL, creatinine ≤1.5 × ULN).

**Sex, contraceptive/barrier method and pregnancy testing requirements**

I 05. Female patients who are of reproductive potential must agree for the duration of the study to use an effective means of contraception (eg, hormonal contraception methods that inhibit ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or condoms).

For females considered not to have reproductive potential:

Any woman of age ≥55 years with amenorrhea for >1 year, will be considered as having confirmed menopause and follicle-stimulating hormone (FSH) or pregnancy testing will not be needed. Postmenopausal females <55 years of age (defined as amenorrhea >1 year) must have menopause confirmed by elevated FSH levels at screening. Surgically sterile females do not require any further confirmation of menopause and will not be considered to have reproductive potential.

For participants in Germany, please see specific instructions in Appendix 10 Section 12.10.

**Informed Consent**

I 06. Able to provide written informed consent and agreeable to the schedule of assessments.

## 5.2 EXCLUSION CRITERIA

Patients will be excluded from the trial if any of the following criteria are met:

**Medical conditions**

E 01. Suspected paraneoplastic pemphigus and other forms of pemphigus that are not pemphigus vulgaris or pemphigus foliaceus.

E 02. Previous use of a Bruton tyrosine kinase (BTK) inhibitor.

E 03. Pregnant or lactating women.

E 04. Electrocardiogram (ECG) findings of QT corrected for heart rate (QTc) >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities.

E 05. A history of malignancy of any type within 5 years before Day 1, other than surgically excised non-melanoma skin cancers or in situ cervical cancer.

**Prior/concomitant therapy**

E 06. Use of immunologic response modifiers as concomitant medication and with the following washout periods: A) stop ***at least 2 weeks prior to Screening***: mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, intravenous immunoglobulin (IVIG), Kinaret (anakinra), Enbrel (etanercept), or any other immunosuppressant not mentioned in this exclusion criterion; B) ***12 weeks prior to Screening***: Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), Orencia (abatercept), Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), plasmapheresis; C) ***6 months prior to Screening (or shorter if there is documented B cell reconstitution for anti-CD20 drugs):*** anti-CD20 drugs such as rituximab, ofatumumab, other long-acting biologics.

E 07. Use of proton pump inhibitor drugs such as omeprazole and esomeprazole within 3 days of Day 1 (it is acceptable to change patient to H2 receptor blocking drugs prior to Day 1).

E 08. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A within 3 days or 5 half-lives (whichever is longer) of Day 1 (Appendix 7 Section 12.7).

E 09. Use of CYP3A-sensitive substrate drugs with a narrow therapeutic index within 3 days or 5 half-lives (whichever is longer) of Day 1 and for the remainder of the trial including, but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus (topical and oral), or terfenadine.

E 10. Has received any investigational drug (or is currently using an investigational device) within the 30 days before Day 1, or at least 5 times the respective elimination half-life time (whichever is longer).

E 11. History of drug abuse within the previous 12 months.

E 12. Alcoholism or excessive alcohol use, defined as regular consumption of more than approximately 3 standard drinks per day.

**Other exclusions**

E 13. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate rilzabrutinib/placebo absorption.

E 14. Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1.

E 15. History of solid organ transplant.

E 16. Positive at Screening for human immunodeficiency virus (HIV), hepatitis B (surface antigen and/or core antibodies), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA).

E 17. Positive interferon-gamma release assay (IGRA) (eg, T-spot TB Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus), at Screening. Unless, the patient has latent tuberculosis (TB) and all of the following 3 conditions are true:

a) Chest X-ray does not show evidence suggestive of active 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 indeterminate for any reason 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.

E 18. History of serious infections requiring intravenous therapy with the potential for recurrence or currently active moderate to severe infection at Screening (Grade 2 or higher).

E 19. Live vaccine within 28 days prior to Day 1 or plan to receive one during the trial.

E 20. Any other clinically significant disease, condition (including contraindication to CS and/or inability to follow CS dosing as outlined in the protocol [see Table 1 for more details]), or medical history that, in the opinion of the Investigator, would interfere with patient safety, trial evaluations, and/or trial procedures. In areas endemic for Chagas disease, screening is recommended prior to enrollment.

For participants in Germany, please see specific instructions in Appendix 10 Section 12.10.

# 6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## 6.1 STUDY INTERVENTION(S) ADMINISTERED

### 6.1.1 Rilzabrutinib/Placebo

Each PRN1008 (Rilzabrutinib) film-coated tablet contains 400 mg of rilzabrutinib drug substance and is [redacted] in color. In addition, the tablet contains [redacted].

The placebo treatment is also film-coated tablets that are identical in appearance and contain the same inactive ingredients as that of the rilzabrutinib trial medication, but do not contain rilzabrutinib. In addition, the inactive ingredient mannitol has been added as a filler to replace rilzabrutinib.

#### *6.1.1.1 Packaging*

PRN1008 (Rilzabrutinib) drug product or placebo will be supplied to the clinical sites in blister cards. Each blister card will contain 14 tablets of rilzabrutinib or placebo with day and night designation to provide guidance to the subject on which tablet to ingest. Subjects will receive rilzabrutinib or placebo tablets in a kit containing 5 blister cards or 5-week supply of rilzabrutinib or placebo (70 tablets).

### 6.1.2 Corticosteroids

Oral corticosteroids (prednisone or prednisolone) will be provided during the Blinded Treatment Period and Open-Label Extension Period. Patients entering the LTE will receive Sponsor-provided CS.

#### *6.1.2.1 Corticosteroid starting doses and management during screening and at Day 1*

Required initial doses of CS for the duration of Screening are ≥0.2 mg/kg/day of CS for patients with relapsing disease (diagnosed >6 months prior to Screening) and ≥0.5 mg/kg/day for patients with newly diagnosed disease (diagnosed ≤6 months prior to Screening). At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, and as required to adequately treat the disease during the Screening period. CS doses may be adjusted per Investigator discretion during the Screening period (Appendix 1 Section 12.1) but the dose should not be reduced below the required minimum initial dose levels (Table 1). CS taper below the required minimum dose level should not begin until ECP has been achieved.

If disease significantly (Investigator judgment) worsens during the Screening period, up titration of CS dose by 50-100% should occur, as often as every 5-7 days if needed (4).

#### *6.1.2.2 Corticosteroid management during blinded treatment period, open-label extension period, and long term extension period*

##### *6.1.2.2.1 Corticosteroid-Tapering (Consensus Guidelines)*

CS will be tapered from ECP towards a goal of 5 mg/day by ≤Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. From Week 37, further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated. At Investigator discretion, the CS may be switched to equivalent doses of oral hydrocortisone instead of prednisone or prednisolone when tapering from 5 mg to 0 mg CS.

CS tapering should follow the modified dosing guidelines below (1). Adjustment of the dosing guideline protocol by investigators is permitted for safety reasons, based on assessment and documentation of clinical need.

- Start tapering CS as soon as ECP is confirmed.
- Decrease CS by 25% every two weeks, until 20 mg per day
- Once at 20 mg per day, decrease CS by 2.5 mg per week
- Once at 10 mg/day, decrease CS by 1 mg per week.

Note, because 1 mg will be the smallest CS dosage provided and tablet splitting is not allowed, the Investigator must round up or down to the nearest whole milligram for CS dose after calculation of the new dose level.

##### *6.1.2.2.2 Corticosteroid-Up-Titration*

Patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1 Section 12.1) until CDA is obtained (4). If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor in such cases.

For full details of up-titration see Appendix 1 Section 12.1.

#### *6.1.2.3 Corticosteroids and rituximab*

Required, initial doses of CS for the duration of Screening are ≥0.2 mg/kg/day for patients with relapsing disease (diagnosed >6 months prior to Screening) and ≥0.5 mg/kg/day for patients with newly diagnosed disease (diagnosed ≤6 months prior to Screening).

Thereafter, CS are managed per the Corticosteroid and Rituximab Management protocol (Appendix 1 Section 12.1).

Rituximab should be managed per the Corticosteroid and Rituximab Management protocol (Appendix 1 Section 12.1), utilizing instructions in the Pharmacy Manual for administration of the to-be-used rituximab product.

### 6.1.3 Rituximab

Rituximab (or biosimilar) will be provided for patients having a second qualifying relapse/flare (Appendix 1 Section 12.1) during the Blinded Treatment Period. However, in the event a patient in the Blinded Treatment Period requires an additional "top up" dose of rituximab after their initial rituximab course of treatment, this will not be provided because the patient must be discontinued. Similarly, if a patient in the Open-Label Extension Period or Long Term Extension Period requires rituximab, the patient must be discontinued and rituximab will not be provided. If a patient has a qualifying relapse/flare during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the open label period, the patient may continue in the trial.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 Preparation, administration and storage

#### *6.2.1.1 Rilzabrutinib/Placebo*

No preparation of the PRN1008 (Rilzabrutinib) or placebo trial medication will be needed. Patients will use the trial medication directly from the dispensed blister cards.

Treatment medication will be taken twice daily by mouth starting on Day 1. Rilzabrutinib or placebo may be taken with or without food. Consecutive rilzabrutinib/placebo doses should not be taken within 8 hours of each other. Tablets should not be broken or crushed. Further details for dispensation and administration of blinded treatment are provided in the Pharmacy Manual.

PRN1008 (Rilzabrutinib) or placebo tablets are supplied in blister cards. The recommended storage condition is 2 to 25°C (IB).

#### *6.2.1.2 Corticosteroids*

No preparation of CS will be needed.

Corticosteroids are recommended to be stored at 2 to 25°C according to product label.

#### *6.2.1.3 Rituximab*

Rituximab, if required, should be administered per the product information in accordance with this protocol and the Pharmacy Manual.

Rituximab (or biosimilar) should be stored according to the instructions in the product label.

### 6.2.2 Drug management

Drug management will be the responsibility of the Investigator of the medical institution. The Investigator, the pharmacist of the medical institution, or another designated person must complete, in real time, all the documents concerning treatment management. Treatment management will be verified on a regular basis by the trial monitor.

The trial medication should be used only by healthcare professionals who are qualified by training and experience in the safe use and handling of investigational drugs.

During the COVID-19 pandemic, drug supply can be delivered to patients when the patient is not able to travel to the site or the site cannot host a patient visit. Site instructions for delivery of supplies directly to patients and procedures for conducting remote site visits inclusive of ensuring drug supply maintenance are described in Appendix 9 Section 12.9 ("Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits Due to Travel Restrictions and Any Foreseeable Impacts of COVID-19"), specifically in Appendix 9B for global sites and for sites in Taiwan.

### 6.2.3 Drug accountability

The Investigator or his/her designated representatives will dispense trial medication per the Schedule of Assessments (Table 2 and Table 3).

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (eg, Drug Receipt Record) and disposition (eg, Investigational Drug Dispensing Log) of the trial medication 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 trial medication was dispensed (for example subject identification number, participant initials, and date of birth)
- The date(s), quantity, and lot number(s) of the trial medication dispensed to the participant
- The identification of the person who dispensed the trial medication

All used and unused drug supplies must be returned by the subject at every visit.

All records and used and unused drug supplies must be available for inspection by the trial monitor at every monitoring visit. Reconciliation of all drug supplies (rilzabrutinib or placebo, rilzabrutinib open-label, CS, and rituximab) will be performed by the trial monitor. When the trial is completed, the Investigator will return any used and unused trial medication (eg, empty, partially used, and unused containers), to the Sponsor as requested. Copies of the completed Drug Dispensing Log and Drug Return Record(s) will be returned to the Sponsor. The Investigator's copy of the Drug Return Record(s) must accurately document the return of all drug supplies to the Sponsor.

### 6.2.4 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 trial 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 trial medication from the site that has not been stored properly should not be destroyed until the monitor and/or Sponsor approve the destruction.

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.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Allocation of patients to treatment groups will proceed through the use of an interactive web response system (IWRS) that is accessible 24 hours a day, 365 days a year.

The pharmacist or designee will be required to enter or select information that will include, but not be limited to: the user ID, and password, subject number, patient year of birth, as well as other information (as allowed locally). The pharmacist or designee will then be provided with a patient randomization number and treatment assignment. Once patient numbers and randomization numbers have been assigned, they cannot be reassigned. The randomization system will also send confirmation of the randomization, by email or fax, to the user. Specific instructions will be provided in the IWRS trial reference guide. Access to the randomization code will be limited; all Sponsor personnel (and representatives), and site personnel who are directly involved in the conduct of the trial will be blinded to randomization codes.

The treatment each patient receives will not be disclosed to the Investigator, trial center personnel, patients, or the Sponsor or representatives on the clinical study team. Further details for blinding and dispensing of blinded treatment are provided in the Pharmacy Manual.

If deemed by the Investigator to be medically necessary, the Investigator can unblind a patient via the IWRS.

## 6.4 STUDY INTERVENTION COMPLIANCE

Accountability and participant compliance will be assessed by maintaining adequate trial medication dispensing records and medication counts. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. See Section 6.2.3 for instructions on Drug Accountability procedures.

## 6.5 CONCOMITANT THERAPY

### 6.5.1 Prohibited medications

The following medications are prohibited for use during the trial:

- Concomitant use of any ***immunosuppressant medication***, other than CS and rituximab as described in this protocol. Patients who need other immunosuppressant therapy during the trial should be withdrawn. See E 06, Section 5.2 for washout periods.
- Concomitant use of known ***strong to moderate inducers or inhibitors of cytochrome P450 (CYP) 3A*** (Appendix 7 Section 12.7) within 3 days or 5 half-lives (whichever is longer) of Day 1.
- Use of ***CYP3A-sensitive substrate drugs with a narrow therapeutic index*** (within 3 days or 5 half-lives (whichever is longer) of Day 1 including, but not limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus (topical and oral), or terfenadine.
- ***Proton pump inhibitors*** are not permitted. Esomeprazole was shown to reduce the exposure of rilzabrutinib by approximately 50%, presumably due to the effects of a lack of an acidic environment on tablet dissolution. Subjects who are on proton pump inhibitors should be changed to histamine (H2) receptor blocking drugs if possible or not enroll in the trial. Details of H2 receptor blocker administration is provided in Section 6.5.2.
- ***Intralesional steroids*** are not permitted within 3 months prior to Screening, during Screening and for the duration of the study.
- ***Warfarin*** use is not permitted within 1 week or 5 half-lives (whichever is longer) of Day 1 and for the duration of the study.
- ***Live vaccines.***

### 6.5.2 Particular permissible medications

The following medications are permitted for use during the trial:

- Local use of topical corticosteroids and oral corticosteroid rinses (mouth washes) are allowed.
- Use of short, defined courses of intravenous corticosteroids are allowed, if deemed clinically necessary and at doses consistent with the oral regimen, after consultation with Medical Monitor. Sites should make all attempts to use Sponsor-provided oral prednisolone during the Blinded Treatment Period.
- Bisphosphonate drugs for osteoporosis prophylaxis.
- Clinically relevant cytochrome P450 (CYP)3A substrate drugs that are not narrow therapeutic index (eg, “sensitive substrate” listed in Appendix 7 Section 12.7). These drugs should be managed by administering rilzabrutinib or placebo on a time schedule such that CYP3A substrate drugs can be given 2 hours or more after rilzabrutinib or placebo.
- Histamine 2 (H2) receptor blocking drugs (ranitidine or famotidine) and antacids are permitted provided they can be given 2 hours or more after administration of rilzabrutinib or placebo.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

### 7.1.1 Permanent discontinuation

The trial will be terminated if major safety concerns related to rilzabrutinib or placebo emerge. Trial safety stopping criteria are:

1. More than one rilzabrutinib-related death
2. Three or more life-threatening (Common Terminology Criteria for Adverse Events [CTCAE], Grade 4) rilzabrutinib-related TEAEs
3. Sponsor chooses to terminate the study (see Section 7.1.2)
4. If the Data Safety Monitoring Board (DSMB) recommends trial termination due to safety reasons.

For participants in Germany, please see specific instructions in Appendix 10 Section 12.10.

### 7.1.2 Sponsor trial termination

The Sponsor has the right to terminate this study at any time for any reason. Reasons for terminating the study may include but are not necessarily limited to the following:

- The incidence or severity of AEs indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory, and the Sponsor wishes to stop the study.
- New scientific knowledge or other conditions place study patients at undue risk by continuing in the study.
- If the DSMB recommends trial termination due to safety reasons.

After having informed the Investigators and the coordinators, the Sponsor may terminate the study before its scheduled term. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and regulatory authorities will be informed according to local regulations.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

### 7.2.1 Patient Discontinuation and Stopping Rules

The Investigator in conjunction with the Sponsor may also, at their discretion, discontinue the patient from participation in the study at any time if discontinuation would be in the patient's best interest. If a patient meets any of the criteria listed below, the patient should complete the assessments for the ET Visit (see Table 2 and Table 3).

Reasons for discontinuing a patient may include, but are not necessarily limited to, the following:

- Severe and life-threatening pemphigus disease activity
- Grade 4 rilzabrutinib-related TEAE
- Serious allergic reaction to rilzabrutinib or placebo including anaphylactic reaction
- A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab course of treatment or a patient in the Open-Label Extension Period or Long Term Extension Period requiring rituximab
- Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), viral hepatitis (B and C) infection occurring during the study
- Pregnancy
- Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the patient to risk if the patient continues with rilzabrutinib or placebo or that prevents the patient's adherence to the protocol
- If in the Investigator's or the Sponsor's judgment, discontinuation is in the patient's best interest
- Violation of protocol inclusion or exclusion criteria, if, in the opinion of the Investigator and the Sponsor, the violation would significantly compromise data interpretation
- Discontinuation of the study by the Sponsor.

For participants in Germany, please see specific instructions in Appendix 10 Section 12.10.

No follow-up or additional procedures will be performed on patients who discontinue before receiving rilzabrutinib or placebo. For patients who discontinue after receiving any amount of rilzabrutinib or placebo, the reason for a patient's discontinuation from the study must be clearly documented in the patient's medical records and on the appropriate page of the eCRF, and patients will be asked to complete the ET assessments (see Table 2 and Table 3).

### 7.2.2 Patient withdrawal

All patients have the right to withdraw consent and discontinue participation without prejudice at any time during the trial. Every effort should be made to comply with the protocol; however, patients will be withdrawn from the trial entirely with no further trial visits if any of the following situation arise:

- Withdrawal of patient's consent or patient's request to discontinue from the trial for any reason.
- The patient is unwilling or unable to comply with the protocol.

Patients who are withdrawn from the trial will not be replaced. The reason for the patient's withdrawal from the trial should be recorded on the electronic case report form (eCRF).

## 7.3 LOST TO FOLLOW-UP

At the start of the study, the Investigator should try to obtain all relevant contact details for the patient to facilitate making contact with the patient, if necessary. In addition, each patient should be encouraged to attend all trial visits for which the patient is scheduled.

If a patient discontinues the study without notifying the Investigator, the Investigator must make every effort to contact the patient to identify the reason for the patient's discontinuation and to encourage the patient to complete the applicable ET visit assessments (see Table 2 and Table 3). If documented attempts to contact the patient fail, and a reason for the patient's discontinuation is undiscoverable, the Investigator can declare the patient as "lost to follow-up" at the end of the study. The Investigator should document in the corresponding medical record all efforts to contact the patient.

# 8 STUDY ASSESSMENTS AND PROCEDURES

## 8.1 TRIAL RECRUITMENT PROCEDURES

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

## 8.2 TRIAL ENROLLMENT PROCEDURES

Participants eligible for Screening cannot commence enrollment study procedures until the informed consent process and form (including voluntary participation/future use of blood samples/optional collection of blood pre-and post-vaccination) has been properly administered and signed. Screening tests are then administered, including blood tests sent for laboratory testing. Where the clinical significance of an abnormal Screening test result (lab or any other tests) is considered uncertain, the test may be repeated once.

The Investigator or designee will enter data for each enrolled participant in the trial electronic case report form (eCRF) and enter the corresponding patient identification number in the appropriate place on each participant's eCRF. Screening eCRFs must be completed in order to verify patient eligibility and should be completed as soon as assessments are performed.
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 trial and complete treatment as specified be permitted to re-enroll in the trial unless in the rare case where Sponsor approval is granted (eg, for a subject who completed and exited the OLE that is eligible to participate in the LTE).

During the COVID-19 pandemic, there is a need to assess the feasibility of implementing a plan for patient access to study drug and any additional measures required to monitor patient safety on an ongoing basis. Investigators should notify Principia and their contract research organization (CRO) study monitor if their site suspend patient enrollment (Appendix 9 Section 12.9).

## 8.3 VISIT OVERVIEW

During the trial, patients will return at specified times on an outpatient basis for assessment of vital signs, physical examination, assessment of AEs and concomitant medication use, assessment of clinical benefit and for provision of blood samples for clinical safety, PK, and PD assessment. For participants in Germany, please see specific instructions for SARS-CoV-2 testing in Appendix 10 Section 12.10.

Trial procedures and activities will occur at each visit as specified in Table 2 and Table 3.

During the COVID-19 pandemic, remote (eg, telephone call, video call) study visits may be performed when a patient is not able to travel to the site or the site cannot host a patient visit. Procedures to be performed during remote site visits are described in Appendix 9A of "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits Due to Travel Restrictions and Any Foreseeable Impacts of COVID-19" (Appendix 9 Section 12.9).

### 8.3.1 Screening (Day -29 to Day -1)

Informed consent will be obtained at Screening before performing any trial procedures.

Patients will undergo Screening assessments, including, but not limited to; blood sampling, ECG, clinical assessment and various quality of life assessments. Please refer to Table 2.

In cases where laboratory assessments are delayed due to logistic considerations, the Sponsor may permit an extension of the Screening Period for laboratory assessments up to 7 business days in order to determine eligibility. Week 1 Day 1 should occur as soon as possible upon evaluation of the delayed assessments and no later than 35 days after the initial Screening Visit.

Medical history and demographic data, including sex, age, race, body weight (kg), height (cm), and body mass index (BMI), will be recorded.

Patients not already on the mandated CS doses for the commencement of the Screening Period will commence the protocol-mandated CS doses.

Patients may be re-screened once following a Screen failure. Any labs performed in prior screening, within 2 weeks of re-screening will remain valid and should not be repeated. Labs performed for a previous screening within 6 weeks, may be considered for determination of eligibility on approval of the Medical Monitor. In the specific cases of QuantiFERON-TB, anti desmoglein antibodies and hepatitis/HIV testing, tests may be considered for determination of eligibility if performed in a previous screen within the last 12 weeks, with the approval of the Medical Monitor. However, pregnancy tests should be repeated at re-screening. Please see Schedule of Assessments Table 2.

When approaching the season appropriate for influenza vaccination, patients will be reminded to inform the clinic staff about vaccination plans. Similarly, when approaching the planned date of any vaccine dose regimen (during all study periods), patients will be reminded about the related pre- and post-vaccination blood sampling for vaccine IgG testing. Those who have not yet consented for collection of blood pre-vaccination (eg, those who make mid-study decisions about vaccinations) may do so just prior to blood collection. Additional details are provided in Appendix 11 Section 12.11.

### 8.3.2 Baseline (Day 1)

Patients will undergo baseline assessments shown in Table 2. The first dose of rilzabrutinib or placebo will be administered after all pre-dose procedures on Day 1 have been completed. Patients will remain in the clinic for 2 hours post-dose for a 2 hour blood collection.

### 8.3.3 Blinded treatment period (Weeks 1 to 37)

Please refer to Table 2 for specific assessments at each visit. CS dosing, and use of rituximab for a second qualifying relapse/flare, are detailed in Appendix 1 Section 12.1. The Efficacy Outcome Assessment Flowchart is detailed in Appendix 8 Section 12.8.

### 8.3.4 Open-label extension period (Weeks 37 to 61)

Please refer to Table 3 for specific assessments at each visit. CS dosing is detailed in Appendix 1 Section 12.1. Rituximab therapy is not allowed during this period unless the patient is withdrawn from the trial.

### 8.3.5 Long term extension period (Beginning Week 61)

Please refer to Table 4 for specific assessments at each visit. CS dosing is detailed in Appendix 1 Section 12.1. Rituximab therapy is not allowed during this period unless the patient is withdrawn from the trial. Please refer to Appendix 11 Section 12.11 for optional collection of blood pre-and post-vaccination.

### 8.3.6 OLE EOT/Week 65 and LTE EOT/Week 113 visits (follow-up period, 4 weeks after last trial dose)

Please refer to Table 3 and Table 4 for specific assessments at the EOT Visit for safety follow-up procedures performed 4 weeks after the last dose of study drug.

### 8.3.7 Early termination visit

Please refer to Table 2 (if terminating during double-blind treatment), Table 3 (if terminating during Open-Label Extension), or Table 4 (if terminating during Long Term Extension) for specific ET assessments. An attempt should be made to have the patient return for the ET Visit as soon as possible after the last dose of rilzabrutinib or placebo.

Patients in the OLE or LTE who are required to discontinue the study early per the rituximab receipt rules (Section 6.2.1.3) should have their ET Visit completed prior to rituximab infusion.

## 8.4 TRIAL ASSESSMENTS

All trial assessments will be collected as outlined at the visits noted in Table 2, Table 3, and Table 4.

### 8.4.1 Body height and weight

Body weight should be measured after checking for accurate zero calibration. Weight is recorded in kg to one decimal place.

Height is only assessed at Screening and is recorded in cm.

### 8.4.2 Physical examination

A full physical examination includes, at a minimum, assessment of the following: skin, eyes, ears, nose, throat, heart, chest/breast, abdomen, neurological system (briefly), lymph nodes, spine and extremities (skeletal).

An abbreviated physical examination is inclusive of general appearance, cardiac, gastrointestinal, and pulmonary assessments.

A licensed physician or nurse practitioner (or equivalent) will examine each patient.

Physical examination may be performed at various unscheduled time points if deemed necessary by the Investigator.

### 8.4.3 Biopsies

A new biopsy (cutaneous and/or mucosal) is not required if there is a prior and available biopsy report documenting histopathologic findings diagnostic for PV or PF. A new biopsy should be performed if an archival biopsy report is not available.

New biopsies should include local hematoxylin and eosin (H&E) histopathological review and direct immunofluorescence (DIF) for the characteristic pattern diagnostic of pemphigus.

Histopathology on biopsies is evaluated for consistency with a diagnosis of PV or PF:

- If DIF is positive, the patient is eligible in the presence of positive anti-desmoglein antibodies.
- If DIF is negative, the patient is not eligible. In these cases, where the H&E histopathology is characteristic of pemphigus and anti-desmoglein antibodies are positive, the biopsy may be repeated at the discretion of the Investigator.
- If DIF is not available, the patient is eligible in the presence of positive anti-desmoglein antibodies, and H&E histopathology characteristic of pemphigus.

### 8.4.4 Medical history

Medical history will be recorded at Screening and will include detailed pemphigus history (special Case Report Form), and history of all other underlying medical conditions.

### 8.4.5 Vital signs

Vital signs include body temperature, respiratory rate, blood pressure, and pulse rate.

Vital signs may be measured at unscheduled time points, if deemed necessary by the Investigator.

### 8.4.6 Electrocardiogram monitoring

Single 12-lead ECGs will be performed at Screening, Week 37, Week 61, and Week 109 (for patients in the Long Term Extension). All ECGs will be performed with the patient in a supine position.

Unscheduled ECGs may be performed as deemed necessary by the Investigator.

### 8.4.7 Clinical laboratory tests

See Table 2, Table 3, and Table 4 for laboratory test panels for chemistry, hematology, urinalysis and pregnancy testing. Laboratory safety tests may be performed at unscheduled time points, if deemed necessary by the Investigator. Screening laboratory safety tests may be repeated upon discussion with the Sponsor/Medical Monitor.

The Laboratory Manual will supply complete written instructions for collection, handling, processing, storage, and shipping of samples.

### 8.4.8 Pharmacokinetic/Pharmacodynamic assessments

Blood samples will be collected at timepoints for rilzabrutinib (and metabolites, as applicable) concentration levels (PK) and for anti-desmoglein-1 and -3 auto antibody titers by enzyme-linked immunosorbent assay (ELISA) (PD) per the Schedules of Assessments in Table 2 and Table 3.

Details regarding the collection, handling, processing, storage, and shipping of samples are provided in the Laboratory Manual.

#### *8.4.8.1 Vaccine IgG*

To explore possible effects on vaccine response, investigators will be encouraged to request injectable vaccination plans in line with age-appropriate local medical practice or guidelines from participants who have entered the study and completed at least 6 weeks of rilzabrutinib/placebo at the time of scheduled vaccination for the Blinded Treatment Period, and 6 weeks of rilzabrutinib for the Open-label or Long-term Extension period such as vaccines for influenza, COVID-19, or tetanus (alone or in combination) (live attenuated vaccines are excluded).

Participants scheduled to receive any of the aforementioned vaccines during the study periods may volunteer, after documenting informed consent, to provide 2 blood samples for vaccine-specific IgG in serum. The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine-specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded. Additional details are provided in Appendix 11 Section 12.11.

### 8.4.9 Pemphigus disease area index (PDAI)

The PDAI total activity score is a clinical assessment with a possible rater score ranging from 0 to 250, consisting of ≤120 points for skin activity, ≤10 points for scalp activity, and ≤120 points for mucosal activity (Appendix 2 Section 12.2). The rater examines each body area with scores assigned according to the number and maximum size of lesions in that area. When a score of 1 is given for a score of 1-3 lesions and none are more than 2 cm, the scorer records the actual number from 1 to 3. There is also a damage component to the score to reflect the non-active lesions such as post-inflammatory hyperpigmentation, but this is not counted in the assessment of disease activity. The PDAI is sensitive to low number of lesions which improves the consistency of score values between physician raters. The PDAI does not use body surface area (BSA) which can be difficult to estimate or lesion type as a scoring variable, both of which can exaggerate small differences between raters (12).

### 8.4.10 Autoimmune bullous disease quality of life (ABQOL)

The Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire was developed in Australia as a patient-based measure to determine quality of life in patients with autoimmune bullous disease (Appendix 3 Section 12.3). The ABQOL was found to be more sensitive than both the 36-Item Short Form Health Survey ($p = 0.01$) and the Dermatology Life Quality Index ($p = 0.02$). It was also found to be a reliable instrument evaluated by internal consistency with a Cronbach $\alpha$ coefficient of 0.84 (13).

### 8.4.11 Treatment autoimmune bullous disease quality of life (TABQOL)

The TABQOL questionnaire is a patient-based tool that measures the subjective element of disease progression and burden attributable to the side effects of autoimmune bullous disease (AIBD) treatment, with higher scores indicating worse quality of life (QOL) (14). Refer to Appendix 4 Section 12.4 for the scale.

### 8.4.12 EuroQOL (EQ-5D-5L)

The EuroQOL-5 Dimension 5 Level (EQ-5D-5L) is a copyrighted, patient-based instrument for a standardized measure of health status developed by the EuroQoL Group in order to provide a simple and generic measure of health for clinical and economic appraisal (15). The health status measured with EQ-5D-5L is used for estimating preference weight for that health status, then by combining the weight with time, quality-adjusted life-year can be computed. Quality-adjusted life-years gained is used as an outcome in cost-utility analysis which is a type of economic evaluation of healthcare programs and intervention. Refer to Appendix 5 Section 12.5 for an example of the copyrighted scale.

### 8.4.13 Glucocorticoid toxicity index (GTI)

The GTI is a copyrighted instrument for measurement of CS toxicity (16). Refer to Appendix 6 Section 12.6.

#### 8.4.14 Photography

Photography of lesions may be performed at selected sites, at the Investigator's discretion as allowed by country and local regulations.

#### 8.4.15 SARS-CoV-2 testing requirement (for German participants only)

For participants in Germany, please see specific instructions for SARS-CoV-2 testing in Appendix 10 Section 12.10.

### 8.5 ASSESSMENT OF EFFICACY

#### 8.5.1 Specification of the efficacy parameters

Efficacy will be evaluated using a combination of lesion assessments, corticosteroid usage, and validated instruments for assessing disease activity and patient quality of life.

A comprehensive list of all the secondary endpoints can be found in Section 3. In summary:

- The primary endpoint requires patients to have no new or established lesions at the Week 29, 33 and 37 Visits, while on a daily corticosteroid dose ≤10 mg/day.
- The first key secondary endpoint is an analysis of the cumulative CS dose from baseline to Week 37.
- The other secondary or exploratory endpoints include analyses of the following instruments: PDAI, ABQOL, TABQOL, EQ-5D-5L, VAS and GTI. Descriptions of the instruments can be found in Section 8.4.9 - Section 8.4.13.

#### 8.5.2 Methods and timing for assessing, recording and analyzing of efficacy parameters

Lesion assessments, the Pemphigus Disease Area Index (PDAI) and prescribed corticosteroid doses are recorded at every visit. The quality of life instruments are administered at the visits specified in the schedule of assessments (Table 2), and the ET Visit and Unscheduled visits. Further assessment details can be found in Section 8.

Descriptions of the analysis of the primary and secondary endpoints can be found in Section 9.3.5 and Section 9.3.6.

### 8.6 ASSESSMENT OF SAFETY

#### 8.6.1 Overview

After a comprehensive baseline evaluation, the safety of the patients will be monitored by assessment of vital signs, laboratory tests (hematology, and chemistry), disease assessments,

and abbreviated physical examinations. Concomitant medications and TEAEs will be monitored and tracked.

The Investigator should take appropriate and prompt remedial measures for AEs, including clinically significant laboratory result abnormalities, while trying to elucidate the etiology of the condition. The patient should then be followed-up until the condition resolves or becomes chronic or stable.

Trial stopping criteria are discussed in Section 7.1.1 and individual stopping criteria in Section 7.2.

### 8.6.2 Data safety monitoring board (DSMB) and interim analysis

An independent DSMB will regularly review and evaluate unblinded patient safety data including reported serious adverse events (SAEs), tabulations of all AEs, and safety laboratory results. The DSMB will agree on the DSMB charter and an initial frequency of meetings. Subsequently, meeting frequency will be determined as appropriate by the DSMB.

Documentation of the patient data reviewed at each meeting, including the individual DSMB member's confirmation of data review and the findings and actions of the DSMB, will be included in the Trial Master File. DSMB findings that impact the safety of patients in this trial will be immediately reported to the local competent authority (CA) and IEC. Details of unblinding procedures, DSMB composition and responsibilities, and other DSMB information will be provided in a separate DSMB charter.

Detailed methodology for summary and evaluation of data to be reviewed by the DSMB will be documented in a Statistical Analysis Plan (SAP) and DSMB charter. These documents may modify the plans outlined in the protocol; however, any major modification of the outcome measures and/or its analysis will also be reflected in a protocol amendment.

### 8.6.3 Adverse Events

#### *8.6.3.1 Adverse event collection period*

The AE Collection Period begins at the time of the first Screening/eligibility assessment and ends at the EOT for each patient.

During the COVID-19 pandemic, AEs will be collected during phone or video calls and recorded by electronic data capture (EDC) as described in Appendix 9A of the "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits Due to Travel Restrictions and Any Foreseeable Impacts of COVID-19" (Appendix 9 Section 12.9).

#### *8.6.3.2 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 case report form (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 expected variation in pemphigus disease activity itself.

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 (except for hypoglycemia) rather than component signs and symptoms on the AE CRF and SAE form (eg, record congestive heart failure rather than dyspnea, rales, and 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 and 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 (eg, colonoscopy, biopsy), the medical condition that led to the procedure is an AE. Elective procedures (eg, vasectomy), planned hospitalizations, and procedures for treatment of conditions noted in the patient's medical history that have not worsened (eg, 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 grouped together in the CRF, and the diagnosis will be clearly described.
- Underlying disease conditions: Unchanged (stable), chronic conditions, or those related to the underlying disease that are consistent with the disease's natural progression are not AEs and are not to be recorded on the AE page of the CRF. These conditions are considered part of the patient's medical history and must be adequately documented on the appropriate page of the CRF. Day-to-day fluctuations of pre-existing disease should not be recorded as an AE on the AE CRF.
- 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 CRF 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 abnormalities: 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.

#### *8.6.3.3 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 National Cancer Institute (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: by definition also a SAE.

Death will not be recorded as Grade 5 severity - rather, the underlying condition will be recorded and its severity graded, with death regarded as an outcome.

#### *8.6.3.4 Adverse event relationship to trial medication*

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 rilzabrutinib or placebo, indicating "yes" or "no" accordingly.

The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of rilzabrutinib or placebo
- Course of the event, considering especially the effects of dose reduction, discontinuation of trial medication, or reintroduction of rilzabrutinib or placebo (if applicable)
- Known association of the event with the rilzabrutinib or placebo 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.

#### *8.6.3.5 Treatment and follow-up of adverse events*

Adverse events (AEs), especially those for which the relationship to the rilzabrutinib or placebo 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.

#### *8.6.3.6 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 (ie, 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 rilzabrutinib or placebo (eg, dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (eg, 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 an SAE should be reported as such, in addition to being recorded as an AE in the CRF.

##### *8.6.3.6.1 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.

### *8.6.3.7 Serious adverse event reporting*

#### *8.6.3.7.1 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.*

#### *8.6.3.7.2 Serious Adverse Event 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 trial 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**

Pharmacovigilance (PVG) must be informed in writing 24 hours from the time the site investigational team first become aware of the event using the EDC system, if possible. Paper SAE report forms should only to be used when the EDC system is not accessible, and SAEs should be transferred into EDC once the system is available.

If EDC is not accessible, a paper SAE form including a written, narrative description of any SAE must be emailed to [redacted] within 24 hours after 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 paper originals of all information that has been emailed must be retained in the Investigator Site File.

*In addition to reporting the SAE in the EDC or via email, the local clinical research associate (CRA) and the Global Medical Monitor must be alerted via phone (refer to Site Manual).*

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

Starting after informed consent, SAEs must be reported within 24 hours (eg, SAEs related to invasive Screening procedures such as biopsies, or SAEs related to corticosteroid treatment during Screening).

Related SAEs ***MUST*** be collected and reported regardless of the time elapsed from the last administration of rilzabrutinib or placebo, even if the study has been closed.

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 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.

#### *8.6.3.7.3 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.

### 8.6.4 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 rilzabrutinib or placebo and immediately inform the Investigator. Pregnancies occurring up to 4 weeks after the last dose of rilzabrutinib or placebo 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.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor.

# 9 STATISTICAL CONSIDERATIONS

Detailed methodology for summary of the data will be documented prior to database lock and unblinding in a SAP. This document may modify the plans outlined in the protocol; however, any major modification of the outcome measures and/or its analysis will also be reflected in the clinical trial (study) report. Additional statistical analyses other than those described in this section may be performed, if deemed appropriate, and included in the SAP.

Descriptive summaries of variables by treatment will be provided where appropriate. Continuous variables will be summarized using the following descriptive statistics: mean, standard deviation (SD), number of observations, median, minimum and maximum. Summaries will also be presented for the change from baseline, when appropriate. For categorical variables, the counts and proportions of each value will be tabulated by treatment. For time to event variables, point estimates (25th, 50th, and 75th percentiles) along with 95% confidence intervals will be tabulated by treatment using Kaplan-Meier methods. Survival estimates will also be shown graphically for each treatment. In general, all data will be listed, sorted by patient and, when appropriate, by study day and study timepoint for each patient.

All statistical tests will be two-sided unless otherwise noted.

## 9.1 SAMPLE SIZE DETERMINATION

The primary efficacy endpoint is the percent of patients who are in CR from Week 29 (Visit) to Week 37 (Visit) with a CS dose of ≤10 mg/day.

[redacted]

## 9.2 POPULATIONS FOR ANALYSES

Four populations will be defined for data analysis: the Safety Population, the Intent-to-Treat (ITT) Population, Modified Intent-to-Treat (mITT) (efficacy) Population, and the Pharmacokinetic Population.

**Safety Population:**

All patients who receive at least one dose of study medication will be included in the Safety Population. The Safety Population is the primary analysis population for safety. Patients will be analysed according to the treatment they actually received, not necessarily the treatment they were allocated to at randomization. Results will be presented "as treated."

**Intent-to-Treat (ITT) Population:**

All patients who are randomized will be included in the ITT Population. Patients will be analyzed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented "as randomized."

**Modified Intent-to-Treat (mITT) Population:**

All patients who are randomized and receive at least one dose of study medication will be included in the mITT Population. The mITT Population is the primary analysis population for efficacy. Patients will be analyzed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented "as randomized."

**Pharmacokinetic (PK) and Pharmacodynamic (PD) Populations:**

All patients who receive at least one dose of study medication and have sufficient data for PK and/or PD analysis will be included in the PK and/or PD populations.

## 9.3 STATISTICAL ANALYSES

### 9.3.1 Disposition of the trial patients

The disposition of patients will be described with summaries of the number of patients treated and discontinued from the trial, including the primary reason for premature discontinuation.

### 9.3.2 Demographic and baseline characteristics

Summaries of patient disposition, demographics, and baseline characteristics will be provided by treatment group.

### 9.3.3 Exposure to study treatment

The number of received doses will be summarized by treatment group. Treatment duration and compliance for all patients will be described.

### 9.3.4 Safety and tolerability analysis (safety population)

The nature, frequency, and severity of AEs, including SAEs, AEs leading to discontinuation and possible corticosteroid-related adverse effects will be summarized descriptively by treatment group. Adverse events (AEs) prespecified as possibly related to CS will be grouped and analyzed separately in addition to the above.

A by-patient TEAE data listing, including verbatim term, preferred term and system organ class (SOC), treatment, severity, and relationship to cohort, will be provided.

The number of patients experiencing AEs and number of AEs will be summarized by treatment group using frequency counts.

Safety data, including laboratory evaluations and vital signs assessments, will be summarized by treatment group and time point of collection.

Descriptive statistics (arithmetic mean, SD, sample size [N], median, minimum, and maximum) will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

A change-from-baseline table will be provided for vital signs and clinical laboratory results by treatment group.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results, as appropriate.

Adverse events will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at the time of entry and the version will not change through completion of trial data available at the Sponsor or designee.

Concomitant medications will be listed by treatment and coded using the most current World Health Organization (WHO) drug dictionary and the version will not change through completion of trial data available at the Sponsor or designee.

Medical history will be listed by patient and treatment assignment.

No formal inferential statistics will be applied to safety assessments.

Additional analyses will be performed as appropriate.

### 9.3.5 Efficacy analysis (mITT Population)

In general, the need for rituximab rescue will be considered "treatment failure" for the analysis of efficacy endpoints except cumulative CS and composite GTI score.

The analyses for efficacy endpoints involving clinical assessment of CR during the blinded treatment period will be performed based on data collected during on-site visits (i.e., not including data collected from remote visits) as the primary analyses.

**Primary:**

The proportion of patients who are in CR from Week 29 (Visit) to Week 37 (Visit) with a CS dose of ≤10 mg/day.

- A Cochran-Mantel-Haenszel (CMH) general association test stratified by disease type (PV or PF) and disease history (newly diagnosed or relapsing) will be used to compare rilzabrutinib with placebo. Newly diagnosed pemphigus is defined as patients diagnosed ≤6 months prior to Screening. Relapsing, chronic pemphigus is defined as patients diagnosed >6 months prior to Screening.

Patients who drop out of the trial, withdraw, or who receive a rituximab dose prior to Week 37 will count as non-responders in the analysis.

The primary efficacy analysis will be performed using a CMH general association test stratified by disease history (newly diagnosed or relapsing) to compare rilzabrutinib with placebo.

**Key Secondary:**

The cumulative oral corticosteroid dose over the first 36 weeks will be summarized descriptively and will be compared across treatment groups using pairwise comparisons from an analysis of variance (ANOVA) model. The ANOVA model will include effects for treatment, and disease history.

Cumulative duration of CR with CS dose ≤ 10mg/day from Baseline to Week 37will be analyzed using a zero-inflated negative binomial model with terms for treatment group and disease history.

Time to first CR with a CS dose ≤10 mg/day, from Baseline to Week 37, will be analyzed using Kaplan Meier method. The median event time (and other quartiles) and 2-sided 95% confidence intervals will be presented. The endpoint will be evaluated based on a p-value from a log-rank test stratified by disease history for treatment group comparison.

Further details of the key secondary endpoints analysis and additional sensitivity analyses will be described in the SAP.

### 9.3.6 Key secondary efficacy sequential testing

After testing the primary endpoint in the PV mITT population and the mITT population (i.e. PV+PF population), key secondary efficacy endpoints will be tested sequentially, first on the PV

mITT population in the order specified below, and then on the mITT population in the same order:

- Cumulative CS dose from Baseline to Week 37
- Cumulative duration of CR with a CS dose ≤10 mg/day, from Baseline to Week 37
- Time to first CR with a CS dose ≤10 mg/day, from Baseline to Week 37

All other analyses will be performed at the 0.05 level and will not be corrected for multiple comparisons, as they will be viewed and handled in the perspective of not testing a formal hypothesis.

**Other secondary:**

The other secondary endpoints will be primarily analyzed descriptively.

The change from baseline in GTI, ABQOL, PDAI, and EQ-5D-5L overall visual analogue scale (VAS) scores to each visit will also be analyzed using restricted maximum likelihood (REML)-based mixed models for repeated measures (MMRM) with fixed effects for treatment, week, Screening score, and the treatment-by-week interaction.

The proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤5 mg/day of CS at any time will be compared using the same method as the primary endpoint.

The difference in the proportion of patients with 3 or more lesions within 1 month that do not heal spontaneously within 1 week, or with extension of established lesions, from Baseline to Week 37, will be tested in the same manner as the primary endpoint.

Proportion of patients with at least one disease relapse/flare from initial CDA to Week 37 will be tested in the same manner as the primary endpoint.

### 9.3.7 Pharmacokinetic and pharmacodynamic analysis

Individual and group PK and PD data will be summarized, displayed graphically, and by descriptive statistics for each visit where measured. Data may be summarized by descriptive statistics and related to clinical responses for each patient and as a group.

### 9.3.8 Exploratory analysis

Other subgroup and exploratory analyses not specified in the protocol may be performed. Health economic utility data related to the costs of AEs and hospitalizations may be explored. If collected, vaccine response parameters may be summarized by treatment group and, by disease and antigenic strain of the vaccine dose regimen. The change from baseline in TABQOL score to each visit (Weeks 5, 13, 25, 37, 61, and 109) will also be analyzed using REML-based MMRM with fixed effects for treatment, week, Screening score, and the treatment-by-week interaction. Full details will be provided in the SAP.

### 9.3.9 Long term extension analysis

The long term extension endpoints will be summarized descriptively in general. Summaries of patient disposition, demographics, and baseline characteristics will be provided. Safety data including AEs, laboratory evaluations and vital signs assessments will also be summarized. More details will be provided in the SAP.

### 9.3.10 Missing data

Missing data will not be imputed except for the situations described in the SAP. Details on the handling of missing data, including missing data due to the COVID-19 pandemic, will be described in the SAP.

# 10 INVESTIGATOR RESPONSIBILITIES

By signing the separate protocol and amended protocol agreement form, the Investigator agrees to do the following:

1. Conduct the trial in accordance with the relevant current protocol and make changes only after notifying the Sponsor, except when immediate changes are necessary to protect the safety, rights, or welfare of the patients
2. Comply with the currently endorsed E6 International Council for Harmonisation Tripartite Guideline on Good Clinical Practice and applicable Food and Drug Administration (FDA) Code of Federal Regulations (CFRs)
3. Personally conduct or supervise the described investigation
4. Inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes
5. Ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval have been met
6. Report to the Sponsor adverse experiences that occur in the course of the investigation as specified in 21 CFR 312.64 and the E6 International Council for Harmonisation Tripartite Guideline on Good Clinical Practice and any local regulations
7. Have read and understood the IB, including potential risks and side effects of the drug
8. Ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments
9. Maintain adequate and accurate records and make these available for inspection by the Sponsor, its designee, the FDA, the IRB/IEC, and other applicable national or local health authorities or agency authorized by law, as defined in 21 CFR 312.68 and currently endorsed E6 International Council for Harmonisation Tripartite Guideline on Good Clinical Practice
10. Ensure that an IRB/IEC that complies with the requirements of 21 CFR Part 56 and applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical investigation
11. Promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to human patients or others
12. Not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human patients
13. Comply with all other requirements regarding the obligations of Investigators and all other pertinent requirements.

## 10.1 DATA QUALITY ASSURANCE

The overall procedures for quality assurance of clinical trial 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 eCRF against the Investigator's records by the trial monitor (source document verification), and the maintenance of Drug Accountability (see Section 6.2.3) by the Investigator.

Data for this trial will be recorded in the trial EDC eCRFs. The data will be entered by the trial center from the source documents into the eCRF or will be loaded from other files (eg, safety lab data). In no case is the CRF to be considered as source data for this trial.

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 data entered in the database will be independently compared with the original Investigator's records.

For classification purposes, preferred terms will be assigned to the original terms recorded on the eCRF, using MedDRA for AEs, diseases and surgical and medical procedures, and the WHO drug dictionary for drug and herbal treatments.

## 10.2 PROTOCOL AMENDMENTS AND TRIAL COMPLETION

Protocol amendments must be made only with the prior approval of the Sponsor or its designees. The IRB/IEC must be informed of all amendments and give approval for all amendments. For studies conducted outside of the US, approval of substantial amendments must be obtained from the relevant Competent Regulatory Authority before implementation. The Investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor and/or the Sponsor's designee.

Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial (eg, change in monitor[s], change of telephone number[s]).

The Sponsor and the Investigator reserve the right to terminate the trial, according to the Clinical Trial Agreement. The Investigator should notify the IRB/IEC in writing of the trial's completion or ET and send a copy of the notification to the Sponsor and/or the Sponsor's designee.

Trial completion is defined as the date when all patients have completed the final study visit, and the trial database has been locked.

## 10.3 INFORMED CONSENT

The Investigator and Sponsor must agree upon the format and content of the informed consent form (ICF) before it is submitted to the IRB/IEC for approval. A copy of the IRB/IEC approved copy of the ICF will be forwarded to the Sponsor. Written IRB/IEC-approved informed consent and Health Insurance Portability and Accountability Act (HIPAA) release (or other privacy protection release, as governed by local regulations) must be obtained from each patient, before any trial related activities are conducted. The Investigator must retain all original signed and dated

ICFs (together with any subsequent IRB/IEC-approved amended versions) in the patient's file. A copy of the signed and dated ICF (and any amendments) must be given to the patient.

The ICF documents the trial-specific information the Investigator provides to the patient the patient's agreement to participate. Among other things, the Investigator or his/her designee will fully explain in layman's terms the nature of the trial, along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. The ICF/patient information sheet must be appropriately signed and dated before the patient enters the trial.

Patients will be informed of findings from earlier or concurrent clinical studies (including AEs), if it is considered that such information could potentially affect patient's willingness to participate or continue in the trial. Depending on the nature, severity, and seriousness of these AEs, the ICF may be amended as deemed appropriate. The original and any amended signed and dated ICF(s) and patient information sheet(s) must be retained in the patient's file at the trial site; and a copy must be given to the patient.

In this study, the optional procedures (eg, photographs and vaccine IgG sample collection) are listed separately at the end of the consent. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in the main consent. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

## 10.4 PATIENT CONFIDENTIALITY AND DISCLOSURE OF DATA

The Investigator must ensure that each patient's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor and/or its designee, patients must only be identified by trial, Patient Identification Number, and demographics, and pertinent restrictions of local regulations. No other personal identifiers will be used, and data will be de-identified in a manner compliant with Privacy Laws and, for US patients, the HIPAA regulations. Documents that are not for submission to the Sponsor and/or its designee (eg, signed ICFs and Patient Information Sheets) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or International Council for Harmonization (ICH) and Good Clinical Practice (GCP) Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor and/or its designee, by representatives of the FDA, national and local health authorities, and the IRB/IEC direct access to review the patient's original medical records for verification of trial-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the trial. The Investigator is obligated to inform the patient in the ICF that his/her trial-related records will be reviewed, by the above-named representatives.

Patients will be informed that data will be held on file, by the Sponsor, and that these data may be viewed by staff including the trial monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Participants will also be informed that a (trial) study report will be prepared and may be submitted to regulatory authorities and for publication. However,

participants will be identified in such reports only by Patient Identification Number and demographics, pertinent to restrictions of local regulations. All patient data will be held in strict confidence, as allowed by law.

Upon the patient's permission, medical information may be given to the patient's personal physician or other appropriate medical personnel responsible for the patient's welfare.

## 10.5 ELECTRONIC CASE REPORT FORMS

The data collected in the source documents for this trial will be entered into the trial EDC eCRF. 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, an eCRF must be completed and signed by the Principal Investigator or authorized delegate from the trial staff. If a participant withdraws from the trial, the reason must be noted in the eCRF. If a participant is withdrawn from the trial 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.

## 10.6 RETENTION AND AVAILABILITY OF RECORDS

The Investigator is required to retain the trial records and reports until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. If no marketing application is to be filed, or an application is not approved for the drug, the Investigator will retain the study (trial) records for 2 years after shipment and delivery of the drug for investigational use is discontinued and the Sponsor has so notified the FDA, per 21 CFR 312.57. Study (trial) records should, however, be retained longer if required by the applicable national and/or local regulatory requirements or by agreement with the Sponsor.

The Investigator must make study (trial) data accessible to the monitor, other authorized representatives of the Sponsor, and regulatory agency inspectors upon request. A file for each patient must be maintained that includes the signed ICF and the Investigator's copies of all source documentation related to that patient. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was transcribed.

## 10.7 AUDITS AND INSPECTIONS

In accordance with ICH, GCP and the Sponsor and/or its designee audit plans, this trial may be selected for audit. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of trial-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH, GCP, and applicable regulatory requirements. The Investigator/ institution should make available for direct access all requested trial-related records (ICH GCP 4.9.7) 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. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents (ie, completed CRFs, Investigator site files, and any source documents should be stored in a protected secure location [ICH GCP 4.9.4]).

If for any reason the study trial) records are moved to another location, the Investigator should notify the Sponsor of the new location.

# 11 ETHICAL ASPECTS

This section provides information for the Investigator on the ethics requirements for the trial, including subject informed consent, IRB/IEC 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.

## 11.1 LOCAL REGULATIONS/DECLARATION OF HELSINKI

The Investigator will ensure that this trial is conducted in full conformance with the ethical principles that have their origin in the "Declaration of Helsinki", and that are consistent with the principles outlined in the current "Guideline for Good Clinical Practice" ICH Tripartite Guideline GCP E6 or with the laws and regulations of the country in which the research is conducted (eg, 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), whichever affords the greater protection to the individual.

## 11.2 INSTITUTIONAL REVIEW BOARD REVIEW

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

An approval letter or certificate (specifying the protocol number and title) from the IRB/IEC must be obtained before starting the trial (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 competent authority approvals before starting the trial.

# 12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 12.1 APPENDIX 1 CORTICOSTEROID AND RITUXIMAB MANAGEMENT

Corticosteroid Starting Doses and Management During Screening and at Day 1:

Topical corticosteroid and oral corticosteroid rinses (mouth washes) are allowed.

Required, initial doses of oral CS (prednisone or prednisolone) for the duration of ***Screening*** are ≥0.2 mg/kg/day of CS for patients with relapsing disease (diagnosed >6 months prior to Screening) and ≥0.5 mg/kg/day for patients with newly diagnosed disease (diagnosed ≤6 months prior to Screening). At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, and as required to adequately treat the disease during the Screening period. CS doses may be adjusted per Investigator discretion during the Screening period but should not be reduced below the required minimum CS dose levels (≥0.2 mg/kg/day for patients with relapsing disease and ≥0.5 mg/kg/day for patients with newly diagnosed diseases. CS taper below the required minimum dose level should not begin until ECP has been achieved.

If disease significantly (Investigator judgment) worsens during the Screening period, up-titration of CS dose by 50-100% should occur, as often as every 5-7 days if needed (4).

**Corticosteroid Management during Blinded Treatment Period, Open-Label Extension Period, and Long Term Extension Period**

**Corticosteroid-Tapering (Consensus Guidelines) (1)**

CS will be tapered upon confirmation of ECP towards a goal of 5 mg/day by ≤Week 29. ECP is defined as the visit at which no new lesions have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions have healed. Once the 5 mg/day level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached.

From Week 37, further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated. At Investigator discretion, the CS may be switched to equivalent doses of oral hydrocortisone instead of prednisone or prednisolone when tapering from 5 mg to 0 mg CS.

CS tapering should follow the modified dosing guideline below, based upon (1). Adjustment of the dosing guideline protocol by investigators is permitted for safety reasons, based on assessment and documentation of clinical need.

- Start tapering CS as soon as ECP is confirmed
- Decrease CS by 25% every two weeks, until 20 mg per day

- Once at 20 mg per day, decrease CS by 2.5 mg per week
- Once at 10 mg/day, decrease CS by 1 mg per week to 5 mg

Note, because 1 mg will be the smallest CS dosage provided and tablet splitting is not allowed, the Investigator must round up or down to the nearest whole milligram for CS dose after calculation of the new dose level.

**Table 6: Example Taper for a 60 mg Dose of CS**

| Current Dose Level (prednisone equivalent) | Size of Dose Reductions (prednisone equivalent) | Example (Note: dosages rounded to nearest mg) | Frequency of Dose Reductions |
|---|---|---|---|
| 60 mg down to ~20 mg | Approximate 25% decrease | 60 mg, 45 mg, 34 mg, 26 mg, 20 mg | Every two weeks |
| ~20 mg to ~10 mg | ~2.5 mg decrease | 20 mg, 18 mg, 15 mg, 13 mg, 10 mg | Weekly |
| ~10 mg to 5 mg | 1 mg | 10 mg, 9 mg, 8 mg, 7 mg, 6 mg, 5 mg until Week 37 then further titration to 0 mg | Weekly[a] |

*a* Per guidelines (1) has a typographical error mistakenly saying "daily" when "weekly" was intended.

**CS dose up-titration for worsening disease:**

1. **Severe relapse/flare or worsening disease at any time, which, in the opinion of the Investigator, is potentially life threatening**

Commence conventional immunosuppressive therapy and discontinue rilzabrutinib/placebo.

2. **Non life-theatening worsening of disease during taper of CS prior to confirmation of ECP**

During Screening or the treatment periods of the trial, where an initial induction of CDA has not been achieved and blistering continues without improvement, CS should be increased by 50 to 100% every 5 to 7 days until confirmation of ECP. After ECP is confirmed CS taper should commence. Rituximab therapy may not be used in this situation. Patients who have been treated with a minimum of 1.5 mg/kg/day of corticosteroids for 2 weeks and have not achieved control of disease activity may be eligible after discussion with Principia to receive rituximab. For patients who are unable to escalate CS up to 1.5 mg/kg/day due to documented AEs related to CS and cannot achieve CDA following 2 weeks of treatment with their maximally tolerated CS dose, rescue with rituximab therapy may be offered. Please consult with the Medical Monitor.

3. **Non life-theatening worsening of disease during taper of CS after confirmation of ECP**

- Go back to last CS dose level if >3 lesions reappear during the tapering of oral corticosteroid therapy (where relapse/flare, as defined below, has not occurred)
- If a more severe full relapse/flare occurs (ie, the appearance of ≥3 new lesions within a month that do not heal spontaneously within 1 week, or there is extension of established

lesions), increase the CS dose by going back to the second to last dose until control of the lesions is achieved within 2 weeks, then resume taper

- If disease control is still not reached despite this, go back to initial dose or higher as necessary, and resume taper when ECP is confirmed again

It is recommended to follow the CS Guidelines during the Long Term Extension.

**Rituximab Management during Blinded Treatment Period**

Rituximab for second "qualifying relapse/flare":

- "Qualifying relapse/flare" for this purpose is defined as a relapse/flare occurring after CDA is achieved, ECP has been confirmed and CS taper has begun, that is not life-threatening (when a patient should be withdrawn) but is severe enough such that the PDAI total activity score is equal to or greater than the Screening or Day 1 baseline PDAI score (whichever is higher) for that patient. For example, if the Screening PDAI was 25, the Day 1 baseline was 21, and the relapse/flare PDAI 23, the relapse/flare would not be severe enough to be "qualifying". Whereas if the relapse/flare PDAI was ≥25 it would be "qualifying".
- Where a second qualifying relapse/flare occurs meeting the above definition, and it is at or after the Week 5 Visit, then one course of rituximab, which consists of two intravenous doses of 1 gram two weeks apart, may be administered, unless contraindicated.
- Oral CS doses should be managed as indicated for the patient at the time of the 2nd qualifying relapse/flare
- Rituximab should be administered as recommended in the Pharmacy Manual.
- Patients should not be unblinded to treatment assignment and should continue in the trial.

**Rituximab Management during Open-Label Extension Period and Long Term Extension Period**

Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse/flare during these study periods, must be discontinued from the study. If a patient has a qualifying relapse/flare during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period the patient may continue in the trial.

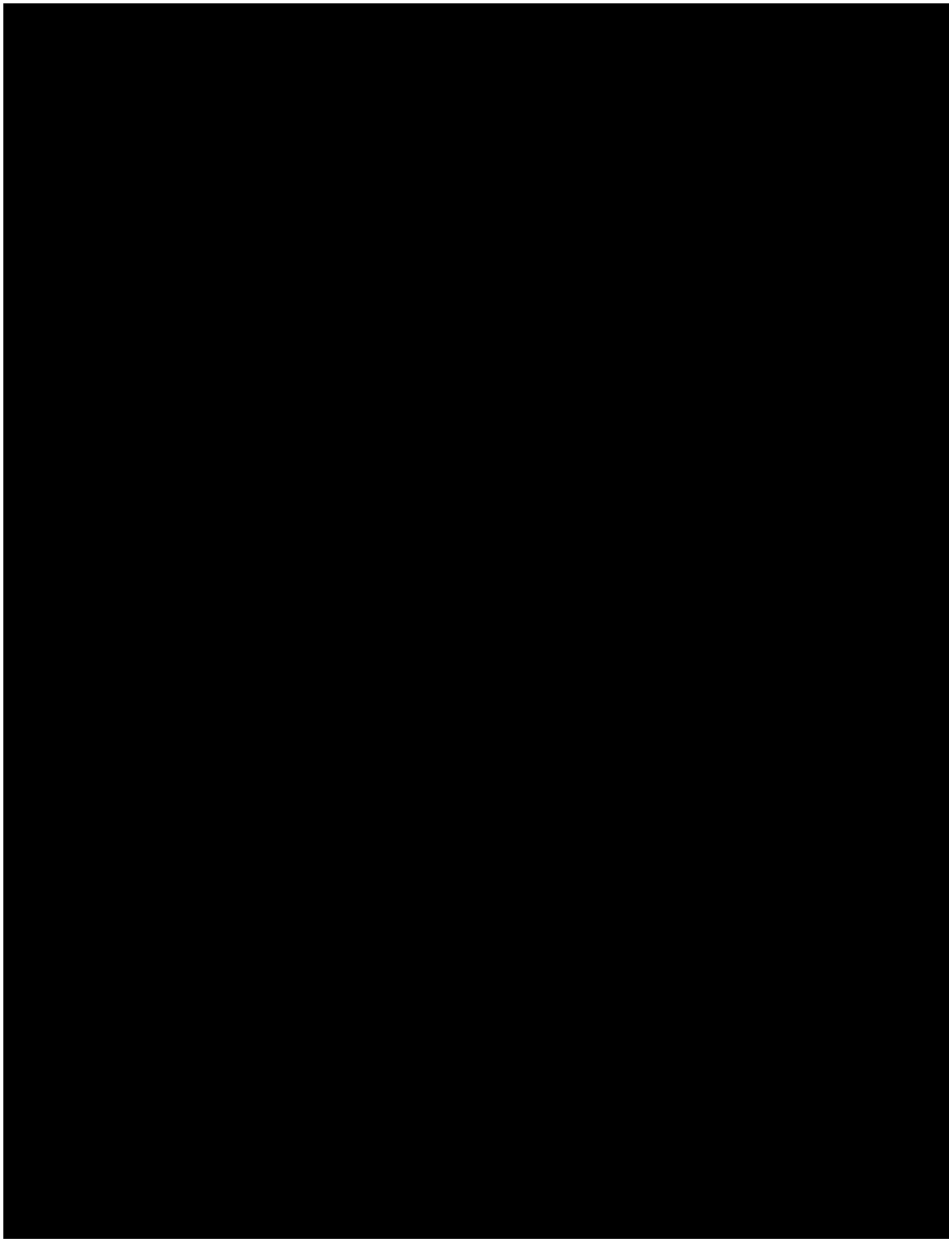
## 12.2 APPENDIX 2 PEMPHIGUS DISEASE ACTIVITY: PDAI

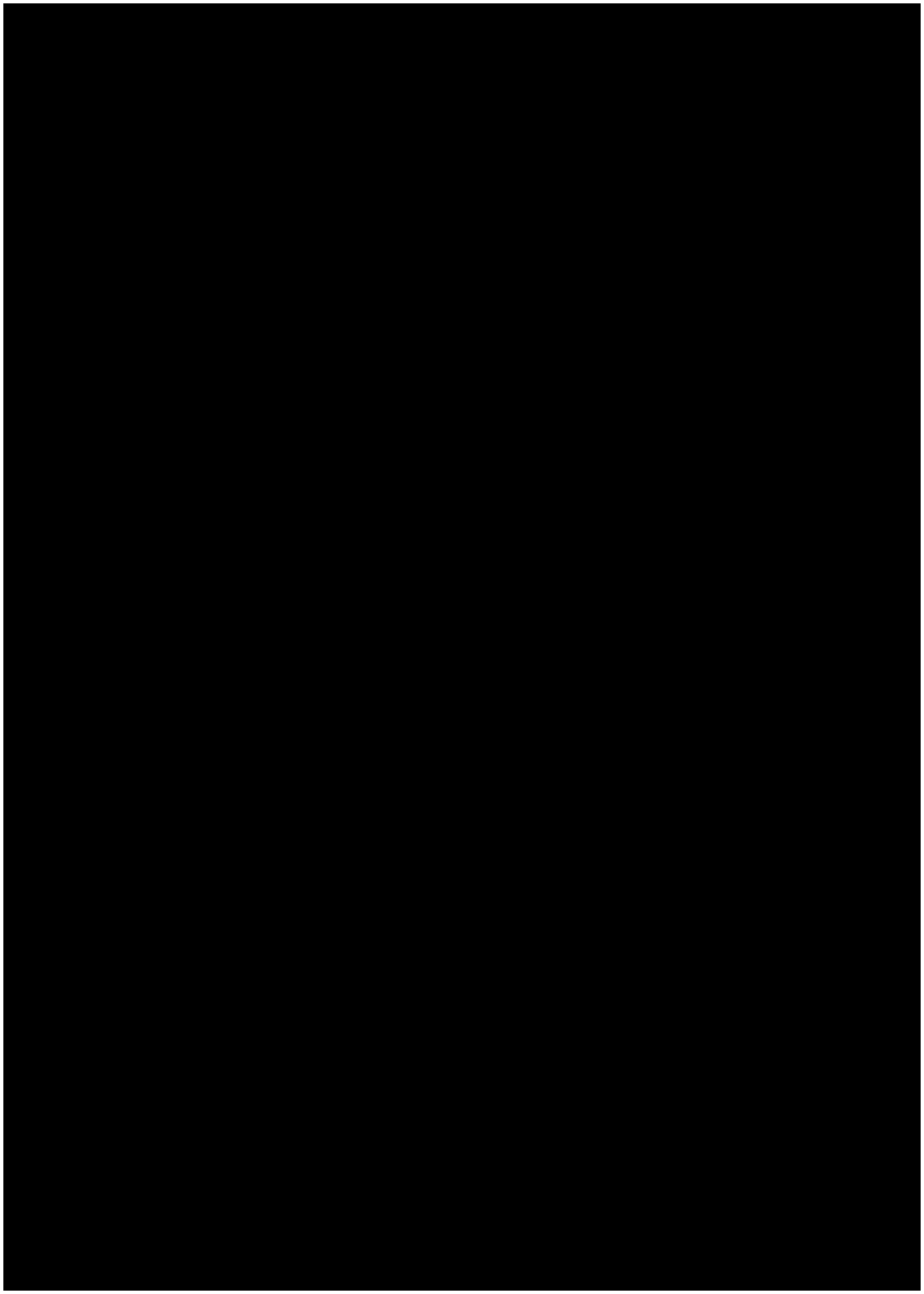
**Pemphigus Disease Area Index (PDAI)** (1, 18)

[redacted]

## 12.3 APPENDIX 3 PEMPHIGUS QUALITY OF LIFE EVALUATION: ABQOL

**ABQOL Questionnaire**

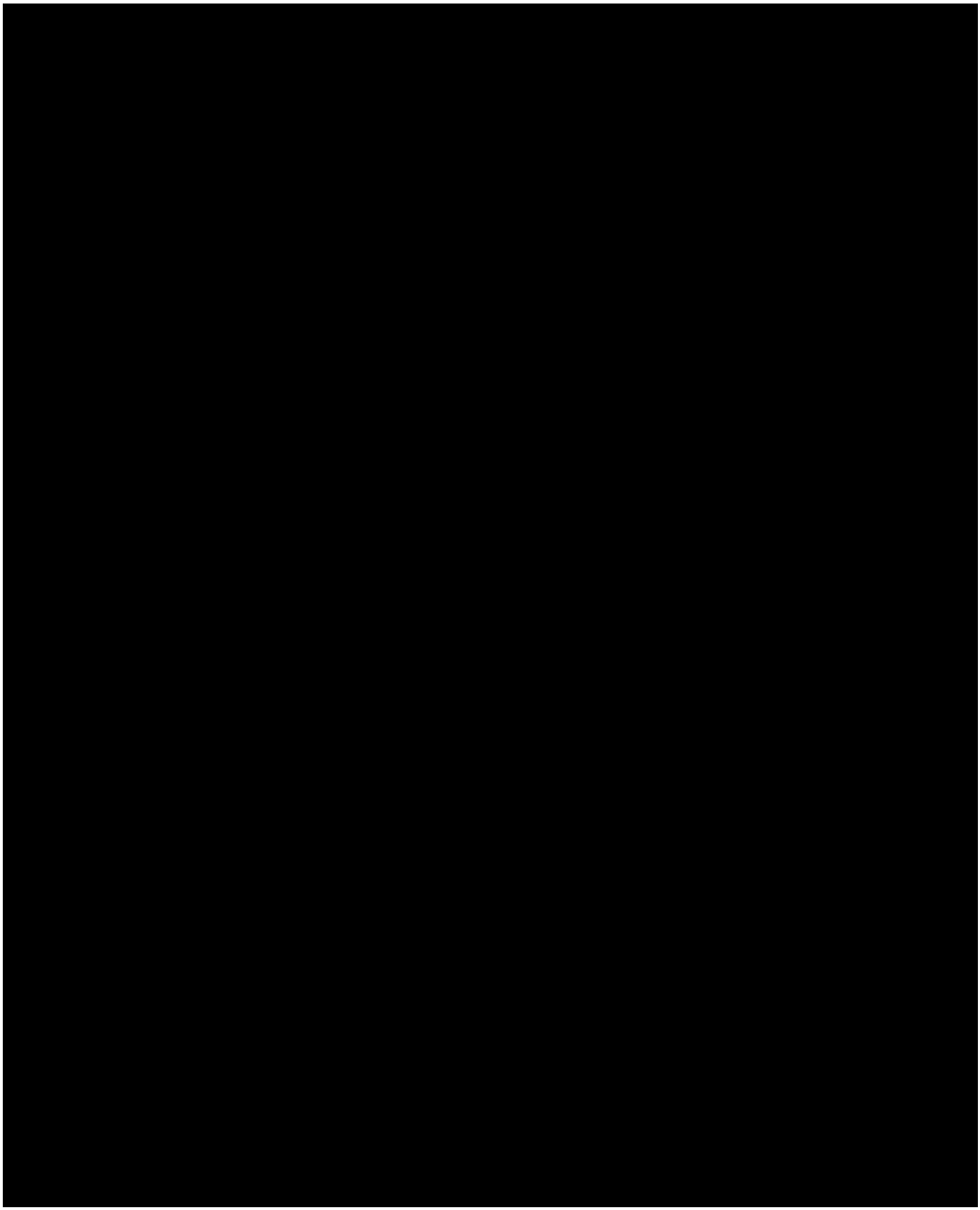


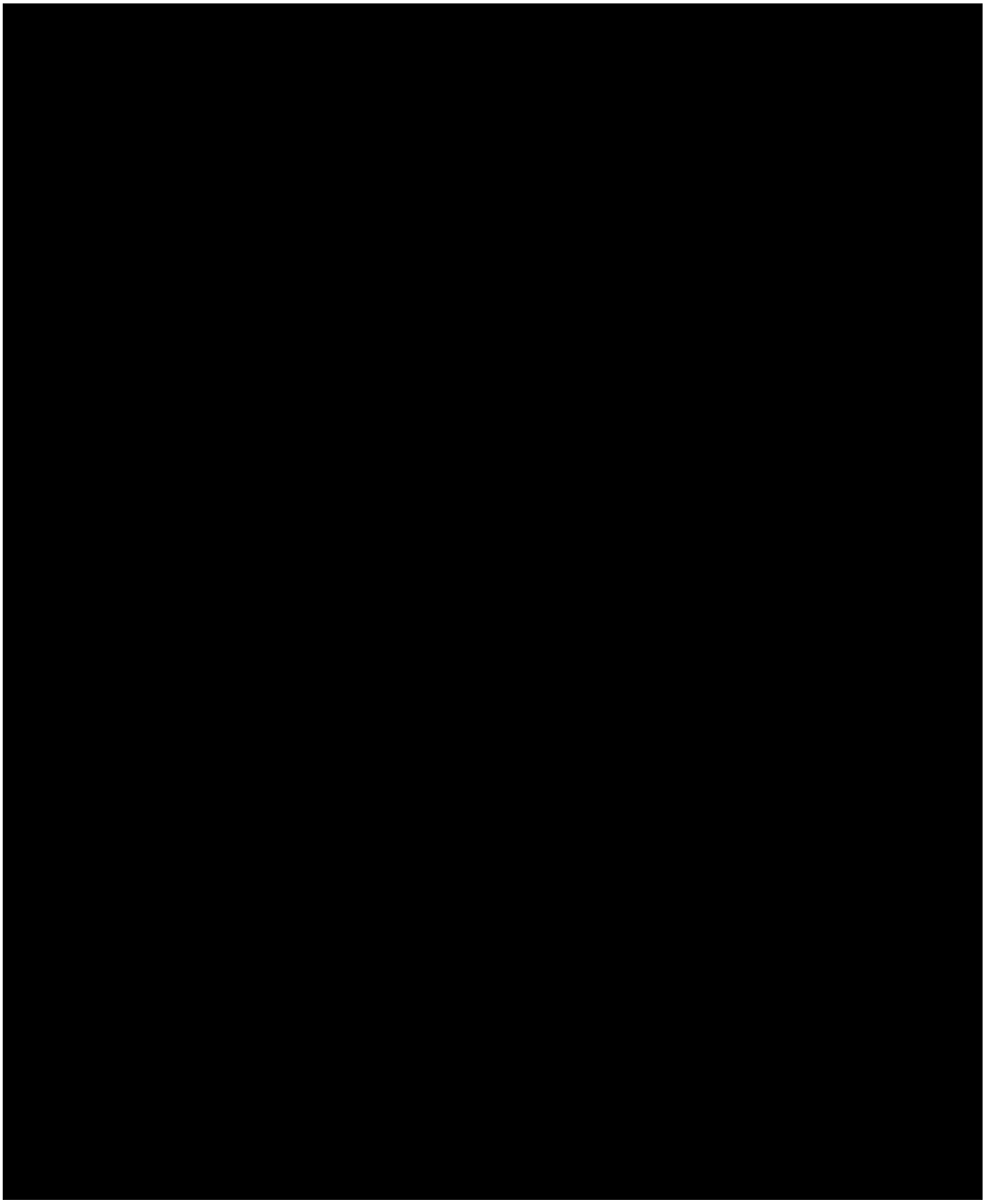


## 12.4 APPENDIX 4 PEMPHIGUS QUALITY OF LIFE EVALUATION: TABQOL

**Treatment of Autoimmune Bullous Diseases Quality of Life Assessment (TABQOL)** (19)

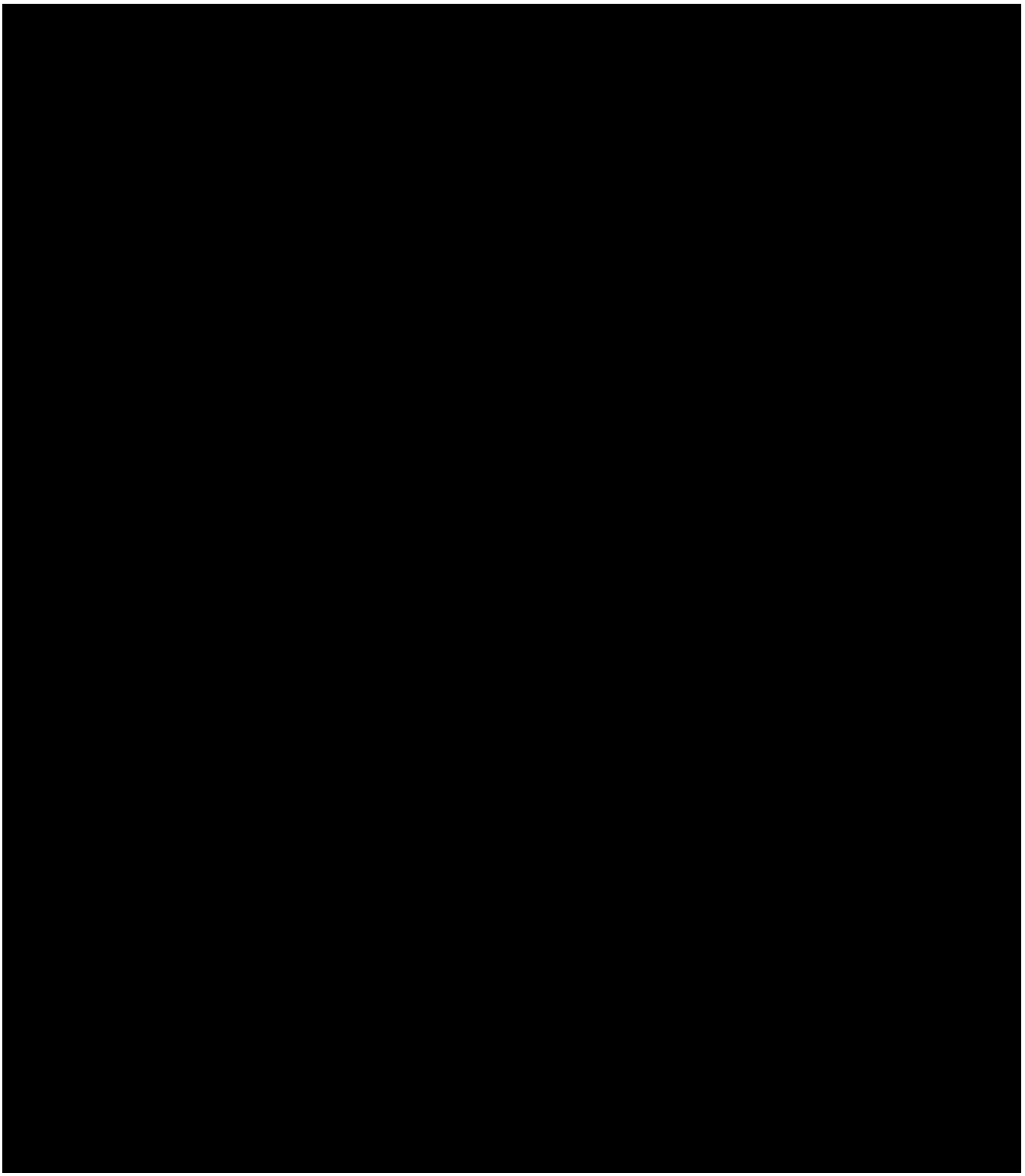
[redacted]

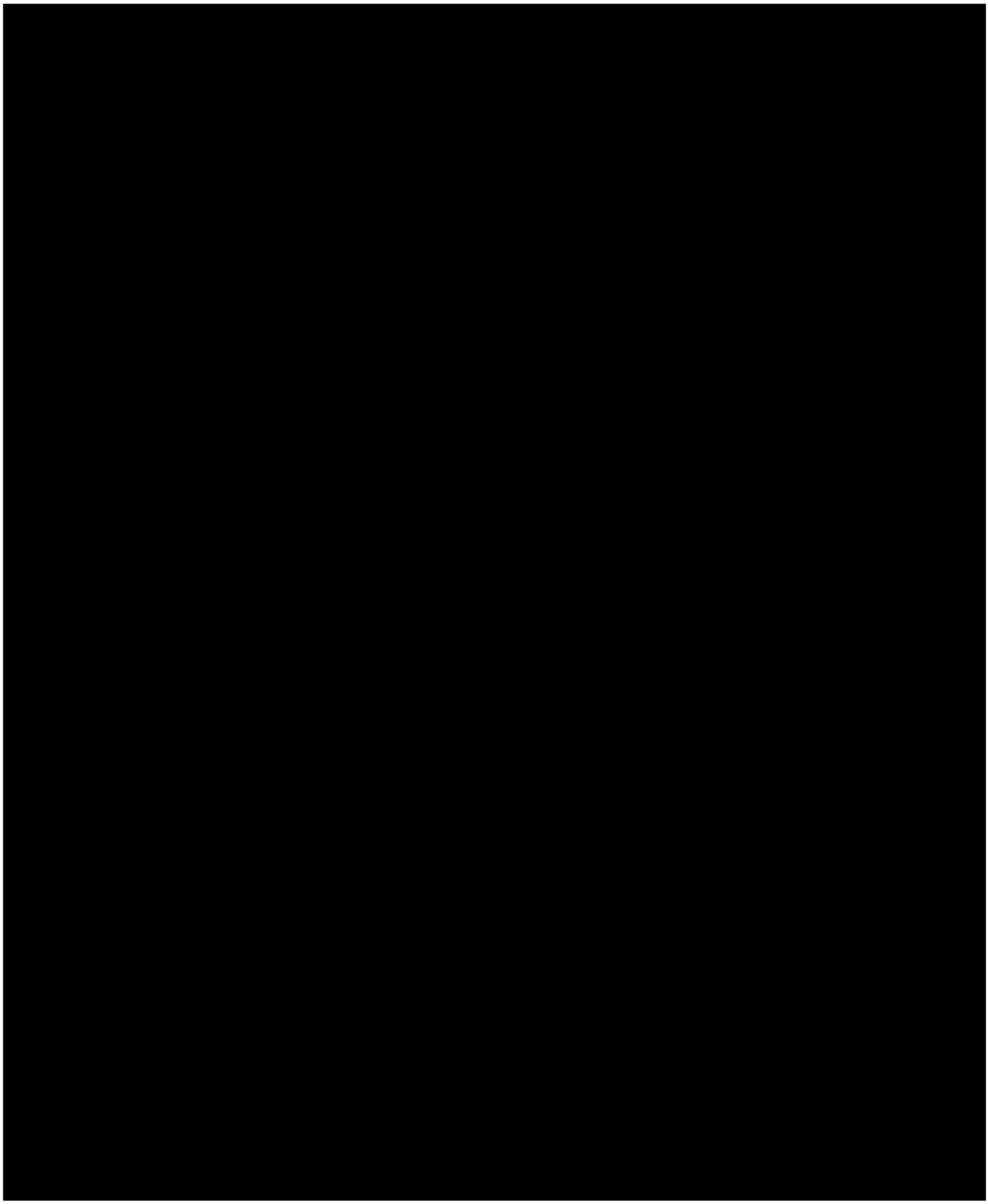




## 12.5 APPENDIX 5 GENERAL QUALITY OF LIFE EVALUATION: EQ-5D-5L

**EuroQOL-5 Dimension 5 Level (EQ-5D-5L)** (20)





## 12.6 APPENDIX 6 GLUCOCORTICOID TOXICITY INDEX (GTI)

The Glucocorticoid Toxicity Index (GTI) is a proprietary licensed instrument from Massachusetts General Hospital (16). It was developed to assess glucocorticoid (GC)-related morbidity and GC-sparing ability of other therapies. The scale collects information about known steroid toxicities and uses a weighted scoring system to assesses toxicity. The instrument calculates a composite index score from data captured related to the following domains: body mass index, glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. In addition, reports of any of the following toxicities are included in the index: endocrine (adrenal insufficiency), gastrointestinal (perforation, peptic ulcer disease), musculoskeletal (ruptured tendon, avascular necrosis) and ocular (retinopathy, increase in ocular pressure, posterior subcapsular cataract).

## 12.7 APPENDIX 7 STRONG TO MODERATE CYP3A INHIBITORS AND INDUCERS AND SENSITIVE CYP3A SUBSTRATES

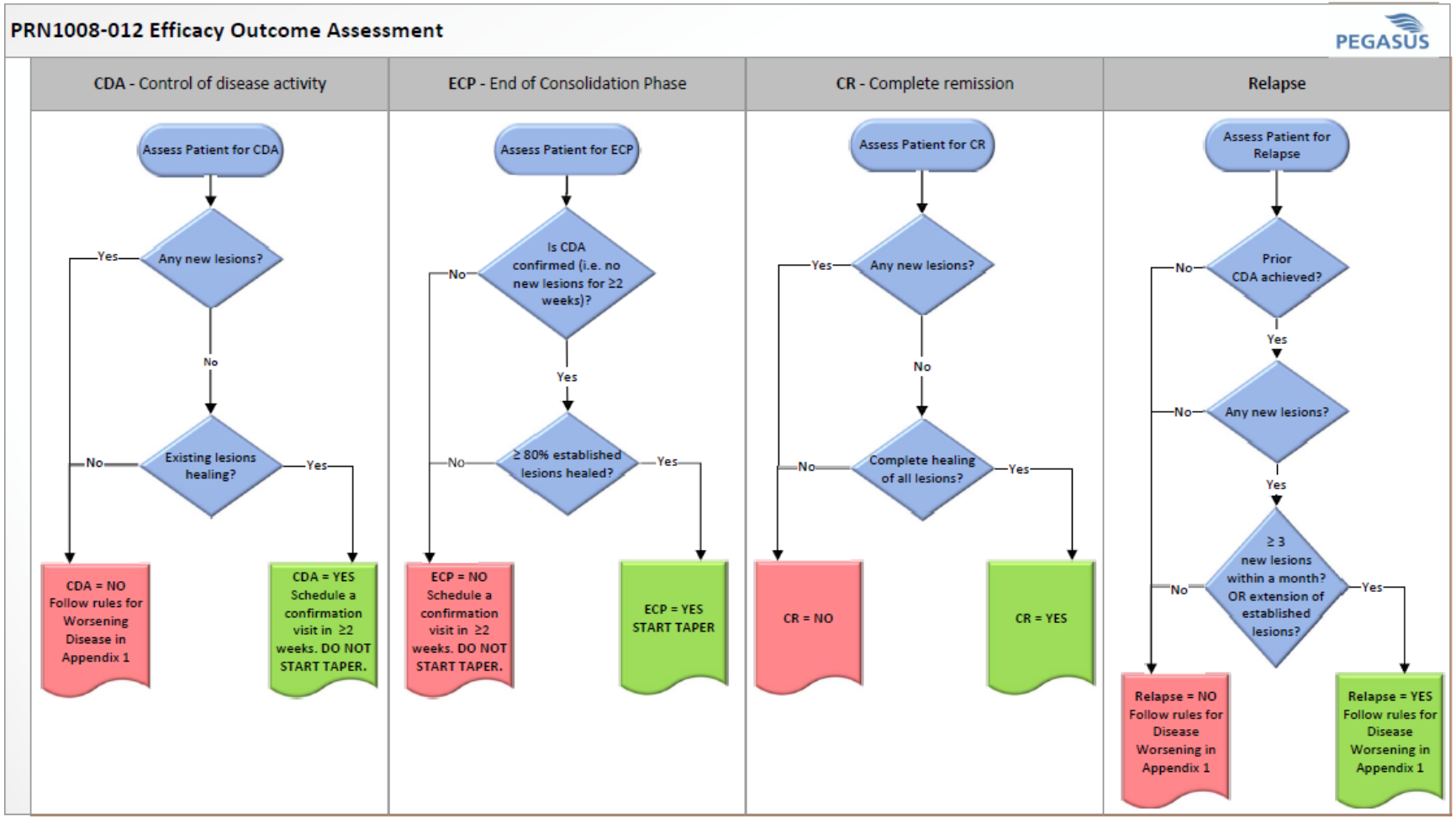
| | Strong | Moderate |
|---|---|---|
| 3A Inducers | Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort | Bosentan, efavirenz, etravirine, modafinil, nafcillin |
| 3A Inhibitors | Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir,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

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

| CYP3A 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 (topical and oral), terfenadine |

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

## 12.8 APPENDIX 8 EFFICACY OUTCOME ASSESSMENT FLOWCHART



## 12.9 APPENDIX 9 UPDATED GUIDELINES TO SITES FOR DELAYED PATIENT VISITS OR MISSED VISITS DUE TO TRAVEL RESTRICTIONS AND ANY FORESEEABLE IMPACTS OF COVID-19

Principia Biopharma understands that many study institutions have implemented restrictions to minimize in-person activities due to the rapidly evolving concerns and risks related to the COVID-19 outbreak.

The safety data to date and the unique mechanism of action of Rilzabrutinib continues to support a favorable benefit/risk profile for pemphigus patients experiencing active disease manifestations.

Principia intends to continue to enroll patients, provide investigational study drug to randomized patients, and to perform protocol assessments as possible during the pandemic whilst following the recent guidance issued from the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) in March 2020. For FDA, the Guidance is dated 18 March 2020 entitled “FDA Guidance on the Conduct of Clinical Trials of Medical Products During COVID-19 Pandemic” and for EMA is dated 27 March 2020 entitled “Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic; Version 2” for the management of trials and subject safety under these circumstances. In addition, with the advent of the COVID-19 pandemic, and in consideration of the recently issued guidance by the EMA referenced above, Principia is committed to provide measures that assure continued drug supply and safety monitoring for patients, and is working in collaboration with sites and their respective Institutional Review Boards/Independent Ethics Committees to implement novel ways that support social distancing and stay at home measures while maintaining access to study drug and safety oversight.

Precautions regarding COVID-19 and management of patients should be followed as there is no data regarding the impact of rilzabrutinib on COVID-19. Please refer to the current version of the Investigator Brochure (IB Edition v11.0) for further information on the potential risks and benefits of treatment with rilzabrutinib.

Since rilzabrutinib is an oral medication, maintaining drug supply for patients during these restrictive times is feasible, especially as drug can be administered at home, and Principia is committed to making drug supply to patients a top priority. This is important because patients with pemphigus require uninterrupted treatment to maintain treatment response.

Recommendations from the CDC and World Health Organization (WHO) for minimizing the risk of exposure to COVID-19 should be followed at all times, and the Investigator should make an assessment of the patient’s benefit/risk profile for inclusion and continuation in the Pegasus trial on a case-by-case basis.

Principia is committed to keeping investigative sites informed in writing if there are any new significant safety findings that emerge affecting a patient’s willingness to participate or pose additional risk. For sites affected by restrictions due to COVID-19, Principia will implement the following changes in research plans in order to eliminate apparent immediate hazards to research participants in PRN1008-012:

## Remote Study Visits for Active Patients

It is expected that if your site is not affected and the patient is able to travel to the site for their regular scheduled protocol visit, that the visit occurs per schedule. It is important to discuss all upcoming visits in the next month with all patients to provide sufficient time to plan for their visits.

In the circumstance that the patient is not able to travel to the site, or the site is quarantined and cannot host a patient visit - please following these guidelines below for allowing continued safety monitoring of the patient and continued supply of corticosteroids and rilzabrutinib/placebo. The priority is to ensure that the patient has continued supply of rilzabrutinib/placebo and corticosteroids to last them through to the next scheduled protocol visit. If the patient has enough supply until their next scheduled protocol visit, then no additional supply needs to be sent. Please remind the patient to bring all medication with them at their next in-clinic visit, and to continue to complete their patient corticosteroid diary.

In-clinic study visits, as outlined in the protocol schedule of assessments, may be changed to a remote visit (eg, telephone call, video call) as needed to address the COVID-19 restrictions. We are mindful that your site resources may be restrictive during this time, so please inform your study monitor of any concerns so we can address any specific needs at your site as well as understand your internet and source documentation access. Please let us know if you have the capability to perform a video teleconference with your currently active enrolled patients via smart phone or computer. Refer to Appendix 9A "Remote Study Visits for Active Patients" on how to perform and document these remote visits.

## Enrollment

Please notify Principia and your CRO study monitor of your Institution policy on enrollment during the pandemic prior to enrolling new patients. We need to ensure patient safety can be adequately monitored, access to study drug is feasible, and a plan is in place for each enrolled patient to determine how this will be implemented.

## Investigational Product (IP) Delivery Direct to Research Patients

Where patients are self-isolating or in quarantine, sites are requested to obtain and document a patient's verbal consent for IP delivery and in the case of shipment consent to provide address details for transport purposes.

## Options for IP Transport

1. No change from current practice in protocol: a patient may obtain dispensed study drug during an in-clinic visit.
2. Study drug may be delivered directly from the site to the patient at the address provided by the patient for the shipment of IP:
    a. Global - using Principia's [redacted] account, insulated shipper, and temperature monitor. Please see Appendix 9B for instructions.

b. Taiwan only - a site member such as a study coordinator may deliver dispensed study drug from site/hospital to the patient's home. Please see Appendix 9B for instructions.

3. If you are not able to use Principia's [redacted] vendor for shipping supplies and delivery of drug to the patient, you will need to provide the information to Principia regarding which local courier will be used, what kind of insulated shipper you will use, and brand and model number of the temperature monitoring device. Principia will need to approve the material and courier prior to shipment to the patient. Upon approval by Principia in writing, the site may arrange the shipment with the local courier.

**Urine Pregnancy Testing (UPT) for Women of Childbearing Potential**

It is important to confirm pregnancy status for women of childbearing potential. Please send 2 urine pregnancy tests to the subject with each shipment of investigational product. If the UPT has a package insert with instructions on collection, include this in the shipment. During the follow up phone call with the patient, confirm pregnancy status (negative or positive) and document the result in the source notes. The subject may confirm the result by showing the test over the video or provide a photo of the test to site staff. A positive test result will need to be reconfirmed with a second test.

**Protocol Deviations**

Where the change to remote visits is being implemented due to COVID-19 to protect the safety and well-being of subjects, failing to obtain assessments will need to be documented (eg, identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessments). Please continue to document in your source documents all protocol deviations and inform your local site monitor. Notify your IRB/IEC as required locally.

**Remote Site Monitoring Visits, If Applicable**

As you know, the Sponsor is required to monitor the safety and benefit/risk for continued conduct of the study. In accordance with the FDA and EMA Guidance, the change in process required for monitoring due to COVID-19 must be documented and agreed upon by the investigative sites. To meet our Sponsor oversight obligations while study monitors are not allowed onsite, we ask that you continue to enter data into the EDC as soon as possible after a subject's visit. Additionally, your study monitor may perform a remote (telephone) monitoring visit, in which they will ask you questions related to subject visit status, disease status, and any adverse events (AEs) or concomitant medications that were reported by the subject. In this event, your study monitor will document this discussion in an Interim Monitoring Visit report and will provide a follow-up letter as always. If permitted, sites are asked to provide source documents with all personal information REDACTED for your study monitor to perform remote source document verification. A separate manual will be sent to you for how this will be performed.

Please share this information with your study site staff and inform your local IRB/IEC.

For participants in Germany, please see specific instructions in Appendix 10 Section 12.10.

### 12.9.1 Appendix 9A - Remote Study Visits for Active Patients

**Remote visit procedures to be performed:**

1. Inform the patient that the study visit will be changed to a remote visit.
2. Obtain rilzabrutinib/placebo and corticosteroid amounts remaining with the patient. Based on the anticipated next in-clinic visit, determine whether the patient requires additional dispensing of rilzabrutinib/placebo and corticosteroids. If additional dispensing is needed, obtain details on date, time, and delivery address for the patient's home to confirm someone will be available to accept/sign for a home delivery. Follow options for IP transport instructions.
3. Email or mail Quality of Life (QOL) questionnaires to patients. The patient should keep them and provide the completed questionnaires when they return to the clinic, or the site can send a pre-printed and labeled Airway Bill to return via courier. The questionnaires include:
    a. Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire
    b. Treatment Autoimmune Bullous Disease Quality of Life (TABQOL) questionnaire
    c. EuroQOL-5 Dimension 5 Level (EQ-5D-5L)
4. Where possible schedule a local lab visit. If a local lab is not available, please notify your local study monitor.
5. Collect the following critical study data via the phone call or video call. Document the conversation of the items below:
    a. At a minimum, the following assessments must be performed by phone call:
        i. New or changes in adverse events/serious adverse events
        ii. New or changes in concomitant medications
        iii. New or changes in Pemphigus concomitant medications
        iv. Confirm IP compliance (corticosteroids and rilzabrutinib/placebo)
        v. Confirm if changes in corticosteroid dosages are needed
    b. If feasible and allowable per local regulations the following assessments should be performed:
        i. PDAI assessment (must be done using video or photography for Investigator to visually review and confirm lesions)
        ii. Disease efficacy outcome assessment (ie, CDA, ECP, CR, or Relapse/flare ; must be done using video or photography for Investigator to visually review and confirm lesions)
        iii. Local labs performed (performed, yes/no, result and units)
        iv. Home monitoring of vital signs (eg, weight and blood pressure)

**Documentation:**

1. Source documents: Continue to observe good documentation practice and record all details of the remote study visit, including:
   a. Patient Study ID
   b. Date and method of remote visit
   c. Site staff who performed remote visit
   d. All remote data collected
2. CRFs: Enter all data collected within 5 days of the remote visit. Any data not collected should be entered as 'Not done' in the applicable CRF.
3. For the QOL questionnaires, after the patient completes the questionnaire, the patient can read their answers to the coordinator over the phone with the coordinator recording the verbal conversation in a telephone report noting the test name, question number, and the subject verbal answer. This telephone report will reside with the source data and be entered into the EDC. The data will then later be verified against the original questionnaire supplied by the patient. This deviation in the process will be noted by the Study Coordinator and documented.

**Dispensing of CS and rilzabrutinib/placebo in Suvoda:**

1. Corticosteroids may be dispensed at any time using Corticosteroid Dispensing Visit Transaction in the IWRS. Reference page 17 of IWRS Site User Manual to dispense additional CS.

   Complete the paper Drug Accountability Log with corticosteroids dispensed.
2. Rilzabrutinib/placebo may only be dispensed at a regular scheduled visit. Select the next scheduled patient visit. Respond "Yes" when asked if the visit was performed. A kit will be dispensed. If you select "No", the visit will be skipped and no kit will be dispensed. If the visit occurs outside the protocol specified window, you will be prompted to confirm that you would like to continue with registering the visit out of window. Respond "Yes."

   **Scheduled Visit**

   This function should be used to perform a scheduled dosing visit.

   Steps:

   1. Confirm Subject
   2. Confirm Visit
   3. Confirm Visit Performed
      a) In the case of a **skipped visit**, select "*No*" when asked if the visit was performed and the system will prompt you to confirm your selection.

   → **Scheduled visit complete. Kit Number assigned.**

Complete the paper Drug Accountability Log with rilzabrutinib/placebo kit dispensed.

**Visit Scheduling:**

The goal is to complete the visit with all associated assessments in its entirety, even if this occurs late and out of window. If the visit is delayed for multiple weeks and rolls over into the next scheduled visit period, the previous visit will be considered missed and the subject should continue with that next scheduled protocol visit.

Aim to return the patient to the original visit schedule, based on the randomization date and Suvoda visit schedule.

**Example Scenario 1**

Patient had the baseline visit on 06-Feb-2020 and are due for the Week 9 visit between 16-Mar-2020 and 22-Mar-2020. Patient is unable to travel to site until 30-Mar-2020.

Aim is to perform the Week 9 visit in its entirety on 30-Mar-2020, even if performed out of window.

Document in source that dispensing of Week 9 IP occurred on *dd-mmm-2020* (earlier) and visit assessments occurred late on dd-mmm-2020, “due to…” and then provide the reason.

**Example Scenario 2**

Patient had the baseline visit on 06-Feb-2020 and are due for the Week 9 visit between 16-Mar-2020 and 22-Mar-2020. Patient is unable to travel to site until 12-Apr-2020. As the next scheduled protocol visit is Week 13 with window 12-Apr to 19-Apr; Week 9 will be considered missed and site should proceed with conducting the Week 13 visit.

Document in source that Week 9 was missed, “due to…” and then provide the reason.

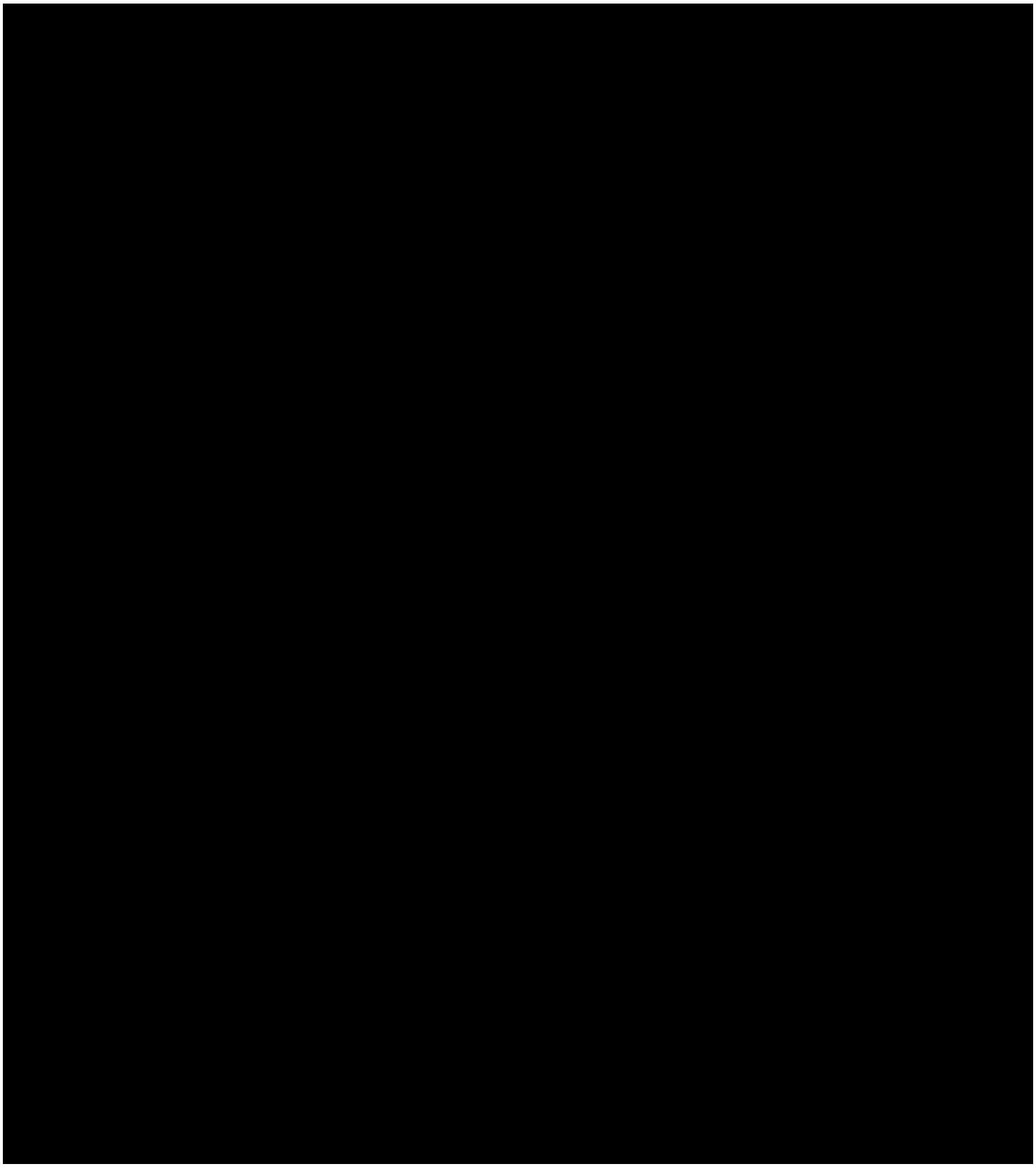
**Data Entry in EDC:**

If a visit is missed, answer “No” to “Was this visit performed” in the Visit Status page. The remaining visit assessments will not load.

If a visit occurs out of window, enter the assessments within the applicable visit folder. A query will be generated asking to confirm if date is correct. Answer confirmed as correct.

Enter any adverse events and concomitant information updates in the Common folder.

### 12.9.2 Appendix 9B - IP Shipment/Delivery Process



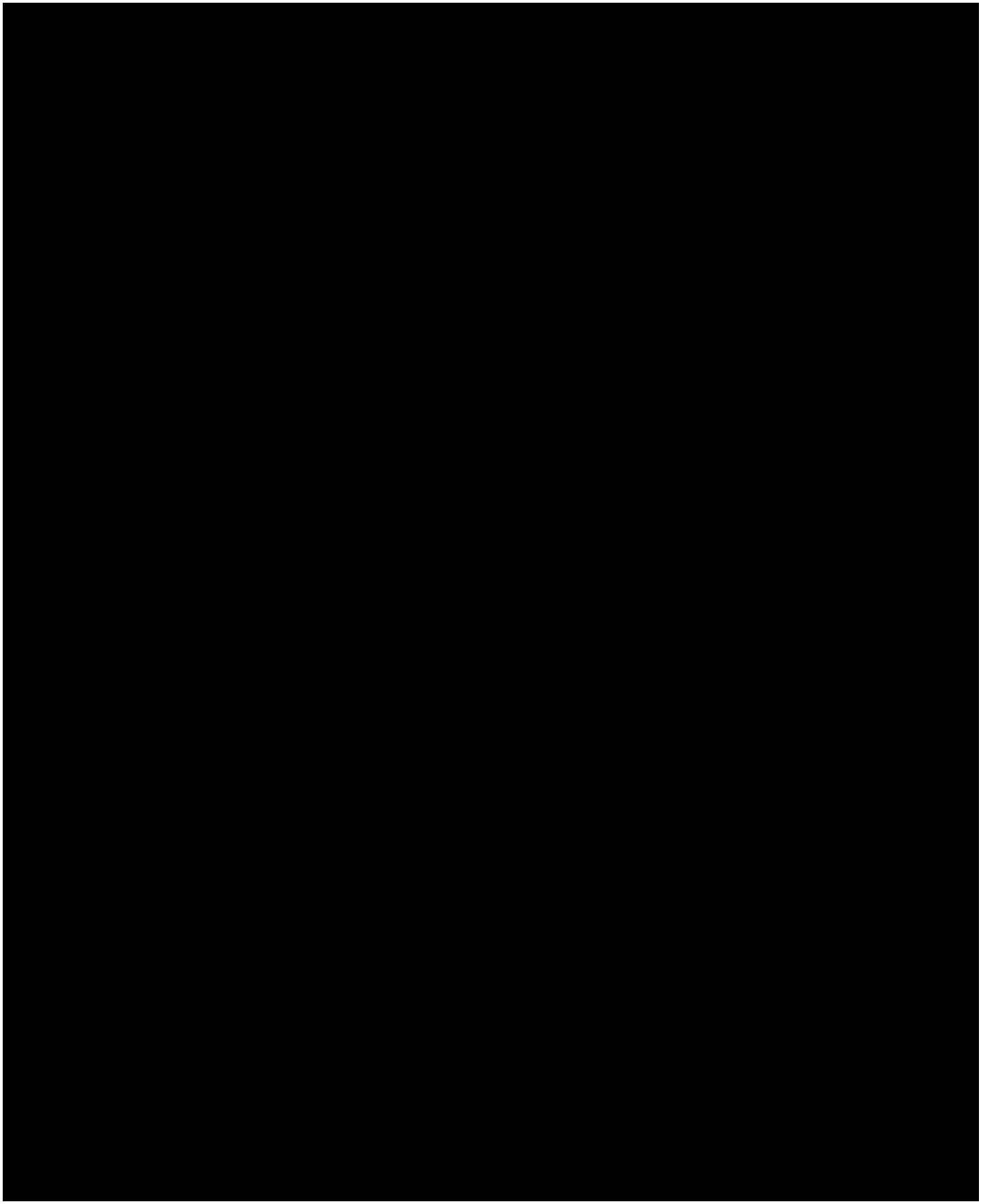
**Instructions for Taiwan Only:**

[redacted]

[redacted]

### 12.9.4 Appendix 9D - [redacted] Ordering Process - Site to Patient Courier Services

[redacted]



## 12.10 APPENDIX 10 COUNTRY-SPECIFIC REQUIREMENTS

**Amendment for Germany**

**Synopsis: Inclusion Criteria** (see Section 1.1) and Section 5.1 **Inclusion Criteria** (see Section 5.1)

I05. Female patients who are of childbearing potential must agree for the duration of the study to use a highly effective means of contraception (eg, combined estrogen-progesterone containing hormonal contraception methods that inhibit ovulation, (oral, intravaginal, transdermal), progesterone-only hormonal contraception methods that inhibit ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or sexual abstinence (only if it is the preferred and usual lifestyle of the patient). A woman is considered of childbearing potential (WOCBP), ie fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However~~,~~ in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

I06. Has been informed and has given written informed consent and agreeable to the schedule of assessments.

I07. Male patients should use condoms during study treatment and until 90-days after the last dose of Rilzabrutinib/placebo, and should not donate sperm during this same time period. For a non-pregnant female partner of childbearing potential, contraception recommendations for the female partner should also be considered.

**Synopsis: Exclusion Criteria** (see Section 1.1) and Section 5.2 **Exclusion Criteria** (see Section 5.2)

E21. Patients who have a known contraindication to Sponsor-provided corticosteroid or with a known sensitivity to Rilzabrutinib or its excipients

E22. Patients who are institutionalized by order of authorities or courts.

E23. Patients who may be unduly influenced by association with or connected to the Sponsor, Investigator, or Site.

E24. Patients who have a positive test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection per local testing standards.

Table 2 **Schedule of Assessments - Blinded Treatment Period (see** Table 2**),** Table 3 **Schedule of Assessments - Open Label Extension Period (see** Table 3), and Table 4 **Schedule of Assessments - Long Term Extension Period (see** Table 4)

At each visit:

Subjects must be tested for SARS-CoV-2 infection within one week prior to each visit or up to 2 days after each visit. Every effort should be made to comply with local or institutional testing procedures. If the time required for obtaining results exceeds this testing window, an extension may be granted by the Medical Monitor. The requirement for the test may be waived by the Medical Monitor (with approval from the Ethics Committee) if the local regulations change with control of the pandemic.

Section 7.1.1 **Permanent discontinuation** (see Section 7.1.1)

The trial will be terminated if major safety concerns related to PRN1008 (Rilzabrutinib) or placebo emerge. Trial safety stopping criteria in Germany are:

5. If the insurance cover cannot be adjusted to the maximum sum necessary in the event that the risk profile worsens.
6. If the approval or the positive assessment has been revoked by the State Office for Health and Social Affairs; Ethics Commission of the State of Berlin.

Section 7.2.1 **Patient Discontinuation and Stopping Rules** (see Section 7.2.1)

Mandatory termination criteria for a patient in this study in Germany include:

- Positive SARS-CoV-2 test at any time during the study

Section 8.3 **Visit Overview** (see Section 8.3)

*Subjects must be tested for SARS-CoV-2 infection within one week prior to each visit or up to 2 days after each visit or per local or institutional testing procedures.*

Section 8.4.15 **SARS-CoV-2 Testing Requirement** (see Section 8.4.15)

Testing for infection with SARS-CoV-2 will be required and collected during screening and for all regular study visits. The testing for SARS-CoV-2 infection must be performed within one-week (7 days) prior to each visit or up to two (2) days after. SARS-CoV-2 tests can be performed following local or institutional guidelines in order to fulfil protocol requirements. Documentation of test results must be provided to the Investigator. If the time required for obtaining results exceeds this testing window, an extension may be granted by the Medical Monitor. The requirement for the test may be waived by the Medical Monitor (with approval from the Ethics Committee) if the local regulations change with control of the pandemic.

Appendix 9 UPDATED GUIDELINES TO SITES FOR DELAYED PATIENT VISITS OR MISSED VISITS DUE TO TRAVEL RESTRICTIONS AND ANY FORESEEABLE IMPACTS OF COVID-19 (see Section 12.9, Appendix 9).

Urgent Safety Measures Initiated Due to COVID-19 Pandemic

Each participating site, ethics committees, and the Federal Institute for Drugs and Medical Devices (BfArM) were informed (22 April 2020) of urgent safety measures implemented to ensure continued supply of study medication and safety monitoring for patients. These measures are described in the "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" (Appendix 9). When the COVID-19 pandemic resolves, the measures will be repealed back to the previous state as government rules and benefit/risk assessment allow.

## 12.11 APPENDIX 11 VACCINE RESPONSE

Investigators are to ask about vaccination plans of all participants treated with rilzabrutinib/placebo (Blinded Treatment Period) or rilzabrutinib for at least 6 weeks and expected to continue in the study for at least 12 weeks in either the Open-Label Period or Long-Term Extension period. Investigators will present an option to volunteer to provide 2 blood samples for vaccine-specific IgG before and after each vaccine dose regimen. Informed consent should be documented from interested participants prior to collecting any blood intended for vaccine response analysis. All pre- and post-vaccine dose regimen samples will be analyzed at a central laboratory.

**Before each eligible vaccination**: Investigators will document any history of injection site pain, swelling, redness, joint pain, excessive itching, hives or other adverse effects of prior vaccination(s) and document dates, location, and type of vaccination in the source document and in the medical history CRF.

The date and time of pre-vaccination blood draw will be recorded in the CRF. Instructions for labeling, collection, storage, and shipping of the sample will be provided in a separate technical procedure manual (ie, PPD Central Lab manual).

Prior to scheduled vaccination, participants will be given an information card labeled with the participant subject ID to collect the following information from the person administering the vaccine dose regimen:

- Date and time of vaccination
- Place of vaccination and contact information to allow investigator follow-up
- Virus and antigenic strain(s) covered by vaccine product
- Brand name of vaccine product (or other vaccine-specific identifier for investigation/generic/un-branded products)
- Manufacturer of vaccine product.

**After each eligible vaccination**: Investigators will collect the vaccination information card from the participant at the next scheduled study visit and complete the corresponding page of the CRF. AEs associated with the vaccination should be documented and recorded in the CRF.

The post-vaccination blood sample is to be collected within approximately 3 to 6 weeks after the vaccination regimen is complete and date and time of sample collection recorded in the CRF.

## 12.12 APPENDIX 12 ABBREVIATIONS

| | |
|---|---|
| ABQOL | autoimmune bullous disease quality of life |
| AE | adverse event |
| AIBD | autoimmune bullous disease |
| AIDS | acquired immune deficiency syndrome |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| anti-dsg | anti-desmoglein |
| AST | aspartate aminotransferase |
| bid/BID | twice daily |
| BMI | body mass index |
| BSA | body surface area |
| BTK | Bruton tyrosine kinase |
| CA | competent authority |
| CDA | control of disease activity |
| CLL | chronic lymphocytic leukemia |
| CMH | Cochran-Mantel-Haenszel |
| CFR | Code of Federal Regulations |
| COVID-19 | Coronavirus disease 2019 |
| CR | complete remission |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CS | corticosteroids |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DIF | direct immunofluorescence |
| DSMB | Data Safety Monitoring Board |
| DSUR | Development Safety Update Report |
| eCRF | electronic case report form |
| ECG | electrocardiogram |
| ECP | end of consolidation phase |
| EDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| EOT | End of Trial |
| EQ-5D-5L | EuroQOL-5 Dimension 5 Level |
| ET | Early Termination |

| | |
|---|---|
| EU | European Union |
| FDA | United States Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GPA | granulomatosis with polyangiitis |
| GTI | Glucocorticoid Toxicity Index |
| H2 | histamine 2 |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| H&E | hematoxylin and eosin |
| Hgb | hemoglobin |
| HgbA1c | hemoglobin A1c |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| IB | Investigator Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonization |
| IEC | Independent Ethics Committee |
| IGRA | interferon-gamma release assay |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IVIG | intravenous immunoglobulin |
| ITK | interleukin-2-inducible T-cell kinase |
| ITP | immune thrombocytopenic purpura |
| IWRS | Interactive Web Response System |
| LTE | Long Term Extension |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified Intent-to-Treat |
| MMRM | mixed models for repeated measures |
| MPA | microscopic polyangiitis |
| NCI | National Cancer Institute |
| OLE | Open-Label Extension |
| PD | pharmacodynamics |
| PDAI | Pemphigus Disease Area Index |
| PF | pemphigus foliaceus |
| PK | pharmacokinetic(s) |
| PML | progressive multifocal leukoencephalopathy |

| | |
|---|---|
| PV | pemphigus vulgaris |
| PVG | pharmacovigilance |
| QOL | quality of Life |
| QTc | QT corrected for heart rate |
| REML | restricted maximum likelihood |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SOC | system organ class |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TABQOL | Treatment of Autoimmune Bullous Disease Quality of Life |
| TBNK | T and B and Natural Killer Lymphocyte Panel |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| US | United States |
| VAS | visual analogue scale |
| WHO | World Health Organization |

## 12.13 APPENDIX 13 PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

### 12.13.1 Clinical Study Protocol Version 2 (12 September 2018)

This was a local amendment to protocol Version 1 (US) and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 2 are:

- To increase the number of sites to 100,
- To add new efficacy objective in order to establish the duration of the response,
- To modify minimum screening CS doses based on the PDAI criteria and to match the disease severity (severe and moderate),
- To clarify CS tapering in accordance with guidelines,
- To add a new inclusion criterion #3 with a minimum PDAI requirement
- To add text related to the rituximab rescue during OLE period that would lead to discontinuation.

**Protocol Amendment summary of changes Table**

# PRN1008-012 Protocol V2.0 (12 September 2018)

Deleted text has ~~strikethrough~~ and new text is **bolded**.

<table>
<tr><th>Section</th><th>Amended or New Wording</th><th>Justification of Change</th></tr>
<tr><td>Cover Page</td><td>Principia Biopharma Inc.<br>[redacted]</td><td>Sponsor address change</td></tr>
<tr><td>2.8<br>Number of Study Sites</td><td>Approximately ~~80~~100 sites worldwide.</td><td>Increased number of sites for the study</td></tr>
<tr><td>3.2.1<br>Efficacy Objectives</td><td>•To evaluate the efficacy of PRN1008 in achieving durable CR on low to zero doses of oral corticosteroid (CS) and on the time course of quantitative disease activity scores<br>•To assess the ability of PRN1008 to reduce CS exposure and the adverse effects of CS<br>•To evaluate the time to specified clinical endpoints<br>•To assess the longer term durability of CR</td><td>Objective added to establish the duration of the response.</td></tr>
<tr><td>3.3.1<br>Study Design - Blinded Treatment Period (Weeks 1 to 37)</td><td>Table 1: Definitions of Moderate to Severe Population and starting CS doses*
<table>
<tr><th></th><th>PDAI entry criteria</th><th>Required prednisone dose starting at Screening**</th></tr>
<tr><td>Newly diagnosed (diagnosed ≤ 6 months prior to Screening)</td><td>PDAI ≥ 15</td><td>≥ 0.5 mg/kg/day</td></tr>
<tr><td>Relapsing, chronic (> 6 months since diagnosis)</td><td>PDAI ≥ 9</td><td>≥ 0.2 mg/kg/day</td></tr>
</table>
* (Shimizu 2014, Boulard 2016)<br>** Doses shown above are minimum requirements. Actual doses will be determined by Investigator judgment</td><td>Modified minimum starting CS doses to align with the PDAI criteria and to match the disease severity (severe and moderate). Minimum PDAI score and CS doses were also defined for newly diagnosed patients and relapsing disease patients to align with available disease guidelines per publications.<br><br>Added text related to the rituximab rescue.</td></tr>
</table>

| Section | Amended or New Wording | Justification of Change |
|---|---|---|
| | After informed consent is obtained, patients with moderate to severe pemphigus (PV and PF~~) (ie, a PDAI score ≥ 15~~) at Screening will be randomized in a 1:1 allocation ratio to receive either PRN1008 400 mg twice daily (bid) (n ~ 60) or placebo bid (n ~ 60) during the Blinded Treatment Period (Week 1 to Week 37).<br>**At Screening, patients will begin to take Sponsor-provided prednisone according to the minimum dose requirements, Table 1** ~~At Screening, patients with moderate disease (ie, a PDAI score 15 to 45) will be initiated on a dose of 0.25 mg/kg prednisone daily; patients with severe disease (ie, PDAI score > 45) will be initiated on a dose of 0.5 mg/kg prednisone daily. If a patient responds to CS and their PDAI score falls below 15 at Day 1, they are still eligible to continue in the study. If a patient's disease worsens during Screening, at the Day 1 visit or earlier the CS dose should be up-titrated to 0.5 to 1.5 mg/kg/day~~ **above, and as required to adequately treat the disease. Prednisone doses may be adjusted per Investigator discretion during the Screening period in the mandated range** (CS and Rituximab Management, Appendix 1).<br>**…….**<br>If rituximab is administered, patients should remain on trial and blinded to treatment assignment, but will be considered treatment failures for all efficacy endpoints except for cumulative CS and composite Glucocorticoid Toxicity Index (GTI) score. After completing the Blinded Treatment Period, patients will enter the Open-Label Extension Period to receive active treatment with PRN1008 described below. ~~If a~~ A patient ~~requires~~ **in the Blinded Treatment Period requiring an additional** "top up" ~~doses~~**dose** of rituximab ~~6 or 12 months~~ after ~~the~~**their** initial **rituximab** dose~~, the patient~~ should be discontinued from the trial. | |
| 3.3.1<br>Study Design - Follow-up Period (Weeks 61 to 65): | End of Trial for each patient is defined as the point at which the patient has completed their Week 65 visit (4 weeks after the patient's last dose of PRN1008). Patients who are not able to complete the planned Week 65 visit and discontinue the study early should be encouraged to come back for their last visit, and this will be recorded as the End of Trial (EOT) visit~~, which will also be denoted as an early termination (ET)~~. Patients that discontinue early will have the ET assessments completed as outlined in the Schedule of Assessments based upon from which phase treatment phase they are terminating, Table 2 (Blinded Treatment Period) and Table 3 (Open-Label Extension Period). | Updated for clarity |

| Section | Amended or New Wording | Justification of Change |
|---|---|---|
| 3.4.1<br>Corticosteroid Starting Doses at and Management during Screening and Baseline (at Day 1) | 3.4.1. Corticosteroid Starting Doses ~~at~~ **and Management during** Screening and ~~Baseline (~~**at** Day 1~~)~~<br>Required, initial doses of CS ~~at~~**for** the ~~commencement~~ **duration** of Screening are ≥ 0.~~25~~**2** mg/kg/day of prednisone for patients with ~~a moderate PDAI total activity score of 15 to 45~~,**relapsing disease (> 6 months since diagnosis)** and ≥ 0.5 mg/kg/day for patients with ~~a PDAI total activity score of > 45~~.<br>~~During the~~ **newly diagnosed disease (diagnosis ≤ 6 months prior to** Screening ~~Period up-titration~~ **). At Screening, patients will begin** to ~~guideline-recommended (Consensus Guideline, ), CS doses (0.~~**5take Sponsor-provided prednisone according** to ~~1.5 mg/kg/day), is recommended if initial starting doses are insufficient to prevent worsening disease. The choice of exact CS dosage if up-titration is~~ **the minimum dose requirements, and as** required ~~is up~~ to **adequately treat** the ~~Investigator.~~<br>~~At the baseline (Day 1) visit, if~~ disease ~~worsened~~ during ~~screening despite initial (as~~ **the Screening period. Prednisone doses may be** adjusted **upward per Investigator discretion during the Screening period but the dose should not be reduced below the initial dose levels (Table 1)** ~~CS treatment, then CS doses must be raised to guideline-recommended CS doses (0.5 to 1.5 mg/kg/day).).~~<br><br>**If disease significantly (Investigator judgment) worsens during the Screening period, up-titration of CS dose by 50-100% should occur, as often as every 5-7 days if needed (Harman 2017).** | Modified minimum starting CS doses to align with the PDAI criteria and to match the disease severity (severe and moderate). Minimum PDAI score and CS doses were also defined for newly diagnosed patients and relapsing disease patients to align with available disease guidelines per publications. |
| 3.4.2.<br>Corticosteroid Management during Treatment Period and Open-Label Extension Period | **3.4.2. Corticosteroid Management during Treatment Period and Open-Label Extension Period**<br><br>Corticosteroid-Tapering (Consensus Guideline, Murrell 2018)<br>**CS will be tapered from CDA-ECP towards a goal of 5 mg/day by ≤ Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. After that, taper towards 0 mg should commence as clinically indicated.** | Clarified CS administration to align with guidelines. |

| Section | Amended or New Wording | Justification of Change |
|---|---|---|
| | **CS tapering should follow the dosing guidelines below (Murrell 2018). Adjustment of the tapering guideline protocol by investigators is permitted, based on assessment of clinical need.**<br>• Start tapering CS as soon as CDA is reached or up to the ECP<br>• Decrease CS by 25% every two weeks, until 20 mg per day<br>• Once at 20 mg per day, decrease CS by 2.5 mg per week<br>• Once at 10 mg/day, decrease CS by 1 mg per week<br>**Note, because 1 mg will be the smallest prednisone dosage provided and tablet splitting is not allowed, the Investigator must round up to the nearest whole milligram for CS dose after calculation of the new dose level.**<br><br>Corticosteroid-Up-Titration ~~(Consensus Guideline, Murrell 2018)~~ (Harman 2017)<br>CS up-titration is allowed if disease significantly worsens prior to initial CDA-ECP or **after CDA-ECP**, during prednisone taper.<br>Up-titration should be a temporary increase until CDA-ECP is achieved (again), after which tapering can recommence.<br>For full details of up-titration see Appendix 1. | |
| 3.5<br>Concomitant Medications | ……<br>Warfarin should be monitored carefully as there is limited experience of co-administration with PRN1008. ~~Factor X inhibitors may be used.~~ **To date, two patients on chronic anticoagulation (rivaroxaban) have been treated without bleeding complications.** | Updated with recent clinical information. |
| 3.6<br>Inclusion Criteria | 1. Male or female patients, aged 18 to 80 years old with moderate to severe, newly diagnosed or relapsing PV or PF ~~(PDAI ≥ 15 at Screening),~~ with a clinical presentation and histopathology consistent with PV or PF~~. Diagnosis requires confirmation with either a positive direct immunofluorescence (DIF) or serological detection of anti-dsg autoantibodies (anti-dsg1 or 3 or both).~~<br>**2**. Positive circulating anti-dsg1 or 3 autoantibody titer<br>~~2~~**3. PDAI score of at least 9 points for relapsing patients (> 6 months since diagnosis) or at least 15 points for newly diagnosed patients (diagnosed ≤ 6 months prior to Screening)** | Updated for clarity and removed redundancy to Inclusion Criterion #2.<br><br>Updated to clarify the diagnoses for newly diagnosed and relapsing disease. |

| Section | Amended or New Wording | Justification of Change |
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| | ……. <br> ~~5~~**6.** 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 (eg, hormonal contraception methods that inhibit ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or condoms). Unless surgically sterile, postmenopausal females should have menopause confirmed by follicle-stimulating hormone (FSH) testing. | |
| 3.7<br>Exclusion Criteria | **1. Suspected paraneoplastic pemphigus and other forms of pemphigus that are not pemphigus vulgaris or pemphigus foliaceus** <br> …….. <br> **17.** ~~A potential patient with a positive~~ **Positive** interferon-gamma release assay (IGRA) (eg, QuantiFERON®-TB Gold or T-spot TB® Test) at Screening. **Unless, all of the following 3 conditions are true:** <br> **a.** ~~is eligible if her/his chest~~ Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease <br> **b.** ~~and there~~**There** are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease~~. The patients with latent TB infection, must have already received~~ <br> **c. Documented receipt of** a course of prophylactic TB treatment of at least 6 months. | Updated for execution clarity |
| 3.8.3<br>Other Secondary Endpoints | …….. <br> • Change in Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) score from baseline to Weeks 5, 13, 25, 37, and 61 <br> • **Proportion of patients in CR for ≥ 8 weeks on zero CS at Week 61 by original PRN1008/placebo group assignment and overall** <br> • Proportion of patients in CR at Week 37 to maintain CR continuously to Week 61 <br> ……. | Updated for execution clarity |
| 3.12<br>Randomization | Patients will be randomized at Day 1, **in a 1:1 allocation**, using a stratification by PV/PF disease type, ~~in a 1:1 allocation ratio to receive PRN1008 400 mg or placebo bid,~~ and by ~~relapsing~~/newly diagnosed disease ~~history~~ (~~newly~~ diagnosed ~~defined as within~~≤ 6 months ~~of~~**prior to** Screening)~~.~~ **or by relapsing disease (> 6 months since diagnosis.)** | Updated to clarify the diagnoses for newly diagnosed and relapsing disease. |

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| 3.13<br>Other Statistical Considerations | …..<br>There will be no interim analysis to assess efficacy. An interim analysis to **possibly** add 24 more patients to the trial will be conducted **by the DSMB** when approximately 50% of patients have reached the Week 29 visit, based on an observed control group rate of CR of any duration at Week 29 that exceeds 20%. The additional 24 will include a minimum of 20 patients with PV.<br>…… | Updated for clarity and to specify that the DSMB will be performing the IA. |
| 5.1<br>Overview of Pemphigus | ……<br>Presently, there are few effective treatment options for pemphigus. Current treatments include corticosteroids (CS) to reduce inflammation and antibiotics to treat associated infections. Agents such as mycofenolate ~~motetil~~mofetil are often used and rituximab has been reported to be effective~~; however, neither therapy is~~. **Mycofenolate mofetil has not been** approved for this indication in any country~~,~~**. Rituximab to treat pemphigus vulgaris has only been approved to date in the US** and **for both of these agents**, beneficial effects take weeks to months. ……. | Updated for clarity |
| 5.4<br>Clinical Experience | In clinical studies to date, PRN1008 has been administered ~~orally to approximately 114~~**to 140** healthy volunteers ~~in six Phase 1 studies and 21 (as of January 18, 2018)~~**, 27** patients with pemphigus **(mainly pemphigus vulgaris variant, ie, PV) and 4 patients with immune thrombocytopenic purpura (ITP).**<br><br>**Patients with PV** in ~~an ongoing, open label~~a Phase 2 study ~~with~~ **(NCT02704429) used** a starting dose of 400 mg ~~twice daily (bid). High clinical response rates have been observed. On a background~~**BID which was shown to produce adequate BTK occupancies in all but one patient. One patient dose-escalated to 500 mg BID and one to 600mg BID, with all other patients using the 400mg BID dose. An interim analysis of the first 27 patients in this study found evidence of clinically significant activity in 80% of patients, with onset of disease control in the first 2 weeks of therapy, and an acceptable safety profile (DSUR 2018 and IB Section 5). The primary endpoint of the study, "control of disease activity by the Week 5 visit on ≤ 0.5mg/kg/day** of prednisone~~ equivalent corticosteroid (CS) doses of 0 to 30 mg per day, "Control of Disease Activity" (CDA) has been seen in the majority of patients within 4 weeks (11/18, 61%), with responses in patients with both PV and PF clinical/laboratory characteristics. ~~**" was** | Updated the number of patients dosed across studies conducted with PRN1008.<br><br>Updated with new available clinical data from Phase 2 PV study (23 April 2018 data cut). |

| Section | Amended or New Wording | Justification of Change |
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| | **met by 54% (14/26) of patients. Complete remission on ≤ 0.5mg/kg/day of prednisone was achieved by 25% (5/20) of patients completing 12 weeks treatment**<br>Treatment ~~-related~~ **emergent** adverse events in the pemphigus study ~~include one severe (Grade 3)~~**related to PRN1008 in ≥ 10% of patients were nausea (15%), abdominal pain (11%) and headache (11%). One** serious adverse event ~~(SAE)~~ of **Grade** 3 "cellulitis ~~(localized leg cellulitis associated with high fever and negative microbial cultures), and mild (Grade 1) headache (10%), moderate (Grade 2) upper respiratory tract infection (10%), and mild and moderate dry mouth (10%). No patients have discontinued therapy due to treatment~~ **" considered** related ~~adverse events. No allergic reactions to PRN1008 have been reported~~**to PRN1008 therapy occurred, resulting in a three day interruption of PRN1008 therapy. This patient continued therapy for two further months without recurrence of the event.**<br><br>Overall, results from Phase 1 and Phase 2 studies demonstrate that PRN1008 has an acceptable safety profile and is well tolerated in healthy subjects and patients with pemphigus. Please refer to **the** Investigator Brochure~~, Edition 9.0~~ for more details. | |
| 5.8<br>Rituximab and Possible Combination with PRN1008 | …..<br>Although it is ~~not~~ approved for the treatment of pemphigus **only in the US** at this time, it is recommended as a possible first-line therapy in combination with CS in newly updated consensus guidelines (Murrell 2018). .....<br>…….<br>RITUXAN, MabThera or other approved, biosimilar agents may be used in this clinical trial per protocol. Instructions for administration of the intravenous infusion ~~for~~**will be provided in** the ~~locally approved rituximab to be used should be followed if administered~~Pharmacy Manual. | Updated with information on recent rituximab US approval for PV |
| 5.9.2<br>Particular Permissible Medications | …..<br>• Anticoagulants: Anticoagulation with warfarin should be monitored actively in the first weeks of PRN1008 or placebo treatment (both the Blinded Treatment Period and the Open-Label Extension Period), as the combination has not been extensively studied. ~~Factor X inhibitors may be used~~**To date, two patients on chronic anticoagulation (rivaroxaban) have been treated without bleeding complications.** | Updated with new clinical information |

| Section | Amended or New Wording | Justification of Change |
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| 5.9.3<br>Corticosteroids and Rituximab | ~~Initial~~**Required, initial** doses of CS ~~at~~**for** the ~~commencement~~**duration** of Screening are ≥ 0.~~25~~**2** mg/kg/day of prednisone for patients with ~~a moderate Pemphigus Disease Area Index (PDAI) total activity score of 15 to 45,~~**relapsing disease (> 6 months since diagnosis)** and ≥ 0.5 mg/kg/day for patients with ~~a PDAI total activity score of > 45.~~**newly diagnosed disease (diagnosis ≤ 6 months prior to Screening).**<br><br>Thereafter, CS are managed per the Corticosteroid and Rituximab Management protocol (Appendix 1).<br><br>Rituximab should be managed per the Corticosteroid and Rituximab Management protocol (Appendix 1), utilizing instructions in the ~~locally approved Product Information~~**Pharmacy Manual** for administration of the to-be-used rituximab product. | Modified minimum starting CS doses to align with the PDAI criteria and to match the disease severity (severe and moderate). Minimum PDAI score and CS doses were also defined for newly diagnosed patients and relapsing disease patients to align with available disease guidelines per publications. |
| 6.1.2<br>Preparation and Administration | …..<br>Treatment medication will be taken twice daily by mouth starting on Day 1. PRN1008 or placebo may be taken with or without food. **Tablets should not be broken or crushed**. Further details for dispensation and administration of blinded treatment are provided in the Pharmacy Manual. | Provided additional instruction on handling drug tablets. |
| 6.2.1<br>Preparation and Administration | No preparation of prednisone will be needed. ~~Patients will use the prednisone medication directly from the dosing container dispensed in accordance with this protocol and the Pharmacy Manual.~~ | Updated for clarity |
| 6.3<br>Rituximab | **Rituximab (or biosimilar) will be provided for patients having a second qualifying relapse (Appendix 1**~~Rituximab will be sourced locally using locally approved product and reimbursed, if required, by the Sponsor.~~**) during the Blinded Treatment Period. However, in the event a patient in the Blinded Treatment Period requires an additional "top up" dose of rituximab after their initial rituximab dose, this will not be provided because the patient must be discontinued. Similarly, if a patient in the Open-Label Extension Period requires rituximab, the patient must be discontinued and rituximab will not be provided.** | Added text related to the rituximab rescue. |
| 6.3.2<br>Storage | Rituximab **(or biosimilar)** should be stored according to the instructions ~~for~~**in** the ~~locally approved rituximab~~ product label. | Updated for clarity |
| 6.4.1<br>Drug Accountability | ….<br>**All used and unused drug supplies must be returned by the subject at every visit.** | Clarified the process for drug accountability |

| Section | Amended or New Wording | Justification of Change |
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| | All records and **used and unused** drug supplies must be available for inspection by the trial monitor at every monitoring visit. ~~When~~**Reconciliation of all drug supplies (PRN1008 or placebo, PRN1008 open-label, prednisone, and rituximab) will be performed by** the trial **monitor. When the trial** is completed, the ~~investigator~~**Investigator** will return any used and unused trial medication (~~eg,~~eg, empty, partially used, and unused containers), ~~occluded labels (or the equivalent)~~ to the Sponsor as requested. ~~The~~**Copies of the** completed Drug Dispensing Log and Drug Return Record(s) will be returned to the Sponsor. The Investigator's copy of the Drug Return Record(s) must accurately document the return of all drug supplies to the Sponsor. | |
| 6.4.2<br>Destruction of Investigational Product | …..<br>Unused trial medication from the site that has not been stored properly should not be destroyed until the ~~final report has been approved~~**monitor and/or Sponsor approve the destruction**.<br>…… | Clarified the instruction for IP destruction |
| 6.6<br>Treatment Blinding | …..<br>The pharmacist or designee will be required to enter or select information that will include, **but not be limited to;** the user ID, and password, subject number, patient ~~date~~**year** of birth, as well as other information (as allowed locally). The pharmacist or designee will then be provided with a patient randomization number and treatment assignment. Once patient numbers and randomization numbers have been assigned, they cannot be reassigned. The randomization system will also send confirmation of the randomization, by email or fax, to the user. Specific instructions will be provided in the IWRS trial reference guide. Access to the randomization code will be limited; all Sponsor personnel (and representatives), and site personnel ~~other than the nominated unblinded representative(s),~~ who are directly involved in the conduct of the trial will be blinded to randomization codes.<br><br>~~The pharmacist or designee will ensure that tablets dispensed for drug administration are prepared such that they are identical in appearance to trial patients and site personnel.~~ The treatment each patient receives will not be disclosed to the ~~investigator~~**Investigator**, trial center personnel, patients, or the Sponsor or representatives **on the clinical study team**. | Updated for clarity |

| Section | Amended or New Wording | Justification of Change |
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| | Further details for blinding and dispensing of blinded treatment are provided in the Pharmacy Manual. | |
| 7.4.1<br>Patient Discontinuation and Stopping Rules | Reasons for discontinuing a patient may include, but are not necessarily limited to, the following:<br>• Severe and life-threatening pemphigus disease activity• Grade 4 PRN1008 -related TEAE<br>• Serious allergic reaction to PRN1008 or placebo including anaphylactic reaction<br>• **A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab dose or a patient in the Open-Label Extension Period requiring rituximab**<br>• Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), viral hepatitis (B and C) infection occurring during the study.<br>……. | Added a stopping rule for rituximab rescue patients to align with Sections 3.3.1. and 6.3. |
| 7.6.1<br>Screening (Day -29 to Day -1) | …….<br>Patients not already on the mandated CS doses for the commencement of the Screening Period will ~~continue or~~ commence the protocol-~~recommended~~**mandated** CS doses. | Updated for clarity |
| 7.7.1<br>Body Height and Weight | Body weight should be measured ~~on the same clinic scale each time~~ after checking for accurate zero calibration. Weight is recorded in kg to one decimal place. | Updated for execution clarity |
| 7.7.2<br>Physical Examination | ….<br>An abbreviated physical examination is inclusive of **general appearance**, cardiac, gastrointestinal, and pulmonary assessments. | Updated for execution clarity |
| [redacted] | | |
| 7.7.15<br>Photography | ~~7.7.14.~~**7.7.15.** Photography<br>Photography of lesions may be performed at selected sites, **at investigator's discretion** as allowed by country and local regulations~~, and at selected centers with sufficient subjects~~. | Clarified photography language |

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| 8.3.7.2<br>Serious Adverse Event Reporting | Initial notification of an SAE<br>~~to XXX~~ Pharmacovigilance (PVG) must be ~~confirmed~~**informed** in writing 24 hours from the time the **site** investigational team first become aware of the event using the ~~XXX~~EDC system, if possible. Paper SAE report forms should only to be used when the ~~XXX~~EDC system is not accessible, and SAEs should be transferred into ~~XXX~~EDC once the system is available.<br>If ~~XXX~~EDC is not accessible, a **paper SAE form including a** written, narrative description of any SAE must be ~~sent to XXX PVG by fax~~**emailed to** [redacted] within 24 hours after awareness of the event.<br>If paper SAE forms are used, copies of the initial and follow-up SAE report forms must be made and the **paper** originals ~~retained~~ of all information ~~faxed to XXX~~**that has been emailed must be retained** in the Investigator Site File.<br><br>~~Fax Number:~~<br>~~Worldwide: TBD~~<br>~~If unable to fax, any SAE must be reported immediately or no later than 24 hours after awareness of the event to the XXX PVG by telephone via the Safety Hotline Number.~~<br>~~Safety Hotline Number:~~<br>~~Worldwide: TBD~~<br><br>**In addition to reporting the SAE in the EDC or via email, the local CRA and the Global Medical Monitor must be alerted via phone (refer to Site Manual).**<br>As further information regarding the SAE becomes available, such follow-up information should be documented as an update in the ~~XXX~~EDC system, or if ~~XXX~~EDC is not accessible, on a new SAE report form, marked as a follow-up report and ~~faxed~~**emailed** to ~~XXX~~ [redacted].<br>~~After~~**Starting after** informed consent, ~~but prior to initiation of study medications, only~~ SAEs ~~caused by a protocol-mandated intervention~~ must be reported within 24 hours (~~eg,~~eg, SAEs related to invasive ~~screening~~Screening procedures such as biopsies, ~~medication washout,~~ or ~~no~~**SAEs related to corticosteroid** treatment ~~run-in). After first study medication, all SAEs must be reported within 24 hours.~~**during Screening).** | Updated contact information and reporting instructions |

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| 8.4<br>Pregnancy | ….. Pregnancies occurring up to ~~90 days~~**4 weeks** after the ~~completion~~**last** dose of PRN1008 or placebo 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. ….. | Updated language based on reproductive preclinical data |
| 9.4.4<br>Safety and Tolerability Analysis (Safety Population) | The nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects will be summarized descriptively by treatment group. AEs prespecified as possibly related to prednisone will be grouped and analyzed separately in addition to the above. ~~Vital signs and clinical laboratory test results (including complete blood count and blood chemistry) will be summarized using actual and change from baseline values.~~<br>…….. | Updated for clarity |
| 9.4.5<br>Efficacy Analysis (ITT Population) | <u>Primary:</u><br>The proportion of patients who are in CR from Week ≤ 29 (visit) to Week 37 (visit) with a ~~daily~~ prednisone dose of ≤ 5 mg/day.<br>• A Cochran-Mantel-Haenszel (CMH) general association test stratified by disease type (PV or PF~~),~~**)** and disease history (newly diagnosed or relapsing) will be used to compare PRN1008 with placebo. Newly diagnosed pemphigus is defined as ~~newly~~**patients** diagnosed ~~within ≤~~ 6 months ~~of~~**prior to** Screening. ~~Severe~~**Relapsing, chronic** pemphigus is defined as ~~a PDAI score of > 45 at Screening.~~ **patients with > 6 months since diagnosis.**<br><br>Patients who drop out of the trial, withdraw, or who undergo rituximab therapy for a qualifying relapse will count as non-responders in the primary efficacy analysis. Additional sensitivity analyses, **including adjusting for severity,** will be described in the SAP.<br><br>**The US primary efficacy analysis will include PV subjects only. This analysis will be performed using a CMH general association test stratified by disease history (newly diagnosed or relapsing) to compare PRN1008 with placebo.**<br><br><u>Key Secondary:</u><br>The cumulative oral corticosteroid dose over first 36 weeks will be summarized | Updated for clarity<br><br>Added the statistical modification to meet the FDA recommendation. |

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| | descriptively and will be compared across treatment groups using pairwise comparisons from an analysis of variance (ANOVA) model. The ANOVA model will include effects for treatment, disease type, ~~disease severity,~~ and disease history.<br><br>Time to initial CR will be analyzed using competing risks methodology. The median event time (and other quartiles) and 2-sided 95% confidence intervals will be presented. Marginal survival curves will also be displayed graphically. Further details will be provided in the SAP.<br>The difference in the proportion of patients with CR from week ≤ 29 to week 37 (≥ 8 weeks) with a ~~daily~~ CS dose of ≤ 10 mg/day will be tested in the same manner as the primary endpoint.<br>**Additional sensitivity analyses, including adjusting for severity, will be described in the SAP.** | |
| 9.4.6<br>Key Secondary Efficacy Sequential Testing | Key secondary efficacy endpoints will be tested sequentially, and use the ITT population. ~~Patients who drop out or withdraw early will only be included if there is sufficient data.~~ A 0.05 alpha level will be used for the sequential testing. Testing will stop once a p-value is > 0.05 for one of the secondary endpoints. The order of the secondary efficacy endpoints is as follows: …… | Updated for clarity |
| 10.1<br>Data Quality Assurance | …..<br>Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against the ~~investigator's~~Investigator's records by the trial monitor (source document verification), and the maintenance of **Drug Accountability (see Section 6.4.1~~a PRN1008/placebo dispensing log~~)** by the ~~investigator~~**Investigator**.<br>….. | Updated for clarity |
| 10.2<br>Protocol Amendments and Trial Completion | Protocol amendments must be made only with the prior approval of the Sponsor or its designees. ~~Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document.~~ The IRB/IEC must be informed of all amendments and give approval for all amendments. For studies conducted outside of the US, approval of substantial amendments must be obtained from the relevant Competent Regulatory Authority before implementation. The ~~investigator~~**Investigator** must send a copy of the approval letter from the IRB/IEC to the Sponsor and/or the Sponsor's designee.<br>…… | Updated for clarity |

| Section | Amended or New Wording | Justification of Change |
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| Appendix 1<br>Corticosteroid and Rituxmab Management | ~~Initial~~ Corticosteroid **Starting** Doses~~:~~ **and Management during Screening and at Day 1:**<br>Required, initial doses of CS ~~at~~**for** the ~~commencement~~**duration** of Screening are ≥ 0.~~25~~**2** mg/kg/day of prednisone for patients with ~~a moderate PDAI total activity score of 15 to 45, and~~ **relapsing disease (> 6 months since diagnosis) and** ≥ 0.5 mg/kg/day for patients with ~~a PDAI total activity score of > 45~~.<br>~~Up-titration to guideline recommended (Consensus Guideline, ), starting CS doses (0.5 to 1.5 mg/kg/day), is recommended if these starting doses are insufficient to prevent worsening disease, per CS up-titration paragraphs below, and as early as~~ **newly diagnosed disease (diagnosed ≤ 6 months prior to Screening). At Screening, patients will begin to take Sponsor-provided prednisone according to the minimum dose requirements, and as required to adequately treat the disease during** the Screening period. ~~At the Baseline (Day 1) visit, if disease has worsened during Screening despite~~**Prednisone doses may be adjusted upward per Investigator discretion during the Screening period but should not be reduced below the** initial ~~(as adjusted) CS treatment, then CS doses must be raised to 0.5 mg/kg/day for moderate patients and 1.0 to 1.5 mg/kg/day for severe patients~~**dose levels.**<br><br>**If disease significantly (Investigator judgment) worsens during the Screening period, up-titration of CS dose by 50-100% should occur, as often as every 5-7 days if needed (Harman 2017).**<br><br>**Corticosteroid Management during Blinded Treatment Period and Open-Label Extension Period**<br><br>Corticosteroid-Tapering (**Consensus Guideline, Murrell 2018~~:~~)**<br>CS will be tapered from CDA-ECP towards a goal of ≦ 5 mg/day by ≤ Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. After that, taper towards ~~zero~~0 mg should commence as clinically indicated. | Modified minimum starting CS doses to align with the PDAI criteria and to match the disease severity (severe and moderate). Minimum PDAI score and CS doses were also defined for newly diagnosed patients and relapsing disease patients to align with available disease guidelines per publications.<br><br>Updated tapering instructions for clarity. |

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CS ~~adjustment~~tapering should follow the dosing guidelines below (Murrell 2018). Adjustment of the dosing guideline protocol by investigators is permitted, based on assessment of clinical need.<br>
~~Guideline for corticosteroid tapering (Consensus Guideline, )~~<br>
• Start tapering CS as soon as ~~disease control~~CDA is reached or up to the ~~end of consolidation phase~~ECP<br>
• Decrease CS by 25% every two weeks, until 20 mg per day<br>
• Once at 20 mg per day, decrease CS by 2.5 mg ~~a~~per week<br>
• ~~At~~Once at 10 mg/day, decrease ~~dose~~CS by 1 mg per week*<br>
Note, because 1 mg will be the smallest prednisone dosage provided and tablet splitting is not allowed, the <u>Investigator must round up to the nearest whole milligram</u> for CS dose after calculation of the new dose level.<br><br>
Table 4: Example Taper for a 60 mg Dose of Prednisone
<table>
<tr><td>Current Dose Level (prednisone equivalent)</td><td>Size of Dose Reductions (prednisone equivalent)</td><td>Example (Note: dosages rounded up to nearest mg)</td><td>Frequency of Dose Reductions</td></tr>
<tr><td>60 mg down to 20 mg</td><td>Approximate 25% decrease ~~e.g. to 45mg, then to 35mg, then to 25mg, then 20 mg~~</td><td>60 mg, 45 mg, 34 mg, 26 mg, 20 mg</td><td>Every two weeks</td></tr>
<tr><td>20 mg to 10 mg</td><td>2.5 mg decrease</td><td>20 mg, 18 mg, 16 mg, 14 mg, 12 mg, 10 mg~~2.5 mg decrease~~</td><td>Weekly</td></tr>
<tr><td>10 mg to zero</td><td>1 mg</td><td>10 mg, 9 mg, 8 mg, 7 mg, 6 mg, 5 mg until Week 37 then further titration to 0 mg as clinically indicated</td><td>Weekly*</td></tr>
</table>
</td><td></td></tr>
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| | 3. Non life-theatening worsening of disease during taper of CS <u>after initial CDA-ECP</u><br><br>•Go back to last CS dose level if > 3 lesions reappear during the tapering of oral corticosteroid therapy (where relapse, as defined below, has not occurred)<br>•If a more severe full relapse occurs (~~ie,~~ie, the appearance of ≥3 new lesions~~/~~ **within a** month that do not heal spontaneously within 1 week, or there is extension of established lesions), increase the oral corticosteroid dose by going back to the second to last dose until control of the lesions is achieved within 2 weeks, then resume taper<br>**…….**<br>Rituximab for second "qualifying relapse":……<br>• Where a <u>second</u> qualifying relapse occurs meeting the above definition, and it is ~~≥~~ **after the** Week 5 **visit**, then one course of rituximab, which consists of two intravenous doses of 1 gram two weeks apart, may be ~~may be~~ administered, unless contraindicated.<br>• Oral CS doses should be managed as indicated for the patient at the time of the 2nd qualifying relapse<br>• ~~Pre-medications for rituximab~~**Rituximab** should be administered as recommended in the ~~locally approved Product Label Information~~**Pharmacy Manual**.<br>…… | |
| [redacted] | | |

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| [redacted] | | |
| Appendix 7<br>Glucorticoid Toxicity Index (GTI) | **APPENDIX 7 GLUCORTICOID TOXICITY INDEX (GTI)**<br>**The Glucocorticoid Toxicity Index (GTI) is a proprietary licensed instrument from Massachusetts General Hospital (Miloslavsky 2017). It was developed to assess** | New Appendix to provide reference to Section 7.7.14 |

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<tr><th>Section</th><th>Amended or New Wording</th><th>Justification of Change</th></tr>
<tr><td></td><td>glucocorticoid (GC)-related morbidity and GC-sparing ability of other therapies. The scale collects information about known steroid toxicities and uses a weighted scoring system to assesses toxicity. The instrument calculates a composite index score from data captured related to the following domains: body mass index, glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. In addition, reports of any of the following toxicities are included in the index: endocrine (adrenal insufficiency), gastrointestinal (perforation, peptic ulcer disease), musculoskeletal (ruptured tendon, avascular necrosis) and ocular (retinopathy, increase in ocular pressure, posterior subcapsular cataract).</td><td></td></tr>
<tr><td>Appendix 8<br>Strong to Moderate CYP3A Inhibitors and Inducers and Sensitive CYP3A Substrates</td><td>
<table>
<tr><th></th><th>Strong</th><th>Moderate</th></tr>
<tr><td>3A Inducers</td><td>Avasimibe, carbamazepine, phenytoin, rifampin, St. John’s wort</td><td>Bosentan, efavirenz, etravirine, modafinil, nafcillin</td></tr>
<tr><td>3A Inhibitors</td><td>Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole</td><td>Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, Seville orange juice, ~~grapefruit juice,~~ imatinib, verapamil</td></tr>
</table>
</td><td>Removed duplication of grapefruit juice in this table (it is a strong, not a moderate inhibitor)</td></tr>
</table>

### 12.13.2 Clinical Study Protocol Version 3 (9 October 2018)

This was a local amendment to protocol Version 2 and was regarded as a non-substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 3 are:

- To clarify corticosteroid drug use that can be either prednisone or prednisolone,
- To allow a permitted use of topical CS and oral CS rinses,
- To add ECG at week 37 for comparison with baseline ECG,
- To clarify that rituximab can be given during BTP in case a second qualifying relapse occurs at or after D29,
- To clarify CS tapering language,
- To clarify relapsing and newly diagnosed definitions throughout protocol,
- To clarify PK timepoints in SoA,
- To clarify control group rate of CR ≤5 mg CS,
- To remove GTI and HbA1c/LDL in OLE SoA.

**Protocol Amendment summary of changes Table**

# PRN1008-012 Protocol V3.0 (9 October 2018)

Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section | Amended or New Wording | Justification of Change |
|---|---|---|
| Throughout the protocol | ~~Prednisone~~**Corticosteroid (CS);**<br>**Oral corticosteroids (**prednisone **or prednisolone)** | Clarified corticosteroid drug use can be either prednisone or prednisolone |
| 3.4.1 Corticosteroid Starting Doses and Management during Screening and at Day 1;<br>5.9.3 Corticosteroids and Rituximab;<br>Appendix 1 Corticosteroid and Rituximab Management | Required, initial doses of CS for the duration of Screening are ≥ 0.2 mg/kg/day of ~~prednisone~~**CS** for patients with relapsing disease (**diagnosed** > 6 months ~~since diagnosis~~**prior to Screening**) and ≥ 0.5 mg/kg/day for patients with newly diagnosed disease (diagnos**ed**~~is~~ ≤ 6 months prior to Screening).<br>……. | Updated to provide clarity |
| 3.4.2 Corticosteroid Management during Treatment Period and Open Label Extension Period;<br>Appendix 1 Corticosteroid and Rituximab Management | Corticosteroid Tapering (Consensus Guideline, Murrell 2018)<br>• Start tapering CS as soon as CDA is reached or up to the ECP<br>• Decrease CS by ~25% every two weeks, until ~20 mg per day<br>• Once at ~20 mg per day, decrease CS by ~2.5 mg per week<br>• Once at ~10 mg/day, decrease CS by 1 mg per week **to 5 mg**<br>Note, because 1 mg will be the smallest ~~prednisone~~**CS** dosage provided and tablet splitting is not allowed, the Investigator must round up **or down** to the nearest whole milligram for CS dose after calculation of the new dose level. | Updated to provide clarity |
| 3.6 Inclusion Criteria | 3.PDAI score of at least 9 points for relapsing patients (**diagnosed** > 6 months ~~since diagnosis~~**prior to Screening**) or at least 15 points for newly diagnosed patients (diagnosed ≤ 6 months prior to Screening) | Updated to provide clarity |
| 3.12 Randomization | Patients will be randomized at Day 1, in a 1:1 allocation, using a stratification by PV/PF disease type, and by newly diagnosed disease (diagnosed ≤ 6 months prior to Screening) or by relapsing disease (**diagnosed** > 6 months ~~since diagnosis~~**prior to Screening**.) | Updated to provide clarity |

| Section | Amended or New Wording | Justification of Change |
|---|---|---|
| Table 2 Schedule of Assessment - Blinded Treatment Period;<br><br>Table 3 Schedule of Assessments - Open-Label Extension Period | Footnotes:<br>h (Table 2) and e (Table 3). PK sample should be taken at random timepoints during the patient visits with as much variation in time since last dose as practicable. Time of draw will be captured as well as time ~~since~~**of** the last **two** PRN1008 or placebo ~~dose, if administered with food~~**doses**, and time ~~since~~**of** the patient's last meal.<br><br>l (Table 2) and h (Table 3). Photography of lesions ~~conducted~~**allowed** at selected centers **at the discretion of the Investigator and as per local regulations**. | Updated to provide clarity<br><br>Photography requirements removed to allow per Investigator's discretion and local legislation. |
| Table 2 Schedule of Assessment - Blinded Treatment Period | Footnotes:<br>k. Rituximab may be administered intravenously during the Blinded Treatment Period, unless contraindicated, after a second "qualifying relapse" occurs **at or** after Day **29** ~~1 and the patient has completed at least Day 29 (Week 5)~~Visit. See Appendix 1. Any rituximab dispensed will undergo drug accountability. | Updated to correct oversight |
| Table 3 Schedule of Assessments - Open-Label Extension Period | Footnotes:<br>c. Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Serum chemistry will include the following: 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; and glucose (random). Creatine phosphokinase (CPK) is to be performed at Screening only. Coagulation will include: PT/INR, thrombin time, aPTT, and fibrinogen level. ~~HbA1c and LDL levels (fasting) will be collected every 3 months with GTI assessment~~. Urinalysis will include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes ~~at EOT~~. | Corrected GTI assessment previously, inadvertently included in open-label extension period |

| Section | Amended or New Wording | Justification of Change |
|---|---|---|
| 5.9.2 Particular Permissible Medications;<br>Appendix 1 Corticosteroid and Rituximab Management | • **Local use of topical corticosteroids and oral corticosteroid rinses (mouth washes) are allowed.** | Included a permitted CS use |
| 7.7.6 Electrocardiogram Monitoring | Single 12-lead ECGs will be performed at Screening **and Week 37**. All ECGs will be performed with the patient in a supine position. | Added ECG at week 37 for comparison with baseline ECG |
| 7.7.7. Clinical Laboratory Tests | See Table 2 and Table 3 for laboratory test panels for **chemistry**, hematology, urinalysis and pregnancy testing. Laboratory safety tests may be performed at unscheduled time points, if deemed necessary by the Investigator. Screening laboratory safety tests may be repeated upon discussion with the Sponsor/Medical Monitor. | Updated to provide clarity |
| 7.7.15 Photography | Photography of lesions may be performed at selected sites, **at the Investigator's discretion** as allowed by country and local regulations~~, and at selected centers with sufficient subjects. A photography manual will be provided to those sites~~. | Photography requirements removed to allow per Investigator's discretion and local legislation. |
| 3.13 Other Statistical Considerations;<br>8.2 Data Safety Monitoring Board (DSMB) and interim Analysis | There will be no interim analysis to assess efficacy. An interim analysis to possibly add 24 more patients to the trial will be conducted and reviewed by the DSMB when approximately 50% of patients have reached the Week 29 visit, based on an observed control group rate of CR **on ≤5 mg CS** of any duration at Week 29 that exceeds 20%. The additional 24 patients will include a minimum of 20 patients with PV. | Updated to correct oversight |
| 9.4.5 Efficacy Analysis (ITT Population) | Primary:<br>• A Cochran-Mantel-Haenszel (CMH) general association test stratified by disease type (PV or PF) and disease history (newly diagnosed or relapsing) will be used to compare PRN1008 with placebo. Newly diagnosed pemphigus is defined as patients diagnosed ≤ 6 months prior to Screening. Relapsing, chronic pemphigus is defined as patients **diagnosed** ~~with~~ > 6 months ~~since diagnosis~~**prior to Screening.** | Updated to provide clarity |

### 12.13.3 Clinical Study Protocol Version 3.1 for Canada (24 April 2019)

This was a local amendment to protocol Version 3 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 3.1 are:

- To remove inclusion criterion #4 and update numbering,
- To update exclusion criterion #17,
- To correct Rituximab approval status globally,
- To correct indication referenced to GPA.

**Protocol Amendment summary of changes Table**

# PRN1008-012 Protocol V3.1 Canada (24 April 2019)

Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section #/Name | Amended or New Wording | Justification of Change |
|---|---|---|
| Protocol Signature page | [redacted] | Change in personnel. |
| Page 1, 2, and 3 | ~~3.0~~<br>**3.1 Canada** | Updated version |
| 3.6 Inclusion Criteria | ~~4. Body mass index (BMI) > 17.5~~ | Removed Inclusion Criteria #4 and updated the inclusion criteria numbering |
| **3.7 Exclusion Criteria** | History of serious infections requiring intravenous therapy with the potential for recurrence **OR currently active moderate to severe infection at screening (Grade 2 or higher).** | [redacted] |
| **5.1 Overview of pemphigus** | Presently, there are few effective treatment options for pemphigus. Current treatments include corticosteroids (CS) to reduce inflammation and antibiotics to treat associated infections. Agents such as mycofenolate mofetil are often used and rituximab has been reported to be effective. Mycofenolate mofetil has not been approved for this indication in any country **and** rituximab to treat pemphigus vulgaris has ~~only been~~ ~~**only been**~~ **not been globally** approved ~~to date in the US and for both of these agentsto date in the US.~~ ~~**and for both of these agents,**~~ **The** beneficial effects **of these 2 products** take weeks to months. Current day practice guidelines recommend first-line therapy with relatively high doses of CS initially (0.5 to 1.5 mg/kg/day of prednisone or equivalent CS), with rituximab also for consideration as first line therapy in combination with CS (Murrell 2018). | Administrative change to correct Rituximab approval status |
| **5.8 Rituximab and Possible Combination with PRN1008** | Rituximab is a chimeric anti-CD20 antibody **authorized** ~~approved approved~~ for the treatment of rheumatoid arthritis, non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL) and granulomatosis with polyangiitis (GPA ~~Waldenstrom's macroglobulinemia~~ ~~**) (Waldenstrom's macroglobulinemia**~~ **also known as Wegener's granulomatosis**) **and** /microscopic polyangiitis (MPA) - ~~GPA and MPA GPA and MPA~~ in combination with CS. | [redacted] |

### 12.13.4 Clinical Study Protocol Version 3.1 for Germany (01 May 2019)

This was a local amendment to protocol Version 3 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 3.1 are:

- To update the abbreviations list,
- To update the definition of WOCBP,
- To update exclusion criterion #6 for male patients,
- To update exclusion criterion #20 with known contraindication to provided CS or with a known sensitivity to PRN1008 or its excipients.

**Protocol Amendment summary of changes Table**

## PRN1008-012 Protocol V3.1 Germany- [redacted] (1 May 2019)

Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section #/Name | Amended or New Wording | Justification of Change |
|---|---|---|
| Headings, Page 1, 2, and 3 | ~~9 Oct 2018~~<br>**1 May 2019** | Country specific amendment to existing protocol. |
| Page 1, 2, and 3 | ~~Version Number 3.0~~<br>Version Number: 3.**1** | Country specific amendment to existing protocol. |
| Protocol Signature Page, 2 | [redacted] | Change in personnel. |
| 1. List of Abbreviations, Page 8 | **WOCBP = Woman of childbearing potential** | Update to abbreviation list based on new edits (see below) |
| 3.6 Inclusion Criteria #6 | Female patients who are of ~~reproductive~~ **childbearing** potential must agree for the duration of the study to use an **highly** effective means of contraception (eg, **combined estrogen-progesterone containing** hormonal contraception methods that inhibit ovulation **(oral, intravaginal, transdermal), progesterone-only hormonal contraception methods that inhibit ovulation (oral, injectable**, **implantable** intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or **sexual abstinence (only if it is the preferred and usual lifestyle of the subject). A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile**). **A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in** | Updated to provide definition of WOCBP [redacted] |

| Section #/Name | Amended or New Wording | Justification of Change |
|---|---|---|
| | **women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.** ~~Unless surgically sterile, postmenopausal females should have menopause confirmed by follicle stimulating hormone (FSH) testing.~~ | |
| 3.6 Exclusion Criteria 6 | **Male patients should use condoms during study treatment and until 90-days after the last dose of PRN1008/placebo, and should not donate sperm during this same time period. For a non-pregnant female partner of childbearing potential, contraception recommendations for the female patients should also be considered**. | New text added to include instructions on avoidance of pregnancy in a partner of male patients. |
| 3.7 Exclusion Criteria #20 | **Patients who have a known contraindication to sponsor-provided corticosteroid or with a known sensitivity to PRN1008 or its excipients.** | Updated to provide consistency to IB [redacted] |
| Section 6.6 Treatment Blinding | Section 6.6 Treatment Blinding/**Unblinding** | Edited for context |
| Section 6.6, last paragraph; new sentence added | **See Section 8.3.5 for unblinding if required to determine best clinical course.** | Link provided for new section; see below. |
| **New section added** | **8.3.5. Treatment Unblinding to Determine Clinical Course**<br>**If deemed by the Investigator to be medically necessary in the event that a suspected unexpected serious adverse reaction (SUSAR) occurs, to determine appropriate clinical treatment, the Investigator can unblind an individual patient via the IWRS. Instructions for Investigators to unblind are located in the Suvoda IWRS Site User Manual, available both in the Investigator Site File as well as available for all Users to download electronically within the IWRS system.** | To provide additional instructions on unblinding for treatment of SUSARs |

### 12.13.5 Clinical Study Protocol Version 3.2 for Germany (22 May 2019)

This was a local amendment to protocol Version 3.1 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 3.2 are:

- To add WOCBP definition as per the CTFG recommendations on contraception (15 Sep 2014),
- To clarify postmenopausal state in the protocol,
- To introduce highly effective methods of contraception,
- To add contraception duration in the protocol,
- To add inclusion criterion #7 “Has been informed and has given written informed consent and agreeable to the schedule of assessments”
- To add exclusion criterion #21 “Patients who have a known contraindication to Sponsor-provided corticosteroid or with a known sensitivity to PRN1008 or its excipients” as it is in the IB,
- To add exclusion criterion #22 “Patients who are institutionalized by order of authorities or courts”
- To add exclusion criterion #23 “Patients who may be unduly influenced by association with or connected to the Sponsor, Investigator, or Site”,
- To add “contraindication of the sponsor’s provided corticosteroid” as an exclusion criterion for safety reasons,
- To add some clarifications to the protocol Section 6.6 for treatment unblinding.
- To add Week 39 in the Open-Label Extension Period,
- To add all endpoints to the body of protocol,
- To add study design to body of protocol.

**Protocol Amendment summary of changes Table**

# PRN1008-012 Protocol V3.2 Germany- BfArM (22 May 2019)

Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Throughout the protocol | ~~01 May 2019~~ **22 May 2019** | Administrative change to reflect new protocol date |
| Throughout the protocol | ~~Version 3.1~~ **Version 3.2** | Administrative change to reflect new protocol date |
| List of abbreviations | List was updated by adding WHO for World Health Organization. | Change for clarity |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Synopsis: Inclusion Criteria #6 | 6. Female patients who are of childbearing potential must agree for the duration of the study to use a highly effective means of contraception (eg, combined estrogen-progesterone containing hormonal contraception methods that inhibit ovulation~~,~~ (oral, intravaginal, transdermal), progesterone-only hormonal contraception methods that inhibit ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or sexual abstinence (only if it is the preferred and usual lifestyle of the ~~subject~~ **patient**). A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. ~~A postmenopausal~~ **A post-menopausal** state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However~~,~~ in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.<br><br>[new inclusion criterion] | As per request from the [redacted] |
| Synopsis: Inclusion Criteria #7 | 7. Has been informed and has given written informed consent and agreeable to the schedule of assessments | |
| Synopsis: Inclusion Criteria #8 | [new inclusion criterion]<br>8. Male patients should use condoms during study treatment and until 90-days after the last dose of PRN1008/placebo, and should not donate sperm during this | |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | same time period. For a non-pregnant female ~~patients~~ **partner** of childbearing potential, contraception recommendations for the female partner should also be considered. | |
| | [remove exclusion criterion]:<br>~~8. Able to provide written informed consent and agreeable to the schedule of assessments~~ | |
| Synopsis: Exclusion Criteria #20 to 24<br>Section 5.2 Exclusion Criteria | [change of wording for exclusion criterion]<br><br>20. ~~Patients who have a known contraindication to sponsor-provided corticosteroid or with a known sensitivity to PRN1008 or its excipients~~. **Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with patient safety, trial evaluations, and/or trial procedures.**<br><br>[new exclusion criteria]<br><br>21. Patients who have a known contraindication to Sponsor-provided corticosteroid or with a known sensitivity to PRN1008 or its excipients<br>22. Patients who are institutionalized by order of authorities or courts.<br>23. Patients who may be unduly influenced by association with or connected to the Sponsor, Investigator, or Site. | As per request from the [redacted] |
| Table 3 Schedule of Assessments - Open Label Extension Period | [Column title added]<br>**Week 39**<br>**[Time interval added] Week 57 ± 5 days**<br>**"X"** added for the weight, Vital Signs, Urinalysis, Urine pregnancy test, PDAI at the ET Visit | As per request from the [redacted] |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | **"X"** added for Vital Signs, PDAI at the ET Visit and Unscheduled visit<br><br>**"X"** added for the Abbreviated physical examination at the Unscheduled Visit<br>**"X"** added for the Hematology, coagulation, and serum chemistry at Week 39, Week 49 and at the ET Visit<br>**"X"** added for the ABQOL and TABQOL, EQ-5D-5L at Week 39, Week 49, the ET Visit and at the Unscheduled Visit<br>**"X"** added for the PK sample, at Week 39, Week 49, at Week 61and at the ET Visit<br>**"X"** added for the PD: anti-desmoglein -1 and -3 autoantibody titers by ELISA at Week 49, at Week 61and at the ET Visit<br>**"X"** added for the Efficacy Outcome Assessment, assessment of AEs, Photography, Concomitant medications at the ET Visit and at the Unscheduled Visit<br>"**X**" added for the PRN1008 dispensed at Week 57<br>"**X**" added for the Drug reconciliation (PRN1008 /CS Dosing Documentation) at Week 61, the ET Visit and at the Unscheduled Visit. | |
| Section 3. Objectives and Endpoints | **3. Objectives and endpoints**<br>**3.1 Objectives**<br>**3.1.1 Efficacy Objectives**<br>• **To evaluate the efficacy of PRN1008 in achieving durable CR on low to zero doses of** | As per request [redacted] |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | **oral corticosteroid (CS) and on the timecourse of quantitative disease activity scores.**<br>• **To assess the ability of PRN1008 to reduce CS exposure and the adverse effects of CS**<br>• **To evaluate the time to specified clinical endpoints**<br>• **To assesss the longer term durability of CR**<br>**3.1.2 Safety Objectives**<br>• **To evaluate the safety of PRN1008**<br>• **To evaluate differences in potentially CS-related adverse events**<br>**3.1.3 PK/PD Objectives**<br>• **To evaluate the population pharmacokinetics (PK) of PRN1008**<br>• **To evaluate pharmacodynamic (PD) effects of PRN1008 on anti-desmoglein (anti-dsg) autoantibody titers (anti-dsg1 and anti-dsg3)**<br>**3.1.4 Exploratory Objectives**<br>• **To examine the effects of PRM1008, if any, of the baseline covariatets on PK and/or PD.**<br>**3.2 Endpoints**<br>**3.2.1 Outcome Assessment Definitions**<br>**Pemphigus Clinical Definitions (Consensus Guideline, Murrel 2018)**<br>***Control of Disease Activity (CDA):***<br>***Control of disease activity* (disease control) is defined as the time at which new lesions cease to form and established lesions begin to heal. This is also considered** | |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | **the beginning of the consolidation phase. The expected interval of time to reach the control of disease activity is on the order of weeks, although it may be shorter.**<br>***End of Consolidation Phase (ECP):***<br>**The *end of the consolidation phase* is defined as the time at which no new lesions have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions have healed. It is at this point that most clinicians begin to taper corticosteroid doses.**<br>***Complete Remission (CR):***<br>***Complete remission* is defined as the absence of new and established lesions and is intended to mean "no disease activity". Various qualifying statements are added to this definition for endpoints in this protocol.**<br>***Relapse/Flare:***<br>**A *relapse* of disease and a *flare* of disease are synonymous. They are defined by the appearance of 3 or more new lesions within a month that do not heal spontaneously within 1 week, *or* by the extension of established lesions, in a patient who has achieved disease control.**<br>**3.2.2 Primary Efficacy Endpoint**<br>• **The proportion of patients who are in CR from Week ≤ 29 to Week 37 with a CS dose of ≤ 5 mg/day** | |

| | | |
|---|---|---|
| | **3.2.3 Key Secondary Efficacy Endpoints**<br>• **Cumulative CS dose over first 36 weeks (to Week 37)**<br>• **Time to the beginning of the CR event used to define success for patients reaching the primary endpoint**<br>• **Proportion of patients with CR from Week ≤ 29 to Week 37 with a CS dose of ≤ 10 mg/day**<br>**3.2.4 Other Secondary Endpoints**<br>• **GTI score at Week 37**<br>• **Change in EuroQOL-5 Dimension 5 Level (EQ-5D-5L) score from baseline to Week 37**<br>• **Change in EQ-5D-5L score from baseline to Weeks 5, 13, 25, and 61**<br>• **Change in Autoimmune Bullous Disease Quality of Life (ABQOL) score from baseline to Weeks 5, 13, 25, 37 and 61**<br>• **Change in PDAI score from baseline to Weeks 5, 13, 25, 37 and 61**<br>• **Change in Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) score from baseline to Weeks 5, 13, 25, 37, and 61**<br>• **Proportion of patients in CR for ≥ 8 weeks on zero CS at Week 61 by original PRN1008/placebo group assignment and overall**<br>• **Proportion of patients in CR at Week 37 to maintain CR continuously to Week 61**<br>• **Proportion of patients not in CR at Week 37 to achieve CR at Week 61** | |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | • **Proportion of patients to achieve CR of any duration at any time up to Week 37**<br>• **Duration of CR**<br>**3.2.5 Safety Endpoints**<br>• **Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects**<br>• **Change from baseline in vital signs and clinical laboratory test results (including complete blood count and blood chemistry)**<br>**3.2.6 Pharmacokinetic Endpoints**<br>• **Plasma concentrations of PRN1008 at approximately the time of maximum concentration at Day 1 and at varied subsequent timepoints (refer to Table 2 and Table 3)**<br>**3.2.7 Pharmacodynamic Endpoints**<br>• **Change from baseline in anti-dsg1 and anti-dsg3 autoantibody levels by enzyme-linked immunosorbent assay (ELISA) at Weeks 13, 25, 37, 49, and 61**<br>**3.2.8 Exploratory Endpoints**<br>• **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.**<br>• **Cost utilities based on the number and type of hospitalizations, outpatient medical visits,** | |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | **concomitant medication use, adverse events and other relevant outcomes**<br>• **Change from baseline in PDAI by visit and the temporal relationship to changes in quality of life and health economic variables and the relationship between PK, PD, and efficacy**<br>• **To examine the effect of PRN1008 on the costs of hospitalizations, outpatient medical visits, adverse events, concomitant medication use and other relevant health economic outcomes**<br>• **To examine the temporal relationship of change from baseline in Pemphigus Disease Area Index (PDAI) total activity score and quality of life and health economic measures** | |
| Section 4. Study Design | **4. Study Design**<br>**This is a randomized, parallel-group, double-blind, placebo-controlled trial with 36 weeks of treatment during a Blinded Treatment Period followed by an Open-Label Extension Period of 24 weeks and a Follow-up Period of 4 weeks (Figure 1). This study will be conducted at approximately 100 global sites.**<br>**4.1 Duration of Trial Participation**<br>For each patient, the trial will last approximately 68 weeks. This includes Screening (up to 4 weeks) through Week 37 in the Blinded Treatment Period and from Week 37 to Week 61 in the Open-Label Extension Period followed by the 4 week post-dose follow-up at Week 65.<br>**4.2 Blinded Treatment Period (Weeks 1 to 37)** | |

**Table 4: Definitions of Moderate to Severe Population and starting CS doses***

| | PDAI entry criteria | Required CS dose starting at Screening** |
|---|---|---|
| Newly diagnosed (diagnosed ≤ 6 months prior to Screening) | PDAI ≥ 15 | ≥ 0.5 mg/kg/day |
| Relapsing, chronic (diagnosed > 6 months prior to Screening) | PDAI ≥ 9 | ≥ 0.2 mg/kg/day |

* (Shimizu 2014, Boulard 2016) ~~To date, two patients on chronic anticoagulation (rivaroxaban) have been treated without bleeding complications.~~

~~**Corticosteroids and Rituximab**~~

~~Required, initial doses of CS for the duration of Screening are ≥ 0.2 mg/kg/day for )~~

** Doses shown above are minimum requirements. Actual doses will be determined by Investigator judgment.

After informed consent is obtained, patients with moderate to severe pemphigus (PV and PF) at Screening will be randomized in a 1:1 allocation ratio to receive either PRN1008 400 mg twice daily (bid) (n ~ 60) or placebo bid (n ~ 60) during the Blinded Treatment Period (Week 1 to Week 37).

At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, shown in Table 4 ~~with relapsing~~ above, and as required to adequately treat the ~~disease (diagnosed > 6 months prior to Screening) and ≥ 0.5 mg/kg/day for patients with newly~~

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | ~~diagnosed disease (diagnosed ≤ 6 months prior to Screening).~~<br>Thereafter,. CS ~~are managed~~ doses may be adjusted per ~~the Corticosteroid~~ Investigator discretion during the Screening period in the mandated range (CS and Rituximab Management ~~protocol (,~~ Appendix 1).<br>PRN1008 (400 mg tablet) or placebo will be taken twice daily by mouth starting on Day 1. Tablets may be taken with or without food.<br>While continuing on PRN1008 or placebo, commencing during the period of achievement of CDA to approximately the ECP (CDA-ECP), patients will undergo a moderately rapid CS taper regimen as recommended by recently published consensus guidelines (Consensus Guidelines, Murrell 2018) with the goal to reduce the CS dose to 5 mg/day by no later than Study Week 29, with CS dose-adjustment as clinically indicated to control disease (CS and Rituximab Management protocol, Appendix 1).<br>Once patients achieve CR on a dose of 5 mg/day of CS, that dose should be maintained (not tapered further) until Study Week 37 (time of primary endpoint).<br>Throughout the Blinded Treatment Period, patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1) until CDA-ECP is obtained and tapering of CS can (re)commence.<br>Rituximab treatment may be administered during the Blinded Treatment Period at or after the Week 5 visit, unless contraindicated, after a second or subsequent, clinically significant “qualifying relapse” occurs (Appendix 1). | |

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| | If rituximab is administered, patients should remain on trial and blinded to treatment assignment, but will be considered treatment failures for all efficacy endpoints except for cumulative CS and composite Glucocorticoid Toxicity Index (GTI) score. After completing the Blinded Treatment Period, patients will enter the Open-Label Extension Period to receive active treatment with PRN1008 described below. A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab dose should be discontinued from the trial.<br><br>**4.3 Open-Label Extension Period (Weeks 37 to 61)**<br><br>From Week 37, all patients will receive active drug in the Open-Label Extension Period. Patients who received placebo will thus receive active treatment with PRN1008 400 mg bid. Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during this period, will be discontinued from the study.<br><br>From Week 37 (time of primary endpoint), further tapering to 0 mg CS should be attempted in patients with CR. Patients who fail to respond to treatment or experience worsening of disease should have their CS dose increased per CS management guidelines (Appendix 1) until control of disease is obtained and tapering of CS can (re)commence.<br><br>**4.4 Follow-up Period (Weeks 61 to 65):**<br><br>End of Trial for the overall clinical trial is defined as the point at which the last patient has completed the last visit of the study.<br><br>End of Trial for each patient is defined as the point at which the patient has completed their Week 65 visit (4 weeks after the patient's last dose of PRN1008). Patients who are not able to complete the planned Week 65 visit and | |

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| | discontinue the study early should be encouraged to come back for their last visit, and this will be recorded as the End of Trial (EOT) visit. Patients that discontinue early will have the ET assessments completed as outlined in the Schedule of Assessments based upon from which phase treatment they are terminating, Table 2 (Blinded Treatment Period) and Table 3 (Open-Label Extension Period).<br>**4.5 Study Population**<br>Initially, approximately 120 male or female patients with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]) will be enrolled with a targeted minimum of 40 patients with PV per group, and a targeted minimum of 10 patients with PF per group. Twenty-four additional patients may be added after an interim analysis that will assess the observed complete remission (CR) rate in the control group.<br>**4.6 Study Assessments Overview**<br>See Figure 1 for a diagram of the study design and the Schedules of Assessments (Table 2 and Table 3) and for description of the assessments. | |
| 5. Eligibility Criteria | **5. ELIGIBILITY CRITERIA**<br>**5.1 Inclusion Criteria**<br>Patients may be included in the study if ALL of the following criteria are met:<br>1. Male or female patients, aged 18 to 80 years old with moderate to severe, newly diagnosed or relapsing PV or PF, with a clinical presentation and histopathology consistent with PV or PF. | As per request [redacted] |

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| | 2. Positive circulating anti-dsg1 or 3 autoantibody titer<br>3. PDAI score of at least 9 points for relapsing patients (diagnosed > 6 months prior to Screening) or at least 15 points for newly diagnosed patients (diagnosed ≤ 6 months prior to Screening)<br>4. Body mass index (BMI) > 17.5<br>5. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥ $1.5 \times 10^9$/L, hemoglobin (Hgb) > 9 g/dL, platelet count ≥ $100 \times 10^9$/L, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 1.5 × upper limit of normal (ULN), albumin ≥ 3 g/dL, creatinine ≤ 1.5 × ULN<br>6. Female patients who are of childbearing potential must agree for the duration of the study to use a highly effective means of contraception (eg, combined estrogen-progresterone containing hormonal contraception methods that inhibit ovulation (oral, intravaginal, transdermal), progesterone-only hormonal contraception methods that inhibit ovulation (oral, injectable, implantable intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or sexual abstinence (only if it is the preferred and usual lifestyle of the patient). A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative | |

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| | medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.<br>7. Has been informed and has given written informed consent and agreeable to the schedule of assessments<br>8. Male patients should use condoms during study treatment and until 90-days after the last dose of PRN1008/placebo, and should not donate sperm during this same time period. For a non-pregnant female partner of childbearing potential, contraception recommendations for the female partner should also be considered<br>**5.2 Exclusion Criteria**<br>Patients will be excluded from the trial if any of the following criteria are met:<br>1. Suspected paraneoplastic pemphigus and other forms of pemphigus that are not pemphigus vulgaris or pemphigus foliaceus<br>2. Previous use of a Bruton's tyrosine kinase (BTK) inhibitor<br>3. Pregnant or lactating women | |

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| | 4. Electrocardiogram (ECG) findings of QT corrected for heart rate (QTc) > 450 msec (males) or > 470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities<br>5. A history of malignancy of any type, other than surgically excised non-melanoma skin cancers or in situ cervical cancer within 5 years before Day 1<br>6. Use of immunologic response modifiers as concomitant medication and with the following washout periods: A) stop ***at least 2 weeks prior to Screening***: mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, intravenous immunoglobulin (IVIG), Kinaret (anakinra), Enbrel (etanercept) or any other immunosuppressant not mentioned in this exclusion criterion; B) ***12 weeks prior to Screening***: Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), Orencia (abatercept), Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), plasmapheresis; C) ***6 months prior to Screening (or shorter if there is documented B cell reconstitution for anti-CD20 drugs):*** antiCD20 drugs such as rituximab, ofatumumab, other long-acting biologics<br>7. Use of proton pump inhibitor drugs such as omeprazole and esomeprazole within 3 days (It is acceptable to change patient to H2 receptor blocking drugs prior to Day 1.) | |

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| | 8. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A within 3 days or 5 half-lives (whichever is longer) of Day 1 (Appendix 8)<br>9. Use of CYP3A-sensitive substrate drugs with a narrow therapeutic index within 3 days or 5 half-lives (whichever is longer) of Day 1 and for the remainder of the trial including, but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or terfenadine<br>10. Has received any investigational drug (or is currently using an investigational device) within the 30 days before Day 1, or at least 5 times the respective elimination half-life time (whichever is longer)<br>11. History of drug abuse within the previous 12 months<br>12. Alcoholism or excessive alcohol use, defined as regular consumption of more than approximately 3 standard drinks per day<br>13. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate PRN1008/placebo absorption<br>14. Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1<br>15. History of solid organ transplant | |

| Section(s) | Amended or New Wording | Justification of Change |
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| | 16. Positive at Screening for human immunodeficiency virus (HIV), hepatitis B (surface and core antibodies unrelated to vaccination, surface antigen), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA)<br>17. Positive interferon-gamma release assay (IGRA) (eg, QuantiFERON®-TB Gold or T-spot TB® Test) at Screening. Unless, all of the following 3 conditions are true:<br>a. Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease<br>b. There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease<br>c. Documented receipt of a course of prophylactic TB treatment of at least 6 months<br>18. History of serious infections requiring intravenous therapy with the potential for recurrence<br>19. Live vaccine within 28 days prior to Day 1 or plan to receive one during the trial<br>20. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with patient safety, trial evaluations, and/or trial procedures<br>21. Patients who have a known contraindication to Sponsor-provided corticosteroid or with a known sensitivity to PRN1008 or its excipients | |

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| | 22. Patients who are institutionalized by order of authorities or courts.<br>23. Patients who may be unduly influenced by association with or connected to the Sponsor, Investigator or Site. | |
| Section 6. Treatments | 6.1.1 PRN1008/**Placebo**<br>6.1.2 ~~**Preparation and Administration**~~ Corticosteroids<br><br>**6.1.2.1 Corticosteroid Starting Doses and Management during Screening and at Day 1**<br><br>**Required, initial doses of CS for the duration of Screening are ≥ 0.2 mg/kg/day of CS for patients with relapsing disease (diagnosed > 6 months prior to Screening) and ≥ 0.5 mg/kg/day for patients with newly diagnosed disease (diagnosed ≤ 6 months prior to Screening). At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, and as required to adequately treat the disease during the Screening period. CS doses may be adjusted upward per Investigator discretion during the Screening period but the dose should not be reduced below the initial dose levels (Table 1).**<br><br>**If disease significantly (Investigator judgment) worsens during the Screening period, up-titration of CS dose by 50-100% should occur, as often as every 5-7 days if needed (Harman 2017).**<br><br>**6.1.2.2. Corticosteroid Management during Treatment Period and Open-Label Extension Period** | As per request [redacted]) |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **6.1.2.2.1. Corticosteroid-Tapering (Consensus Guideline, Murrell 2018)**<br><br>CS will be tapered from CDA-ECP towards a goal of 5 mg/day by ≤ Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. After that, taper towards 0 **mg should commence as clinically indicated.**<br><br>**CS tapering should follow the dosing guidelines below (Murrell 2018). Adjustment of the tapering guideline protocol by investigators is permitted, based on assessment of clinical need.**<br>• **Start tapering CS as soon as CDA is reached or up to the ECP**<br>• **Decrease CS by ~25% every two weeks, until ~20 mg per day**<br>• **Once at ~20 mg per day, decrease CS by ~2.5 mg per week**<br>• **Once at ~10 mg/day, decrease CS by 1 mg per week**<br><br>**Note, because 1 mg will be the smallest CS dosage provided and tablet splitting is not allowed, the Investigator must round up or down to the nearest whole milligram for CS dose after calculation of the new dose level.** | |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **6.1.2.2.2. Corticosteroid-Up-Titration (Harman 2017)**<br>**CS up-titration is allowed if disease significantly worsens prior to initial CDA-ECP or after CDA-ECP, during CS taper.**<br>**Up-titration should be a temporary increase until CDA-ECP is achieved (again), after which tapering can recommence.**<br>**For full details of up-titration see Appendix 1.** | |
| Section 7.4.1 Patient Discontinuation and Stopping Rules | The Investigator ~~in conjunction with the~~ **or** Sponsor may ~~also, at their discretion,~~ discontinue the patient from participation in the study at any time if ~~both~~ **they** consider discontinuation to be in the patient's best interest. If a patient meets any of the criteria listed below, the patient should complete the assessments for the Early Termination (ET) visit (see Table 2 and Table 3).<br>~~Reasons~~ **Mandatory termination criteria** for ~~discontinuing~~ a patient ~~may~~ **in this study** include, ~~but are not necessarily limited to, the following:~~<br>• Severe and life-threatening pemphigus disease activity<br>• Grade 4 PRN1008 -related TEAE<br>• Serious allergic reaction to PRN1008 or placebo including anaphylactic reaction<br>• A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab dose or a patient in the Open-Label Extension Period requiring rituximab<br>• Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), viral hepatitis (B and C) infection occurring during the study<br>• Pregnancy | As per request [redacted] |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **There may be additional reasons for patient discontinuation, such as the following examples:**<br>• Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the patient to risk if the patient continues with PRN1008 or placebo or that prevents the patient's adherence to the protocol<br>~~If in the Investigator's or the Sponsor's judgment, discontinuation is in the patient's best interest~~<br>• Violation of protocol inclusion or exclusion criteria, if, in the opinion of ~~the Investigator and~~ the Sponsor, the violation would significantly compromise data interpretation<br>• Discontinuation of the study by the Sponsor | |
| Section 8. Assessments of Efficacy | **8. Assessments of Efficacy**<br>**8.1 Specification of the Efficacy Parameters**<br>Efficacy will be evaluated using a combination of lesion assessments, corticosteroid usage, and validated instruments for assessing disease activity and patient quality of life.<br>A comprehensive list of all the secondary endpoints can be found in Sections 3.21 -3.2.3. In summary:<br>• The primary endpoint requires patients to have no new or established lesions at the Week 29, 33 and 37 visits, while on a daily corticosteroid dose ≤5 mg/day.<br>• The first key secondary endpoint is an analysis of the cumulative corticosteroid dose over the first 36 weeks of the study (to Week 37). | As per request [redacted] |

| Section(s) | Amended or New Wording | Justification of Change |
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| | • The other secondary endpoints include analyses of the following instruments: PDAI, ABQOL, TABQOL, EQ-5D-5L, VAS and GTI. Descriptions of the instruments can be found in Sections 7.7.9 - 7.7.14.<br>**8.2 Methods and timing for assessing, recording and analyzing of efficacy parameters**<br>Lesion assessments, the Pemphigus Disease Area Index (PDAI) and prescribed corticosteroid doses are recorded at every visit. The quality of life instruments are administered at the visits specified in the schedule of assessments (Table 2), and the Early Termination visit and Unscheduled visits. Further assessment details can be found in Section 7.<br>Descriptions of the analysis of the primary and secondary endpoints can be found in Section 10.2.10 and Section 10.2.11 | |
| Section 10.2 Objectives and Endpoints | **10.2 Objectives and Endpoints**<br>Please refer to ~~**Synopsis**~~ Section 4.<br>~~**Outcome Measures**~~<br>~~Please refer to Synopsis Section .~~<br>**Analysis Populations**<br>Three populations will be defined for data analysis: the Safety Population, the Intent-to-Treat (efficacy) Population, and the Pharmacokinetic Population. | As per request [redacted] |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **10.2.2 Safety Population**<br>All patients who are randomized and receive at least one dose of study medication will be included in the ~~ITT~~ **Safety** Population. The ~~ITT population~~ **Safety Population** is the primary analysis population for ~~efficacy.~~ **safety. Patients will be analysed according to the treatment they actually received, not necessarily the treatment they were allocated to at randomization**. Results will be presented "as ~~randomized~~ **treated.**<br>**10.2.3 Intent-to-Treat (ITT) Population**<br>All patients who are randomized will be included in the ITT Population. The ITT Population will be used for sensitivity analyses. Patients will be analyzed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented "as randomized."<br>**10.2.4 Modified Intent-to-Treat (mITT) Population**<br>All patients who are randomized and receive at least one dose of study medication will be included in the mITT Population. The mITT Population is the primary analysis population for efficacy. Patients will be analyzed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented "as randomized." | |

### 12.13.6 Clinical Study Protocol Version 4 (29 August 2019)

This was a global amendment to protocol Version 3 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 4 are:

- To align number of PV/PF patients with the analysis plan,
- To remove interim analysis,
- To clarify to reduce unnecessary FSH/pregnancy testing for women with confirmed menopause,
- To clarify CDA, ECP, and CR timing and requirements,
- To clarify CS dosing and adjustment, and that CS tapering occurs after ECP confirmation,
- To add provision to extend screening window,
- To add the allowed dose interval of 8 hours for consecutive PRN1008/placebo doses,
- To add washout period for warfarin and intralesional steroid use,
- To remove Warfarin statement due to the potential of CYP3A inhibition,
- To update clinical data in alignment with IB V10 dated 17May2019,
- To add a Week 39 visit in open-label extension,
- To remove the inclusion criterion #4 linked to BMI restriction,
- To update exclusion criteria #17, #18 and #20,
- To clarify biopsy requirements to ensure pemphigus diagnosis for eligibility,
- To clarify that rituximab may be allowed if disease control is never achieved,
- To clarify qualifying relapse and rituximab management in OLE,
- To add flow chart to assist Investigator with Efficacy Outcome Assessment.

**Protocol Amendment summary of changes Table**

## PRN1008-012 Protocol V4.0 (29 August 2019)

The protocol Version 4.0, 29 August 2019 has been updated throughout to correct errors and to clarify or adjust study procedures and assessments. Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section(s) | Amended or New Wording | Justification of Change |
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| Throughout the protocol | ~~9 Oct 2018~~**29 Aug 2019**, Version ~~3~~**4** | Administrative change. |
| Protocol Signature Page | [redacted] | Updated Chief Medical Officer information. |
| 2.6 Study Population,<br>3.13. Other Statistical Considerations,<br>8.2 Data Safety Monitoring Board (DSMB) and Interim Analysis<br>And<br>9.1 Determination of Sample Size | 2.6: ~~Initially, approximately~~**Approximately** 120 male or female patients with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]) will be enrolled with a targeted minimum of ~~40~~ **45** patients with PV per group, and a ~~targeted minimum~~ **maximum** of 10 patients with PF per group. ~~Twenty-four additional patients may be added after an interim analysis that will assess the observed complete remission (CR) rate in the control group.~~ | Updated to ensure that the number of PV patients is consistent with the analysis plan in Section 3.13. The interim analysis was removed to avoid any potential issues in controlling the Type I error rate. |
| 3.1. Pemphigus Clinical Definitions (Consensus Guideline, Murrell 2018) | ***Control of Disease Activity (CDA):***<br>*Control of disease activity* (disease control) is defined as the ~~time~~**visit** at which new lesions cease to form and established lesions begin to heal. This is also considered the beginning of the consolidation phase. The expected interval of time to reach the control of disease activity is<br>on the order of weeks, although it may be shorter. | Clarification that "time" when referenced with CDA refers to the visit the CDA was assessed at and achieved. |

| Section(s) | Amended or New Wording | Justification of Change |
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| 3.1. Pemphigus Clinical Definitions (Consensus Guideline, Murrell 2018) | ***End of Consolidation Phase (ECP):***<br>The *end of the consolidation phase* is defined as the ~~time~~**visit** at which no new lesions have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions have healed. ~~It is at this point that most clinicians begin to taper corticosteroid doses.~~**Therefore, in order to achieve ECP, CDA must be confirmed at a visit ≥ 2 weeks later and 80% of the lesions seen previously must have healed.** | Clarification that "time" when referenced with ECP refers to the visit a minimum of 2 weeks after CDA was documented. Language regarding the ECP milestone. clarified for ease of understanding, as consistent with guidelines. |
| 3.3.1 Study Design<br>(Blinded Treatment Period - Weeks 1 to 37) | After informed consent is obtained, patients with moderate to severe pemphigus (PV and PF)<br>~~at Screening~~**will be screened and if eligible** will be randomized in a 1:1 allocation ratio to receive either PRN1008 400 mg twice daily (bid) (n ~ 60) or placebo bid (n ~ 60) during the Blinded Treatment Period (Week 1 to Week 37).<br><br>At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, shown in Table 1 above, and as required to adequately treat the disease. CS<br>doses may be adjusted per Investigator discretion during the Screening period ~~in the mandated range~~ (~~CS and Rituximab Management,~~ Appendix 1) **but the dose should not be reduced below the required minimum initial dose levels (Table 1). CS taper should not being until ECP has been achieved.**<br><br>PRN1008 (400 mg tablet) or placebo will be taken twice daily by mouth starting on Day 1. Tablets may be taken with or without food.<br><br>**If a patient achieves CDA (no new lesions and established lesions begin to heal), a follow-up visit ≥ 2 weeks later must confirm the finding of no new lesions prior to declaring ECP and tapering CS. ECP is achieved with the confirmation of CDA (no new lesions for ≥ 2 weeks) with approximately 80% of the established lesions epithelialized (healed). If needed, confirmation of CDA and achievement of ECP may be documented at an Unscheduled Visit, prior to the next scheduled study visit. See** | Clarified "at screening" means the patients will be screened and that randomization would occur only if eligible.<br><br>Updated text for consistency with Appendix 1, which specifies that only up-titration is allowed for CS during Screening.<br><br>Added clarifying text regarding the use of Unscheduled Visits as allowed per protocol to document CDA and/or ECP. Minor changes were made to language throughout Sec 3.3.1 to ensure clarity and for consistency with these clarifications. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **Table 2 for all required assessments for an Unscheduled Visit, which also includes Efficacy Outcome Assessment and PDAI.**<br><br>While continuing on PRN1008 or placebo, ~~commencing during~~**following** the ~~period of~~ achievement of ~~CDA to approximately the~~ ECP ~~(CDA ECP)~~, patients will undergo a moderately rapid CS taper regimen as recommended by recently published consensus guidelines (Consensus Guidelines, Murrell 2018) with the goal to reduce the CS dose to 5 mg/day by no later than Study Week 29, with CS dose-adjustment as clinically indicated to<br>control disease (CS and Rituximab Management protocol, Appendix 1).<br><br>**CS taper should not begin until ECP has been achieved.**<br><br>**If the first documentation of CDA coincides with no disease activity (PDAI=0), a follow-up visit ≥ 2 weeks later must still confirm that no new lesions are seen and PDAI=0. At this time the patient is deemed to have confirmed CDA, ECP, and CR and therefore CS tapering can begin. If new lesion(s) are seen, the patient is no longer in CDA and therefore CS tapering should not begin. If a patient has not achieved CDA or new lesions emerge or existing lesions worsen but do not meet definition of relapse, refer to Appendix 1 regarding increasing steroid dosage.**<br><br>~~Once patients achieve CR on a dose of 5 mg/day of CS, that dose should be maintained (not tapered further) until Study Week 37 (time of primary endpoint).~~<br><br>Throughout the Blinded Treatment Period, patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1) until CDA ~~ECP~~ is obtained ~~and tapering of CS can (re)commence~~.<br>**If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor in such cases.**<br><br>**Efficacy Outcome Assessment should be performed per the Efficacy Outcome Assessment** | Updated to clarify CS tapering occurs after ECP confirmation.<br><br>Added context for CDA, ECP and CR. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **Flowchart, Appendix 9.**<br><br>**Once patients achieve CR on a dose of 5 mg/day of CS, that dose should be maintained (not tapered further) until Study Week 37 (time of primary endpoint).**<br><br>Rituximab treatment may be administered during the Blinded Treatment Period at or after the Week 5 visit, ~~unless contraindicated,~~**only** after a second ~~or subsequent, clinically significant~~ "qualifying relapse" occurs, **unless contraindicated** (Appendix 1).<br><br>If rituximab is administered, patients should remain on trial and blinded to treatment assignment, but will be considered treatment failures for all efficacy endpoints except for cumulative CS and composite Glucocorticoid Toxicity Index (GTI) score. After completing the Blinded Treatment Period, patients will enter the Open-Label Extension Period to receive active treatment with PRN1008 described below. A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab ~~dose should~~**course of treatment must** be discontinued from the trial. | |
| 3.3.1 Study Design (Open Label Extension Period - Weeks 37 to 61) | From Week 37, all patients will receive active drug in the Open-Label Extension Period. Patients who received placebo will thus receive active treatment with PRN1008 400 mg bid. Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during this period, ~~will~~**must** be discontinued from the study.<br><br>From Week 37 (time of primary endpoint), further tapering to 0 mg CS should be attempted in patients with CR **unless medically contraindicated**. Patients who fail to respond to treatment or experience worsening of disease should have their CS dose increased per CS management guidelines (Appendix 1) until ~~control of disease is obtained and tapering of CS can (re)commence.~~ **CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor is such cases.** | Updated to clarify CS dosing and adjustment. |

| Section(s) | Amended or New Wording | Justification of Change |
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| 3.4.1 Corticosteroid Starting Doses and Management during Screening and at Day 1, and<br>Appendix 1 | 3.4.1:<br>**Corticosteroid Starting Doses and Management during Screening and at Day 1**<br>Required, initial doses of CS for the duration of Screening are ≥ 0.2 mg/kg/day of CS for patients with relapsing disease (diagnosed > 6 months prior to Screening) and ≥ 0.5 mg/kg/day for patients with newly diagnosed disease (diagnosed ≤ 6 months prior to Screening). At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, and as required to adequately treat the disease during the Screening period. CS doses may be adjusted ~~upward~~ per Investigator discretion during the Screening period (**Appendix 1**) but the dose should not be reduced below the ~~initial~~ **required minimum initial dose levels (Table 1). CS taper should not begin until ECP has been achieved.** | Clarified that tapering can begin during Screening if ECP is achieved. |
| 3.4.2. Corticosteroid Management during Treatment Period and Open-Label Extension Period, Appendix 1 CORTICOSTEROID AND RITUXIMAB MANAGEMENT, Figure 1 Study Design Flow Chart, and 5.5 Trial Design Rationale | 3.4.2:<br>**Corticosteroid-Tapering (Consensus Guideline, Murrell 2018)**<br>CS will be tapered from ~~CDA~~ ECP towards a goal of 5 mg/day by ≤ Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. ~~After that, taper towards 0 mg should commence as clinically indicated.~~**From Week 37, further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated.**<br><br>CS tapering should follow the **modified** dosing guidelines below (Murrell 2018). Adjustment of the ~~tapering~~**dosing** guideline protocol by investigators is permitted **for safety reasons**, based on assessment **and documentation** of clinical need.<br><br>• Start tapering CS as soon as ~~CDA is reached or up to the~~ ECP **is confirmed**.<br>• Decrease CS by ~~~~25% every two weeks, until ~20 mg per day<br>• Once at ~~~~20 mg per day, decrease CS by ~2.5 mg per week | Clarified tapering to zero after Week 37 should occur unless medically contraindicated. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | • Once at ~10 mg/day, decrease CS by 1 mg per week<br><br>Note, because 1 mg will be the smallest CS dosage provided and tablet splitting is not allowed,<br>the Investigator must round up or down to the nearest whole milligram for CS dose after calculation of the new dose level.<br><br>**Corticosteroid-Up-Titration (Harman 2017)**<br>~~CS up-titration is allowed if disease significantly worsens prior to initial CDA-ECP or after CDA-ECP, during CS taper. Up-titration should be a temporary increase until CDA-ECP is achieved (again), after which tapering can recommence.~~<br><br>**Patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1) until CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor in such cases.**<br><br>For full details of up-titration see Appendix 1. | Text replaced with updated language to clarify CS up-titration should occur if patients fail to respond or experience worsening of disease. |
| 3.5. Concomitant Medications and 5.9.2 Particular Permissible Medications | 3.5:<br>Strong to Moderate Inducers or Inhibitors of cytochrome P450 (CYP)3A, and "Sensitive" CYP3A Substrate Drugs with a narrow therapeutic index are not permitted (Appendix 8). Other "Sensitive" CYP3A drugs should be used cautiously by administering them only if the<br>benefit-risk is favorable, using staggered administration at least 2 hours after PRN1008 or placebo.<br><br>Patients on proton pump inhibitor drugs should have their medication changed to histamine 2<br>(H2) blockers during Screening and at least 3 days before Day 1. H2 blockers should be administered at least 2 hours after PRN1008 or placebo. | Warfarin statement removed due to the potential of CYP3A inhibition (see Section 5.9.1 and Appendix 8). |

| Section(s) | Amended or New Wording | Justification of Change |
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| | ~~Warfarin should be monitored carefully as there is limited experience of co-administration with PRN1008. To date, two patients on chronic anticoagulation (rivaroxaban) have been treated without bleeding complications.~~ | |
| 3.6 Inclusion Criteria #1, and Section 7.7.3 | 7.7.3. Biopsies<br>A new biopsy **(cutaneous and/or mucosal)** is not required if there is a prior and available biopsy report documenting histopathologic findings diagnostic for PV or PF. A new biopsy should be performed if an archival biopsy report is not available.<br>New biopsies should include local hematoxylin and eosin (H&E) histopathological review and direct immunofluorescence (DIF) for the characteristic pattern diagnostic of pemphigus ~~(Note: anti-desmoglein antibodies may be used as an alternative confirmation if DIF is negative and histopathology is characteristic of pemphigus).~~<br>**Histopathology on biopsies is evaluated for consistency with a diagnosis of PV or PF:**<br>• **If DIF is positive, the patient is eligible in the presence of positive anti-desmoglein antibodies.**<br>• **If DIF is negative, the patient is not eligible. In these cases, where the H&E histopathology is characteristic of pemphigus and anti-desmoglein antibodies are positive, the biopsy may be repeated at the discretion of the investigator.**<br>• **If DIF is not available, the patient is eligible in the presence of positive anti-desmoglein antibodies and H&E histopathology characteristic of pemphigus.** | Biopsy requirements to ensure pemphigus diagnosis for eligibility were clarified. |
| 3.6. Inclusion Criteria #4 | Body mass index (BMI) > 17.5 **(only applicable through Protocol v3.0)** | The setting of BMI > 17.5 was based on early pre-clinical findings of weight loss in the 4-13-week repeat dose GLP toxicity study in dogs (see IB Version 10 dated 17May2019, Sections 4.2.3.1 and 4.5.2.2). In the absence of human data at the |

| Section(s) | Amended or New Wording | Justification of Change |
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| | | time of the first clinical study in pemphigus patients (PRN1008-005), BMI restriction was used to exclude patients with low body weight. As there were no changes in weight or appetite in the Phase 2 study, PRN1008-005, the BMI criteria has now been removed in this protocol. |
| 3.7. Exclusion Criteria #17 | Positive interferon-gamma release assay (IGRA) (eg, **T-spot TB Test,** QuantiFERON®-TB Gold, or ~~T-spot TB® Test)~~**QuantiFERON®-TB Gold Plus (QFT Plus),** at Screening. Unless, **the patient has latent TB and** all of the following 3 conditions are true:<br>a) Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease<br>b) There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease<br>**c)** Documented receipt of ~~a course~~**one** of **the following** prophylactic ~~TB~~ treatment ~~of at least~~ **regimens:**<br>**i. Oral daily Isoniazid for 6 months**<br>**or**<br>**ii. Oral daily Rifampin (RIF) for 4 months**<br>**or**<br>**iii. Isoniazid and Rifapentine weekly for 3 months (3HP)**<br>**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.** | Clarification of the options for TB testing and conditions to reduce the number of false positive and indeterminate test results, and to enable accurate results in patients who have received the BCG vaccine. |

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| 3.7. Exclusion Criteria #18 | History of serious infections requiring intravenous therapy with the potential for recurrence **or currently active moderate to severe infection at Screening (Grade 2 or higher).** | Clarification to ensure that patients with moderate to severe active infection are not enrolled. |
| 3.7. Exclusion Criteria #20 | Any other clinically significant disease, condition **[including contraindication to CS and/or inability to follow CS dosing as outlined in the protocol (see Table 1 for more details)]**, or medical history that, in the opinion of the Investigator, would interfere with patient safety, trial evaluations, and/or trial procedures. **In areas endemic for Chagas disease, screening is recommended prior to enrollment.** | Provided recommendation for areas where Chagas may be endemic to screen and rule out the disease prior to enrolling. |
| Table 2 Schedule of Assessments | Footnote f: ~~To confirm postmenopausal status for women who are not surgically sterile only.~~<br>**Any woman of age ≥ 55 years with amenorrhea for >1 year, will be considered as having confirmed menopause and will not need FSH or pregnancy testing. Postmenopausal females < 55 years of age (defined as amenorrhea > 1 year) should have menopause confirmed by follicle-stimulating hormone (FSH) and serum pregnancy testing at screening. Surgically sterile females do not require any further confirmation of menopause and will not be considered to have reproductive potential.** | Clarified to reduce unnecessary FSH/pregnancy testing for women with confirmed menopause. |
| Table 3 Schedule of Assessments | **Week 39 ± 3 days** / Weight: **X**<br>**Week 39 ± 3 days** / Abbreviated physical exam: **X**<br>**Week 39 ± 3 days** / Vital Signs: **X**<br>**Week 39 ± 3 days** / Hematology, coagulation, and serum chemistry[c]: **X**<br>**Week 39 ± 3 days** / PK Sample[e]: **X**<br>**Week 39 ± 3 days** / PDAI: **X**<br>**Week 39 ± 3 days** / ABQOL: **X**<br>**Week 39 ± 3 days** / TABQOL: **X**<br>**Week 39 ± 3 days** / EQ-5D-5L: **X**<br>**Week 39 ± 3 days** / Efficacy Outcome Assessment[f]: **X**<br>**Week 39 ± 3 days** / Adverse events: **X**<br>**Week 39 ± 3 days** / Photography[h]: **X**<br>**Week 39 ± 3 days** / Concomitant medications: **X** | A Week 39 visit in open-label was added for consistency, to match the Week 3 double-blind Visit, so that patients starting active PRN1008 for the first time in the Open Label Extension have a visit two weeks after starting PRN1008 dosing in this protocol. |

| Section(s) | Amended or New Wording | Justification of Change |
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| 5.4 Clinical Experience | In clinical studies to date, PRN1008 has been administered to ~~140~~**more than 200 people, including** healthy volunteers, 27 **and** patients with pemphigus ~~(mainly pemphigus vulgaris variant, i.e. PV) and 4~~**and Idiopathic thrombocytopenia. Twenty-**seven patients ~~with immune thrombocytopenic purpura (ITP). Patients~~ with PV in a Phase 2 study (NCT02704429) used a starting dose of 400 mg BID which was shown to produce adequate BTK occupancies in all but one patient. One patient dose escalated to 500 mg BID and ~~one~~**two** to 600mg BID, with all other patients using the 400mg BID dose. ~~An interim analysis of the first 27 patients in this study found evidence of clinically significant activity in 80% of patients, with onset of disease control in the first 2 weeks of therapy, and an acceptable safety profile (DSUR 2018 and IB Section 5).~~ The primary endpoint of the study, "control of disease activity by the Week 5 visit on ≤ 0.5mg/kg/day of prednisone (or equivalent CS)" was met by 54% (14/26) of patients. Complete remission on ≤ 0.5mg/kg/day of CS was achieved by 25% (5/20) of patients completing 12 weeks treatment. | Additional clinical data provided in alignment with current IB V10 dated 17May2019. |
| 5.9.1 Prohibited Medications | The following medications are prohibited for use during the trial:<br>• Concomitant use of any ***immunosuppressant medication***, other than CS and rituximab as described in this protocol. Patients who need other immunosuppressant therapy during the trial should be withdrawn. See Exclusion # 6 Section 3.7 for washout periods.<br>• Concomitant use of known ***strong to moderate inducers or inhibitors of cytochrome*** *P450 (CYP) 3A* (Appendix 8) within 3 days or 5 half-lives (whichever is longer) of Day<br>• Use of *CYP3A-sensitive substrate drugs with a narrow therapeutic index* (within 3 days or 5 half-lives (whichever is longer) of Day 1 including, but not limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus~~,~~ **(topical and oral),** or terfenadine.<br>• *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. Subjects who are on proton | Washout period for warfarin use and intralesional steroid use were added. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | pump inhibitors should be changed to histamine (H2) receptor blocking drugs if possible or not enroll in the trial. Details of H2 receptor blocker administration is provided in Section 5.9.2.<br>• ***Intralesional steroids*** **are not permitted within 3 months of Screening, during Screening and for the duration of the study.**<br>• ***Warfarin*** **use is not permitted within 1 week or 5 half-lives (whichever is longer) of Day 1 and for the duration of the study.** | |
| 6.1.2 Preparation and Administration | Treatment medication will be taken twice daily by mouth starting on Day 1. PRN1008 or placebo may be taken with or without food. **Consecutive PRN1008/placebo doses should not be taken within 8 hours of each other.** Tablets should not be broken or crushed. Further details for dispensation and administration of blinded treatment are provided in the Pharmacy Manual. | Added the allowed dose interval. |
| 7.6.1 Screening (Day -29 to Day -1)<br>And<br>Table 2 | **7.6.1. Screening (Day -29 to Day -1)**<br>Informed consent will be obtained at Screening before performing any trial procedures.<br>Patients will undergo Screening assessments, including, but not limited to; blood sampling, ECG, clinical assessment and various quality of life assessments. Please refer to Table 2.<br>**In cases where laboratory assessments are delayed due to logistic considerations, the Sponsor may permit an extension of the Screening Period for laboratory assessments up to 7 days in order to determine eligibility. Week 1 Day 1 should occur as soon as possible upon evaluation of the delayed assessments and no later than 35 days after the initial Screening visit.** | Added a provision for Screening window extension by ≤7 days in the case where laboratory assessments are delayed for a logistical reason, after discussion with Sponsor. |
| 7.6.3 Blinded Treatment Period (Weeks 1 to 37)<br>and<br>Appendix 9 EFFICACY OUTCOME ASSESSMENT FLOWCHART | Please refer to Table 2 for specific assessments at each visit. CS dosing, and use of rituximab for a second qualifying relapse, are detailed in Appendix 1. **The Efficacy Outcome Assessment Flowchart is detailed in Appendix 9.** | Added Appendix 9 flow chart to assist Investigator with Efficacy Outcome Assessment. |

| Section(s) | Amended or New Wording | Justification of Change |
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| Appendix 1 CORTICOSTEROID AND RITUXIMAB MANAGEMENT | 2. Non life-theatening worsening of disease during taper of CS **prior to** ~~initial CDA~~ **confirmation of** ECP<br><br>During Screening or the treatment periods of the trial, where an initial induction of CDA has not been achieved and blistering continues without improvement, CS should be increased by 50 to 100% every 5 to 7 days until ~~CDA~~ **confirmation of ECP. After ECP is** ~~achieved, and~~ confirmed CS taper ~~can~~ **should** commence. Rituximab therapy may not be used in this situation. **Patients who have been treated with a minimum of 1.5mg/kg/day of corticosteroids for 2 weeks and have not achieved control of disease activity may be eligible after discussion with Principia to receive rituximab.** | Added to clarify that Sponsor may provide rituximab (if approved as rescue medication, by the relevant Competent Authority and Ethics Committees) in cases where disease control is never reached, despite adequate treatment with CS, upon discussion with Sponsor. |
| Appendix 1 CORTICOSTEROID AND RITUXIMAB MANAGEMENT | **Rituximab Management during Blinded Treatment Period**<br><br>Rituximab for second "qualifying relapse":<br>• "Qualifying relapse" for this purpose is defined as a relapse occurring after CDA ~~ECP~~ is achieved**, ECP has been confirmed** and CS taper has begun, that is not life-threatening (when a patient should be withdrawn) but is severe enough such that the PDAI total activity score is equal to or greater than the Screening or Day 1 baseline PDAI score (whichever is higher) for that patient. For example, if the Screening PDAI was 25, the Day 1 baseline was 21, and the relapse PDAI 23, the relapse would not be severe enough to be "qualifying". Whereas if the relapse PDAI was ≥ 25 it would be "qualifying".<br>• Where a second qualifying relapse occurs meeting the above definition, and it is at or after the Week 5 visit, then one course of rituximab, which consists of two intravenous doses of 1 gram two weeks apart, may be administered, unless contraindicated.<br>• Oral CS doses should be managed as indicated for the patient at the time of the 2nd qualifying relapse<br>• Rituximab should be administered as recommended in the Pharmacy Manual.<br>• Patients should not be unblinded to treatment assignment and should continue in the trial. | Updated to match the same discontinuation instruction from Section 3.3.1. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | • The need for rituximab rescue will be considered "treatment failure" for the analysis of all efficacy endpoints except cumulative CS and composite GTI score.<br>**Rituximab Management during Open-Label Extension Period**<br>• **Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during this period, will be discontinued from the study.** | |

### 12.13.7 Clinical Study Protocol Version 4.1 for Germany (30 September 2019)

This was a local amendment to protocol Version 4 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 4.1 are:

- To revise Week 39 window to 3 days for consistency and to match the Week 3 double-blind Visit,
- To update the number of PV patients in accordance with the analysis plan, and to remove the interim analysis,
- To clarify text regarding the use of Unscheduled Visits as allowed per protocol to document CDA and/or ECP,
- To clarify CS dosing and adjustment,
- To remove Warfarin statement due to the potential of CYP3A inhibition.

**Protocol Amendment summary of changes Table**

## PRN1008-012 Protocol V4.1 (30 September 2019)

The protocol Version 4.1, 30 September 2019 has been updated throughout to correct errors and to clarify or adjust study procedures and assessments. Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section(s) | Amended or New Wording | Justification of Change |
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| Throughout the protocol | ~~22 May 2019~~ **30 Sep 2019**, Version ~~3.2~~ **4.1** | Administrative change. |
| 1. Synopsis (Study Population and Other Statistical Considerations), 4.5 Study Population, 9.2 Data Safety Monitoring Board (DSMB) and Interim Analysis and 10.1 Determination of Sample Size | 2.6: ~~Initially, approximately~~**Approximately** 120 male or female patients with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]) will be enrolled with a targeted minimum of ~~40~~ **45** patients with PV per group, and a ~~targeted minimum~~ **maximum** of 10 patients with PF per group. ~~Twenty-four additional patients may be added after an interim analysis that will assess the observed complete remission (CR) rate in the control group.~~ | Updated to ensure that the number of PV patients is consistent with the analysis plan in Section 3. The interim analysis was removed to avoid any potential issues in controlling the Type I error rate. |
| 1. Synopsis (Outcome Assessment Definitions), and 3.2.1. Pemphigus Clinical Definitions (Consensus Guideline, Murrell 2018) | ***Control of Disease Activity (CDA):*** *Control of disease activity* (disease control) is defined as the ~~time~~**visit** at which new lesions cease to form and established lesions begin to heal. This is also considered the beginning of the consolidation phase. The expected interval of time to reach the control of disease activity is on the order of weeks, although it may be shorter. | Clarification that "time" when referenced with CDA refers to the visit the CDA was assessed at and achieved. |
| 1. Synopsis (Outcome Assessment Definitions), and 3.2.1. Pemphigus Clinical Definitions (Consensus Guideline, Murrell 2018) | ***End of Consolidation Phase (ECP):*** The *end of the consolidation phase* is defined as the ~~time~~**visit** at which no new lesions have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions have healed. ~~It is at this point that most clinicians begin to taper corticosteroid doses.~~**Therefore, in order to achieve ECP, CDA must be confirmed at a visit ≥ 2 weeks later and 80% of the lesions seen previously must have healed.** | Clarification that "time" when referenced with ECP refers to the visit a minimum of 2 weeks after CDA was documented. Language regarding the ECP milestone. clarified for ease of understanding, as consistent with guidelines. |

| Section(s) | Amended or New Wording | Justification of Change |
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| 1. Synopsis (Study Design), and<br>4.2 Study Design<br>(Blinded Treatment Period - Weeks 1 to 37) | After informed consent is obtained, patients with moderate to severe pemphigus (PV and PF)<br>~~at Screening~~**will be screened and if eligible** will be randomized in a 1:1 allocation ratio to receive either PRN1008 400 mg twice daily (bid) (n ~ 60) or placebo bid (n ~ 60) during the Blinded Treatment Period (Week 1 to Week 37).<br><br>At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, shown in Table 1 above, and as required to adequately treat the disease. CS<br>doses may be adjusted per Investigator discretion during the Screening period ~~in the mandated range~~ (~~CS and Rituximab Management,~~ Appendix 1) **but the dose should not be reduced below the required minimum initial dose levels (Table 1). CS taper should not begin until ECP has been achieved.**<br><br>PRN1008 (400 mg tablet) or placebo will be taken twice daily by mouth starting on Day 1. Tablets may be taken with or without food.<br><br>**If a patient achieves CDA (no new lesions and established lesions begin to heal), a follow-up visit ≥ 2 weeks later must confirm the finding of no new lesions prior to declaring ECP and tapering CS. ECP is achieved with the confirmation of CDA (no new lesions for ≥ 2 weeks) with approximately 80% of the established lesions epithelialized (healed). If needed, confirmation of CDA and achievement of ECP may be documented at an Unscheduled Visit, prior to the next scheduled study visit. See Table 2 for all required assessments for an Unscheduled Visit, which also includes Efficacy Outcome Assessment and PDAI.**<br><br>While continuing on PRN1008 or placebo, ~~commencing during~~**following** the ~~period of~~ achievement of ~~CDA to approximately the~~ ECP ~~(CDA ECP)~~, patients will undergo a moderately rapid CS taper regimen as recommended by recently published consensus guidelines (Consensus Guidelines, Murrell 2018) with the goal to reduce the CS dose to 5 mg/day by no later than Study Week 29, with CS dose-adjustment as clinically indicated to control disease (CS and Rituximab Management protocol, Appendix 1). | Clarified "at Screening" means the patients will be screened and that randomization would occur only if eligible.<br><br>Updated text for consistency with Appendix 1, which specifies that only up-titration is allowed for CS during Screening.<br><br>Added clarifying text regarding the use of Unscheduled Visits as allowed per protocol to document CDA and/or ECP. Minor changes were made to language throughout Sec 3.3.1 to ensure clarity and for consistency with these clarifications.<br><br>Updated to clarify CS tapering occurs after ECP confirmation. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **CS taper should not begin until ECP has been achieved.**<br><br>**If the first documentation of CDA coincides with no disease activity (PDAI=0), a follow-up visit ≥ 2 weeks later must still confirm that no new lesions are seen and PDAI=0. At this time the patient is deemed to have confirmed CDA, ECP, and CR and therefore CS tapering can begin. If new lesion(s) are seen, the patient is no longer in CDA and therefore CS tapering should not begin. If a patient has not achieved CDA or new lesions emerge or existing lesions worsen but do not meet definition of relapse, refer to Appendix 1 regarding increasing steroid dosage.**<br><br>~~Once patients achieve CR on a dose of 5 mg/day of CS, that dose should be maintained (not tapered further) until Study Week 37 (time of primary endpoint).~~<br><br>Throughout the Blinded Treatment Period, patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1) until CDA ~~ECP~~ is obtained ~~and tapering of CS can (re)commence~~. **If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor in such cases.**<br><br>**Efficacy Outcome Assessment should be performed per the Efficacy Outcome Assessment**<br>**Flowchart, Appendix 9.**<br><br>**Once patients achieve CR on a dose of 5 mg/day of CS, that dose should be maintained (not tapered further) until Study Week 37 (time of primary endpoint).**<br><br>Rituximab treatment may be administered during the Blinded Treatment Period at or after the<br>Week 5 visit, ~~unless contraindicated,~~**only** after a second ~~or subsequent, clinically significant~~ "qualifying relapse" occurs, **unless contraindicated** (Appendix 1).<br><br>If rituximab is administered, patients should remain on trial and blinded to treatment | Added context for CDA, ECP and CR. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | assignment, but will be considered treatment failures for all efficacy endpoints except for cumulative CS and composite Glucocorticoid Toxicity Index (GTI) score. After completing the Blinded Treatment Period, patients will enter the Open-Label Extension Period to receive active treatment with PRN1008 described below. A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab ~~dose should~~**course of treatment must** be discontinued from the trial. | |
| 1. Synopsis (Study Design), and<br>4.3 Study Design<br>(Open Label Extension Period - Weeks 37 to 61) | From Week 37, all patients will receive active drug in the Open-Label Extension Period. Patients who received placebo will thus receive active treatment with PRN1008 400 mg bid. Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during this period, ~~will~~**must** be discontinued from the study.<br><br>From Week 37 (time of primary endpoint), further tapering to 0 mg CS should be attempted in patients with CR **unless medically contraindicated**. Patients who fail to respond to treatment or experience worsening of disease should have their CS dose increased per CS management guidelines (Appendix 1) until ~~control of disease is obtained and tapering of CS can (re)commence.~~ **CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor is such cases.** | Updated to clarify CS dosing and adjustment. |
| 1. Synopsis (Corticosteroid Management),<br>6.1.2.1 Corticosteroid Starting Doses and Management during Screening and at Day 1, and<br>Appendix 1 CORTICOSTEROID AND RITUXIMAB MANAGEMENT | **Corticosteroid Starting Doses and Management during Screening and at Day 1**<br><br>Required, initial doses of CS for the duration of Screening are ≥ 0.2 mg/kg/day of CS for patients with relapsing disease (diagnosed > 6 months prior to Screening) and ≥ 0.5 mg/kg/day for patients with newly diagnosed disease (diagnosed ≤ 6 months prior to Screening). At Screening, patients will begin to take Sponsor-provided CS according to the minimum dose requirements, and as required to adequately treat the disease during the Screening period. CS doses may be adjusted ~~upward~~ per Investigator discretion during the Screening period (**Appendix 1**) but the dose should not be reduced below the ~~initial~~ **required minimum initial dose levels (Table 1). CS taper should not begin until ECP has been achieved.** | Clarified that tapering can begin during Screening if ECP is achieved. |
| 1. Synopsis (Corticosteroid Management), | **Corticosteroid-Tapering (Consensus Guideline, Murrell 2018)** | Clarified tapering to zero after Week 37 should occur |

| Section(s) | Amended or New Wording | Justification of Change |
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| 6.1.2.2 Corticosteroid Management during Treatment Period and Open-Label Extension Period,<br>Appendix 1 CORTICOSTEROID AND RITUXIMAB MANAGEMENT,<br>Figure 1 Study Design Flow Chart,<br>and<br>2.6 Trial Design Rationale | CS will be tapered from ~~CDA~~ ECP towards a goal of 5 mg/day by ≤ Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. ~~After that, taper towards 0 mg should commence as clinically indicated.~~**From Week 37, further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated.**<br><br>CS tapering should follow the **modified** dosing guidelines below (Murrell 2018).<br>Adjustment of the ~~tapering~~**dosing** guideline protocol by investigators is permitted **for safety reasons**, based on assessment **and documentation** of clinical need.<br><br>• Start tapering CS as soon as ~~CDA is reached or up to the~~ ECP **is confirmed**.<br>• Decrease CS by ~~–~~25% every two weeks, until ~20 mg per day<br>• Once at ~~–~~20 mg per day, decrease CS by ~2.5 mg per week<br>• Once at ~~–~~10 mg/day, decrease CS by 1 mg per week<br><br>Note, because 1 mg will be the smallest CS dosage provided and tablet splitting is not allowed, the Investigator must round up or down to the nearest whole milligram for CS dose after calculation of the new dose level.<br><br>**Corticosteroid-Up-Titration (Harman 2017)**<br>~~CS up-titration is allowed if disease significantly worsens prior to initial CDA-ECP or after CDA-ECP, during CS taper. Up-titration should be a temporary increase until CDA-ECP is achieved (again), after which tapering can recommence.~~<br><br>**Patients who fail to respond to treatment or experience a worsening of disease should have their CS dose increased per CS Management Guidelines (Appendix 1) until CDA is obtained. If ECP is not achieved in a timely manner, it is encouraged that CS dose be further increased unless clinically contraindicated. The PI should consult with the Medical Monitor in such cases.** | unless medically contraindicated.<br><br>Text replaced with updated language to clarify CS up-titration should occur if patients fail to respond or experience worsening of disease. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | For full details of up-titration see Appendix 1. | |
| 1. Synopsis (Concomitant Medications),<br>and<br>6.5.2 Particular Permissible Medications | Strong to Moderate Inducers or Inhibitors of cytochrome P450 (CYP)3A, and "Sensitive" CYP3A Substrate Drugs with a narrow therapeutic index are not permitted (Appendix 8). Other "Sensitive" CYP3A drugs should be used cautiously by administering them only if the benefit-risk is favorable, using staggered administration at least 2 hours after PRN1008 or placebo.<br><br>Patients on proton pump inhibitor drugs should have their medication changed to histamine 2 (H2) blockers during Screening and at least 3 days before Day 1. H2 blockers should be administered at least 2 hours after PRN1008 or placebo.<br><br>~~Warfarin should be monitored carefully as there is limited experience of co-administration with PRN1008. To date, two patients on chronic anticoagulation (rivaroxaban) have been treated without bleeding complications.~~ | Warfarin statement removed due to the potential of CYP3A inhibition (see Section 6.5.1 and Appendix 8). |
| 1, Synopsis (Inclusion Criteria #1),<br>5.1 Inclusion Criteria #1,<br>and<br>7.7.3 Biopsies | 7.7.3. Biopsies<br><br>A new biopsy **(cutaneous and/or mucosal)** is not required if there is a prior and available biopsy report documenting histopathologic findings diagnostic for PV or PF. A new biopsy should be performed if an archival biopsy report is not available.<br><br>New biopsies should include local hematoxylin and eosin (H&E) histopathological review and direct immunofluorescence (DIF) for the characteristic pattern diagnostic of pemphigus ~~(Note: anti-desmoglein antibodies may be used as an alternative confirmation if DIF is negative and histopathology is characteristic of pemphigus).~~<br><br>**Histopathology on biopsies is evaluated for consistency with a diagnosis of PV or PF:**<br>• **If DIF is positive, the patient is eligible in the presence of positive anti-desmoglein antibodies.**<br>• **If DIF is negative, the patient is not eligible. In these cases, where the H&E histopathology is characteristic of pemphigus and anti-desmoglein antibodies are positive, the biopsy may be repeated at the discretion of the investigator.** | Biopsy requirements to ensure pemphigus diagnosis for eligibility were clarified. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | • **If DIF is not available, the patient is eligible in the presence of positive anti-desmoglein antibodies and H&E histopathology characteristic of pemphigus.** | |
| 1. Synopsis (Inclusion Criteria #4),<br>and<br>5.1 Inclusion Criteria #4 | Body mass index (BMI) > 17.5 **(only applicable through Protocol v3.2)** | The setting of BMI > 17.5 was based on early pre-clinical findings of weight loss in the 4-13-week repeat dose GLP toxicity study in dogs (see IB Version 10 dated 17May2019, Sections 4.2.3.1 and 4.5.2.2). In the absence of human data at the time of the first clinical study in pemphigus patients (PRN1008-005), BMI restriction was used to exclude patients with low body weight. As there were no changes in weight or appetite in the Phase 2 study, PRN1008-005, the BMI criteria has now been removed in this protocol. |
| 1. Synopsis (Exclusion Criteria #17),<br>and<br>5.2. Exclusion Criteria #17 | Positive interferon-gamma release assay (IGRA) (eg, **T-spot TB Test,** QuantiFERON®-TB Gold, or ~~T-spot TB® Test)~~**QuantiFERON®-TB Gold Plus (QFT Plus),** at Screening. Unless, **the patient has latent TB and** all of the following 3 conditions are true:<br>a) Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease<br>b) There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease<br>**c)** Documented receipt of ~~a course~~**one** of **the following** prophylactic ~~TB~~ treatment ~~of at least~~ **regimens:** | Clarification of the options for TB testing and conditions to reduce the number of false positive and indeterminate test results, and to enable accurate results in patients who have received the BCG vaccine. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | **i. Oral daily Isoniazid for 6 months**<br>**or**<br>**ii. Oral daily Rifampin (RIF) for 4 months**<br>**or**<br>**iii. Isoniazid and Rifapentine weekly for 3 months (3HP)**<br>**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.** | |
| 1. Synopsis (Exclusion Criteria #18),<br>and<br>5.2. Exclusion Criteria #18 | History of serious infections requiring intravenous therapy with the potential for recurrence **or currently active moderate to severe infection at Screening (Grade 2 or higher).** | Clarification to ensure that patients with moderate to severe active infection are not enrolled. |
| 1. Synopsis (Exclusion Criteria #20 & 21),<br>and<br>5.2 Exclusion Criteria #20 | Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with patient safety, trial evaluations, and/or trial procedures. **In areas endemic for Chagas disease, screening is recommended prior to enrollment.** | Provided recommendation for areas where Chagas may be endemic to screen and rule out the disease prior to enrolling. |
| 5.2 Exclusion Criteria #21 | Patients who have a known contraindication to Sponsor-provided corticosteroid **and/or inability to follow corticosteroid dosing as outlined in the protocol (see Table 1 for more details)** or with a known sensitivity to PRN1008 or its excipients | Clarification to ensure that patients that are unable (for reasons other than contraindication) to take the required corticosteroid doses are not enrolled. |
| Table 2 Schedule of Assessments | Footnote f: ~~To confirm postmenopausal status for women who are not surgically sterile only.~~<br>**To be drawn only in women with amenorrhea > 12 months who require confirmation of menopause (refer to protocol Section 5).** | Clarified to reduce unnecessary FSH/pregnancy testing for women with confirmed menopause. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Table 3 Schedule of Assessments | Week 39 ± **3** ~~5~~ **days** | The Week 39 visit window was revised for consistency, to match the Week 3 double-blind Visit. |
| 2.4 Clinical Experience | In clinical studies to date, PRN1008 has been administered to ~~140~~**more than 200 people, including** healthy volunteers, 27 **and** patients with pemphigus ~~(mainly pemphigus vulgaris variant, i.e. PV) and 4~~**and Idiopathic thrombocytopenia. Twenty-**seven patients ~~with immune thrombocytopenic purpura (ITP). Patients~~ with PV in a Phase 2 study (NCT02704429) used a starting dose of 400 mg BID which was shown to produce adequate BTK occupancies in all but one patient. One patient dose escalated to 500 mg BID and ~~one~~**two** to 600mg BID, with all other patients using the 400mg BID dose. ~~An interim analysis of the first 27 patients in this study found evidence of clinically~~ ~~significant activity in 80% of patients, with onset of disease control in the first 2 weeks of~~ ~~therapy, and an acceptable safety profile (DSUR 2018 and IB Section 5).~~ The primary endpoint of the study, "control of disease activity by the Week 5 visit on ≤ 0.5mg/kg/day of prednisone (or equivalent CS)" was met by 54% (14/26) of patients. Complete remission on ≤ 0.5mg/kg/day of CS was achieved by 25% (5/20) of patients completing 12 weeks treatment. | Additional clinical data provided in alignment with current IB V10 dated 17May2019. |
| 6.5.1 Prohibited Medications | The following medications are prohibited for use during the trial:<br>• Concomitant use of any *immunosuppressant medication*, other than CS and rituximab as described in this protocol. Patients who need other immunosuppressant therapy during the trial should be withdrawn. See Exclusion # 6 Section 3.7 for washout periods.<br>• Concomitant use of known *strong to moderate inducers or inhibitors of cytochrome P450 (CYP) 3A* (Appendix 8) within 3 days or 5 half-lives (whichever is longer) of Day<br>• Use of *CYP3A-sensitive substrate drugs with a narrow therapeutic index* (within 3 days or 5 half-lives (whichever is longer) of Day 1 including, but not limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus~~,~~ **(topical and oral),** or terfenadine. | Washout period for warfarin use and intralesional steroid use were added. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | • *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. Subjects who are on proton pump inhibitors should be changed to histamine (H2) receptor blocking drugs if possible or not enroll in the trial. Details of H2 receptor blocker administration is provided in Section 5.9.2.<br>• ***Intralesional steroids*** **are not permitted within 3 months of Screening, during Screening and for the duration of the study.**<br>• ***Warfarin*** **use is not permitted within 1 week or 5 half-lives (whichever is longer) of Day 1 and for the duration of the study.** | |
| 6.2.1 Preparation and Administration | Treatment medication will be taken twice daily by mouth starting on Day 1. PRN1008 or placebo may be taken with or without food. **Consecutive PRN1008/placebo doses should not be taken within 8 hours of each other.** Tablets should not be broken or crushed. Further details for dispensation and administration of blinded treatment are provided in the Pharmacy Manual. | Added the allowed dose interval. |
| 7.6.1 Screening (Day -29 to Day -1), and Table 2 Schedule of Assessments | **7.6.1. Screening (Day -29 to Day -1)**<br>Informed consent will be obtained at Screening before performing any trial procedures.<br>Patients will undergo Screening assessments, including, but not limited to; blood sampling, ECG, clinical assessment and various quality of life assessments. Please refer to Table 2.<br>**In cases where laboratory assessments are delayed due to logistic considerations, the Sponsor may permit an extension of the Screening Period for laboratory assessments up to 7 days in order to determine eligibility. Week 1 Day 1 should occur as soon as possible upon evaluation of the delayed assessments and no later than 35 days after the initial Screening visit.** | Added a provision for Screening window extension by ≤7 days in the case where laboratory assessments are delayed for a logistical reason, after discussion with Sponsor. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| 7.6.3 Blinded Period (Weeks 1 to 37),<br>and<br>Appendix 9 EFFICACY OUTCOME ASSESSMENT FLOWCHART | Please refer to Table 2 for specific assessments at each visit. CS dosing, and use of rituximab for a second qualifying relapse, are detailed in Appendix 1. **The Efficacy Outcome Assessment Flowchart is detailed in Appendix 9.** | Added Appendix 9 flow chart to assist Investigator with Efficacy Outcome Assessment. |
| Appendix 1 CORTICOSTEROID AND RITUXIMAB MANAGEMENT | 2. Non life-theatening worsening of disease during taper of CS prior to ~~initial CDA~~ **confirmation of ECP**<br><br>During Screening or the treatment periods of the trial, where an initial induction of CDA has not been achieved and blistering continues without improvement, CS should be increased by 50 to 100% every 5 to 7 days until ~~CDA~~ **confirmation of ECP. After ECP is** ~~achieved, and~~ confirmed CS taper ~~can~~ **should** commence. Rituximab therapy may not be used in this situation. **Patients who have been treated with a minimum of 1.5mg/kg/day of corticosteroids for 2 weeks and have not achieved control of disease activity may be eligible after discussion with Principia to receive rituximab.** | Added to clarify that Sponsor may provide rituximab (if approved as rescue medication, by the relevant Competent Authority and Ethics Committees) in cases where disease control is never reached, despite adequate treatment with CS, upon discussion with Sponsor. |
| Appendix 1 CORTICOSTEROID AND RITUXIMAB MANAGEMENT | **Rituximab Management during Blinded Treatment Period**<br><br>Rituximab for second "qualifying relapse":<br>• "Qualifying relapse" for this purpose is defined as a relapse occurring after CDA-~~ECP~~ is achieved**, ECP has been confirmed** and CS taper has begun, that is not life-threatening (when a patient should be withdrawn) but is severe enough such that the PDAI total activity score is equal to or greater than the Screening or Day 1 baseline PDAI score (whichever is higher) for that patient. For example, if the Screening PDAI was 25, the Day 1 baseline was 21, and the relapse PDAI 23, the relapse would not be severe enough to be "qualifying". Whereas if the relapse PDAI was ≥ 25 it would be "qualifying".<br>• Where a second qualifying relapse occurs meeting the above definition, and it is at or after the Week 5 visit, then one course of rituximab, which consists of two | Updated to match the same discontinuation instruction from Section 4.2. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | intravenous doses of 1 gram two weeks apart, may be administered, unless contraindicated.<br>• Oral CS doses should be managed as indicated for the patient at the time of the 2nd qualifying relapse<br>• Rituximab should be administered as recommended in the Pharmacy Manual.<br>• Patients should not be unblinded to treatment assignment and should continue in the trial.<br>• The need for rituximab rescue will be considered "treatment failure" for the analysis of all efficacy endpoints except cumulative CS and composite GTI score.<br><br>**Rituximab Management during Open-Label Extension Period**<br>• **Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during this period, will be discontinued from the study.** | |

### 12.13.8 Clinical Study Protocol Version 4.1 for US (04 December 2019)

This was a local amendment to protocol Version 4 and was regarded as a nonsubstantial amendment.

**Overall Rationale for the Amendment**

[redacted]

**Protocol Amendment summary of changes Table**

## PRN1008-012 Protocol V4.1 (4 December 2019)

The protocol Version 4.1, 4 December 2019 has been updated throughout as shown in the following Table. Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Throughout the protocol | ~~29 Aug 2019~~, **4 Dec 2019**, Version ~~4.0~~ **4.1** | Administrative change. |
| [redacted] | | |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| [redacted] | | |

### 12.13.9 Clinical Study Protocol Version 5 (22 January 2020)

This was a global amendment to protocol Version 4 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 5 are:

- To update molecule name to rilzabrutinib,
- To add LTE Period and eligibility criteria,
- To add study design flow chart,
- To clarify dosing requirements for patients on rituximab,
- To clarify text related to a second infusion of rituximab during OLE period that would not lead to discontinuation,
- To add TBNK at Week 37,
- To allow hydrocortisone for tapering at 5 mg,
- To clarify that patients intolerant to CS dose can receive rituximab,
- To remove the inclusion criterion #4 and renumber inclusion/exclusion criteria,
- To allow patients previously vaccinated against hepatitis B,
- [redacted]
- To update SoA visit windows and footnotes,
- To clarify that LTE patient will not receive sponsor provided CS,
- To add assessments to Week 61,
- To clarify an extended screening window of 7 business days,
- To clarify that previous labs are allowed for rescreen patients,
- To update allowed concomitant medications,
- To clarify ITT and mITT,
- To update efficacy outcome flowchart.

**Protocol Amendment summary of changes Table**

# PRN1008-012 Protocol V5.0 (22 January 2020)

The protocol Version 5.0, 22 January 2020 has been updated throughout to correct errors and to clarify or adjust study procedures and assessments. Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Throughout the protocol | ~~29 Aug 2019~~ **22 Jan 2020**, Version ~~4~~**5**.0 | Administrative change. |
| Throughout the protocol | PRN1008 **(Rilzabrutinib)** | Recommended name by the World Health Organization (WHO) International Nonproprietary Names (INN) Committee. |
| 2.6 Study Population,<br>And<br>9.1 Determination of Sample Size | Section 2.6: Approximately 120 male or female patients with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]) will be enrolled with a targeted minimum of ~~45~~**90** patients with PV ~~per group~~ and a **target** maximum of ~~10~~**22** patients with PF ~~per group.~~<br><br>Section 9.1: …Assuming a response is achieved in 50% of ITT patients treated with PRN1008 versus 15% in placebo treated patients, then, a sample size of ≥ 55 patients (there is a targeted minimum of 45 PV patients and a maximum of 10 PF patients in each treatment group) results in > 90% power at a 0.05 significance level using a 2-sided Pearson chi-square test for the analysis of PV disease type alone and PV and PF combined. Up to a total of approximately 120 patients may be enrolled, with a targeted cap of ~~30~~**22** PF patients. | The targeted minimum number of enrolled PV patients was updated from a per group total (45) to a per study total (90) to ensure the number of PV patients in each group are reasonably balanced (placebo and active) using the block randomization schedule in this study, without requiring Sponsor unblinding.<br>The text, "maximum of 10 PF patients in each treatment group" changed to "maximum of 22 PF patients" to ensure the number of PF patients in each group are reasonably balanced (placebo and active) using the block randomization schedule in this study, without requiring Sponsor unblinding. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| 2.7 Duration of Trial Participation | **Long Term Extension Period**<br>**Study duration for the patients who enter the Long Term Extension Period will be determined by the criteria described in the Study Design Section 3.3.1 of the Study Synopsis.**<br>**After completing the Open-Label Extension Period, eligible patients may continue in the Long Term Extension Period of 48 weeks. Patients will continue to have a 4 week follow-up visit after the patient's last dose of PRN1008 as detailed in the Follow-Up Period** ~~and a Follow-up Period of 4 weeks~~**. section below**.<br>**Long Term Extension (LTE) Period (Week 61 to Week 109):**<br>**After completing the Open-Label Extension Period, patients who are responding to PRN1008 treatment will be eligible to enter the Long Term Extension Period and will continue to receive open-label PRN1008 400 mg bid for 48 weeks per Table 4: Schedule of Assessments Long Term Extension Period.**<br>**Patients are eligible to participate in the LTE if:**<br>**a) they have achieved and/or maintained an ECP with ≤ 10 mg/day CS at any time between 37 and 61 weeks in the study.**<br>**Patients are not eligible to participate in the LTE if:**<br>**a) they have more than one relapse following ECP requiring treatment with > 10 mg/day CS (excluding CS taken short-term for dental work or surgery) or**<br>**b) have failed to adequately recover after a relapse despite maximal tolerated CS dose.**<br>**Failure to adequately recover is defined as: <25% decrease from peak PDAI despite treatment with maximal steroid doses (minimum of 1.5mg/kg/d unless there is a specific documented medical contraindication) for at least 2 weeks.**<br>**CS doses above refer to doses of prednisone or its equivalent.**<br>**Patients may continue in the LTE until:**<br>**13.9.1.1 they have had more than one relapse following ECP that requires > 10 mg/day CS (excluding CS taken short-term for dental work or surgery) or have failed to adequately recover after a relapse despite maximal tolerated CS dose (per definition of failure to adequately recover above);** | The primary purpose of the 48-week, Long Term Extension Period (LTE) is to provide extended access to PRN1008 for patients who are receiving clinical benefit and to accrue additional long term data on the safety of PRN1008.<br><br>Patients will be eligible for the LTE if they show adequate response to PRN1008 during the Open Label Period ie, achieve or maintain ECP (at least 80% healing of lesions and no new lesions for at least 2 weeks) while on a low CS dose (≤ 10 mg/day prednisone or equivalent) as defined in the pemphigus treatment guidelines. |

| Section(s) | Amended or New Wording | Justification of Change |
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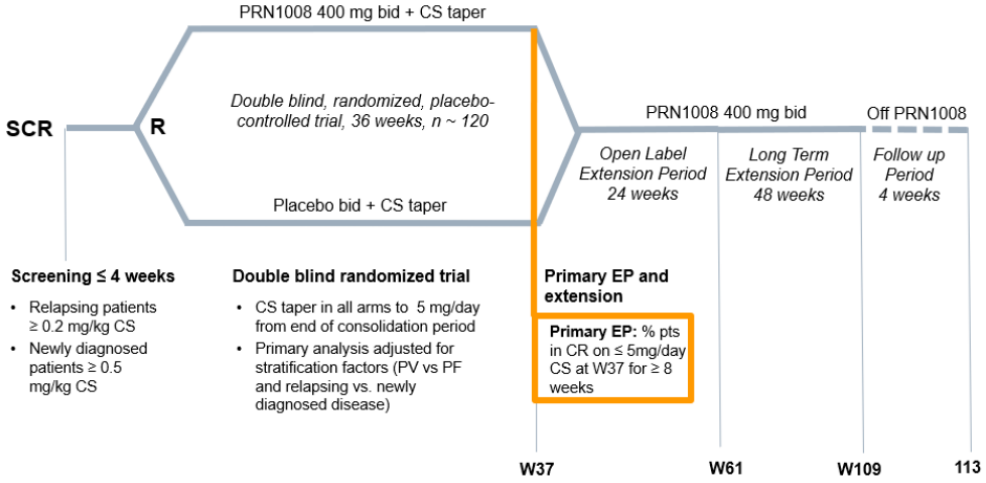
| | **b) the drug is no longer being developed by the Sponsor for this indication;**<br>**c) the program is stopped for safety reasons.**<br>**Patients who have previously completed the Open-Label Extension Period prior to this amendment and were responders per the LTE requirement may enroll into the LTE.**<br>**Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS, but can receive site-provided CS per required standard of care. From Week 61, following CS Management Guidelines (Appendix 1) is recommended.**<br>**Patients requiring rituximab during the Long Term Extension Period will be discontinued from the trial.**<br>Follow-up Period (**4** Weeks ~~61 to 65~~**after last Trial Visit**):<br>End of Trial for the overall clinical trial is defined as the point at which the last patient has completed the last visit of the study.<br>~~End of Trial for each patient~~**For patients eligible for the Long Term Extension, the End of Trial is defined as the point at which the patient has completed their Week 113 visit (4 weeks after the patient's last dose of PRN1008).**<br>**For patients that are not eligible for the Long Term Extension, the End of Trial** is defined as the point at which the patient has completed their Week 65 visit (4 weeks after the patient's last dose of PRN1008).<br>Patients who are not able to complete the **Open-Label Extension Period or Long Term Extension Period (for patients who qualify) as** planned ~~Week 65 visit~~ and discontinue the study early should be encouraged to come back for their last visit, and this will be recorded as the End of Trial (EOT) visit. Patients that discontinue early will have the ~~ET~~**Early Termination (ET)** assessments completed as outlined in the Schedule of Assessments based upon from which phase treatment they are terminating, Table 2 (Blinded Treatment Period) and**),** Table 3 (Open-Label **Extension Period), or** Table 4 **(Long Term** Extension Period). | |
| | Study PRN1008-012 is a randomized, parallel-group, double-blind, placebo-controlled trial over 36 weeks (Blinded Treatment Period) followed by an Open-Label Extension Period of 24 weeks**, Long Term Extension Period of 48 weeks,** and a follow-up period of 4 weeks, which | |

<table>
<tr><th>Section(s)</th><th>Amended or New Wording</th><th>Justification of Change</th></tr>
<tr><td>Table 3 Schedule of Assessments - Open Label Extension Period</td><td>is intended to evaluate the efficacy and safety of oral PRN1008 (Rilzabrutinib) in moderate to severe pemphigus.<br><br>…The primary purpose of the 24-week, Open-Label Extension Period is(OLE) is to allow access to study drug who were on placebo medication as well as to evaluate durability of clinical response and accrue additional long term data on the safety of PRN1008.<br><br>The primary purpose of the 48-week, Long Term Extension Period (LTE) is to provide extended access to PRN1008 for patients who are receiving clinical benefit and to accrue additional long term data on the safety of PRN1008.<br><br>Footnote l: If patient is eligible for the Long Term Extension Period at Week 61 they will continue to receive PRN1008 per Table 4: Schedule of Assessments Long Term Extension Period. If the patient is not eligible for the Long Term Extension Period at Week 61 they will discontinue PRN1008 and complete the EOT visit at Week 65.</td><td></td></tr>
<tr><td>Table 4 Schedule of Assessments - Long Term Extension Period</td><td>
Table 4: Schedule of Assessments – Long Term Extension Period
<table>
<tr><th rowspan="2">Visit Windows</th><th colspan="8">Long Term Extension Period</th><th rowspan="2">Early Termination (ET) [a]</th><th rowspan="2">Unscheduled Visit</th></tr>
<tr><th>Week 61[l]<br>± 5 days</th><th>Week 65<br>±5 days</th><th>Week 69<br>±5 days</th><th>Week 73<br>±5 days</th><th>Week 85<br>± 10 days</th><th>Week 97<br>± 10 days</th><th>Week 109<br>± 10 days</th><th>LTE EOT Week 113 4 wk FU Visit<br>± 5 days</th></tr>
<tr><td>Weight</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Abbreviated physical examination</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>12-lead ECG</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td><td>(X)[b]</td><td>(X)[b]</td></tr>
<tr><td>Vital Signs</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Urinalysis[c]</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td>X</td><td>X</td><td>X</td><td>(X)[b]</td></tr>
<tr><td>Urine pregnancy test[d]</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td></tr>
<tr><td>Hematology, coagulation, and serum chemistry[e]</td><td>X</td><td></td><td></td><td></td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>(X)[b]</td></tr>
<tr><td>HbA1c and LDL[c] (fasting)</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>PK Sample[a]</td><td>X</td><td></td><td></td><td>X</td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>(X) [b]</td></tr>
<tr><td>PD: anti-desmoglein -1 and -3 autoantibody titers by ELISA</td><td>X</td><td></td><td></td><td>X</td><td>X</td><td>X</td><td>X</td><td></td><td>X</td><td>(X)[b]</td></tr>
<tr><td>PDAI</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>ABQOL and TABQOL</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>EQ-5D-5L</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>GTI Index</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Efficacy Outcome Assessment[f]</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Adverse events</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Photography[g]</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Concomitant medications</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>PRN1008 dispensed</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Drug reconciliation[k] (PRN1008 /CS Dosing Documentation)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>CS Daily Dosing[l]</td><td colspan="8">X See Appendix 1</td><td>X</td></tr>
</table>
ABQOL = Autoimmune Bullous Disease Quality of Life; CDA = control of disease activity; CR = complete remission; CS = corticosteroids; ECG = electrocardiogram; ECP = End of consolidation phase; ELISA = enzyme-linked immunosorbent assay; EOT = End of Trial; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; FU = follow-up; HgbA1c = hemoglobin A1c; LDL = low-density lipoprotein; PD = pharmacodynamics; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetics; TABQOL = Treatment of Autoimmune Bullous Disease Quality of Life; wk = week
<br>a. The early termination (ET) visit should also be performed for patients who are not able to complete the planned Week 113 visit and discontinue from the trial early.
<br>b. Only if clinically indicated
</td><td></td></tr>
</table>

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | c. Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Serum chemistry will include the following: 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; and glucose (random). Coagulation will include: PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Weeks 61, 85, 97, 109, ET, and EOT. Urinalysis will include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes and reflex microscopy. HbA1c and LDL level (fasting) will be collected with GTI assessment.<br>d. For women of childbearing potential only<br>e. PK sample should be taken at random timepoints during the patient visits with as much variation in time since last dose as practicable. Time of draw will be captured as well as time of the last two PRN1008 doses, and time since the patient's last meal.<br>f. Pemphigus Clinical Response Definitions for CDA, CR, ECP, Relapse (refer to protocol Section 3.1)<br>g. Any photos should be taken and stored in accordance with local regulations.<br>h. Subjects are required to bring all used and unused PRN1008 study drug supplies with them to every clinic visit.<br>i. For CS management, refer to Appendix 1. Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS, but can receive site-provided CS per required standard of care. At any point if CS needs to be adjusted between required visits, the patient may return for an unscheduled visit and additional CS may be dispensed.<br>j. Assessments performed at the Week 61 Visit of the Open-Label Period should not be repeated at this visit. | |
| Figure 1: Study Design Flow Chart |  | |
| 3.3.1 Study Design | If rituximab is administered, patients should **continue to take PRN1008/placebo,** remain on trial and blinded to treatment assignment, but will be considered treatment failures for all efficacy endpoints except for ~~cumulative~~ **CS dosing** and composite Glucocorticoid Toxicity Index (GTI) score. After completing the Blinded Treatment Period, patients will enter the Open-Label | Updated to clarify that patients who receive rituximab should continue to take PRN1008/placebo and remain on trial unless they meet a discontinuation criterion. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | Extension Period to receive active treatment with PRN1008 described below. A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab course of treatment must be discontinued from the trial. | |
| 3.3.1 Study Design, And<br><br>Table 3 Schedule of Assessments | Open-Label Extension Period (Weeks 37 to 61):<br>From Week 37, all patients will receive active drug in the Open-Label Extension Period **for 24 weeks per Table 3: Schedule of Assessments Open-Label Extension Period.** Patients who received placebo will thus receive active treatment with PRN1008 400 mg bid. Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during this period, must be discontinued from the study. **If a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period, the patient may continue in the trial. Patients that received rituximab during the Blinded Treatment Period and are continuing in the study, will complete TBNK testing (T and B and Natural Killer Lymphocyte Panel) at their Week 37 visit.**<br><br>Footnote m: **Patients that received rituximab during the Blinded Treatment Period and are continuing in the study, TBNK panel will be drawn at their Week 37 visit.** | Updated to clarify that if a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period, the patient may continue in the trial.<br><br>TBNK Pantel is an assessment of T, B, and Natural Killer cell counts in patients who received rituximab rescue. This will establish a baseline prior to open-label PRN1008 treatment to assist in better understanding the action of PRN1008 in patients already treated with rituximab. |
| Appendix 1 Corticosteroid and Rituximab Management | Corticosteroid Management during **Blinded** Treatment Period ~~and~~, Open- Label Extension Period**, and Long Term Extension Period**<br>CS will be tapered from ECP towards a goal of 5 mg/day by ≤ Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. From Week 37, further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated. **At Investigator discretion, the CS may be switched to** | Hydrocortisone, a short acting steroid, is often used as the preparation of choice for graduated tapering off of steroids in patients with a history of chronic use and potential dependence. Since |

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| | **equivalent doses of oral hydrocortisone instead of prednisone or prednisolone when tapering from 5 mg to 0 mg CS.**<br><br>During Screening or the treatment periods of the trial, where an initial induction of CDA has not been achieved and blistering continues without improvement, CS should be increased by 50 to 100% every 5 to 7 days until confirmation of ECP. After ECP is confirmed CS taper should commence. Rituximab therapy may not be used in this situation. Patients who have been treated with a minimum of 1.5 mg/kg/day of corticosteroids for 2 weeks and have not achieved control of disease activity may be eligible after discussion with Principia to receive rituximab. **For patients that have a documented and specific medical contraindication, the maximally tolerated dose of corticosteroid may be considered for this purpose following consultation with the medical monitor.**<br><br>**It is recommended to follow the CS Guidelines during the Long Term Extension.** | this may be standard of care in some places, replacement of prednisone/prednisolone with equivalent doses of oral hydrocortisone will be permitted to taper off from 5mg of prednisone.<br><br>Updated to clarify that patients who are intolerant to high doses of corticosteroid may be eligible for rescue medication |
| 3.6 Inclusion Criteria | ~~4. Body mass index (BMI) > 17.5 (only applicable through Protocol v3.0)~~ | Removed as this criterion was only applicable through Protocol v3.0. |
| 3.7 Exclusion Criteria | Positive at Screening for human immunodeficiency virus (HIV), hepatitis B (surface **antigen** and core antibodies ~~unrelated to vaccination, surface antigen~~), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA) | Clarified language on Hepatitis B positive patients to ensure that vaccinated patients can be included and patients with prior exposure to Hepatitis B are excluded from the study. |
| 3.7 Exclusion Criteria #16 | On a case by case basis, after discussion and approval by the Sponsor, a local TB test hat 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~~**indeterminate for any reason** and a local blood test or TSpot TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor. | Clarified that a positive central lab test for TB will satisfy the exclusion criteria. Local lab results may be used when central lab is indeterminate for any reason. |

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| [redacted] | | |
| Table 2 Schedule of Assessments | Footnote e: PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Screening, Day 1 Week 1 Pre-dose, and Weeks 3, **5,** 9, ~~17~~**13**, 25, & 37. | Footnote correction to match assessments listed in Table 2. |
| Table 3 Schedule of Assessments | Week 37 Visit Window: ± ~~5~~**3** days | Clarified for consistency through protocol. |
| Table 3 Schedule of Assessments | Week 39 ± 3 days / Drug reconciliation (PRN1008 /CS Dosing Documentation): **X** | Clarified to match Week 3 and the other follow-up study visits. |
| Table 3 Schedule of Assessments | Footnote c: PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Weeks **39,** 49, 61, ET, and EOT (if applicable)... | Footnote correction to match assessments listed in Table 3. |
| Table 3 Schedule of Assessments | Footnote i: **Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS, but can receive site-provided CS per required standard of care. From Week 61, following CS Management Guidelines (Appendix 1) is recommended.** | Clarified that during the LTE patients will no longer receive Sponsor-provided CS, but can receive site-provided CS per standard of care. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | Oral corticosteroids (prednisone or prednisolone) will be provided **during the Blinded Treatment Period and Open-Label Extension Period. Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS, but can receive site-provided CS per required standard of care.** | |
| Table 3 Schedule of Assessments | Week 61 ± 5 days / 12-lead ECG: **X**<br>Week 61 ± 5 days / Urinalysis: **X**<br>Week 61 ± 5 days / HbA1c and LDL (fasting): **X**<br>Week 61 ± 5 days / GTI Index: **X**<br>Week 61 ± 5 days / PRN1008 dispensed: **X** | Week 61 is the end of the primary study and the last visit for patients not rolling over to the LTE. These tests are performed to document end of study safety. |
| Table 3 Schedule of Assessments<br><br>7.6.1 Screening (Day -29 to Day -1) | Footnote n: As described in Section 7.6.1, laboratory assessments delayed due to logistic considerations may be performed with an extended Screening window (up to 7 additional **business** days), upon Sponsor review and approval. Patients may be re-screened once. Any labs completed in prior Screening, within 2 weeks of re-screening will remain valid and should not be repeated. **Labs performed for a previous screening within 6 weeks, may be considered for determination of eligibility on approval of the medical monitor. In the specific cases of QuantiFERON-TB, anti desmoglein antibodies and hepatitis/HIV testing, tests may be considered for determination of eligibility if performed in a previous** | Clarified that 7 days is 7 business days to allow for adequate processing.<br><br>Labs done for safety screening are likely to remain stable over short periods. The medical monitor will review for any change in the patient's status that requires a repeat.<br>Anti-dsg antibodies once confirmed during screening, should not need to be repeated in most cases. This will reduce burden on patient's and avoid repeat assessments when not necessary. |

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| | **screen within the last 12 weeks, with the approval of the medical monitor.** However, pregnancy tests should be repeated at re-screening.<br><br>In cases where laboratory assessments are delayed due to logistic considerations, the Sponsor may permit an extension of the Screening Period for laboratory assessments up to 7 **business** days in order to determine eligibility. Week 1 Day 1 should occur as soon as possible upon evaluation of the delayed assessments and no later than 35 days after the initial Screening visit.<br>Medical history and demographic data, including sex, age, race, body weight (kg), height (cm), and body mass index (BMI), will be recorded.<br>Patients not already on the mandated CS doses for the commencement of the Screening Period will commence the protocol-mandated CS doses.<br>Patients may be re-screened once following a Screen failure. **Any labs performed in prior screening, within 2 weeks of re-screening will remain valid and should not be repeated. Labs performed for a previous screening within 6 weeks, may be considered for determination of eligibility on approval of the medical monitor. In the specific cases of QuantiFERON-TB, anti desmoglein** | |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **antibodies and hepatitis/HIV testing, tests may be considered for determination of eligibility if performed in a previous screen within the last 12 weeks, with the approval of the medical monitor. However, pregnancy tests should be repeated at re-screening.** Please see Schedule of Assessments Table 2. | |
| 5.9.2 Particular Permissible Medications | Histamine 2 (H2) receptor blocking drugs (**ranitidine or famotidine**) and antacids are permitted provided they can be given 2 hours or more after ~~doses~~**administration** of PRN1008 or placebo. | Clarified that ranitidine and famotidine are preferred H2 antagonists. When administered 2 hours or more after PRN1008, their effects on PK of the study drug are minimal. |
| 6.3 Rituximab<br><br>7.4.1 Patient Discontinuation and Stopping Rules | Rituximab (or biosimilar) will be provided for patients having a second qualifying relapse (Appendix 1) during the Blinded Treatment Period. However, in the event a patient in the Blinded Treatment Period requires an additional "top up" dose of rituximab after their initial rituximab course of treatment, this will not be provided because the patient must be discontinued. Similarly, if a patient in the Open-Label Extension Period **or Long Term Extension Period** requires rituximab, the patient must be discontinued and rituximab will not be provided. **If a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the open label period, the patient may continue in the trial.**<br><br>Reasons for discontinuing a patient may include, but are not necessarily limited to, the following:<br>• A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab course of treatment or a patient in the Open-Label Extension Period **or Long Term Extension Period** requiring rituximab | Updated to clarify that if a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period, the patient may continue in the trial. |

| Section(s) | Amended or New Wording | Justification of Change |
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| 7.6.5 Long Term Extension Period<br>Appendix 1 | **Please refer to Table 4 for specific assessments at each visit. CS dosing is detailed in Appendix 1. Rituximab therapy is not allowed during this period unless the patient is withdrawn from the trial.**<br>Rituximab Management during Open-Label Extension Period **and Long Term Extension Period:** Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during ~~this period, must be discontinued from the study~~**these study periods, must be discontinued from the study. If a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period the patient may continue in the trial.** | |
| 7.7.6 Electrocardiogram Monitoring | Single 12-lead ECGs will be performed at Screening**, Week 37, Week 61,** and Week ~~37~~.**109 (for patients in the Long Term Extension).** All ECGs will be performed with the patient in a supine position. | Updated to match Schedule of Assessments and addition of LTE. |
| 9.4 Analysis Populations | ~~Three~~**Four** populations will be defined for data analysis: the Safety Population, the Intent-to- Treat **Population, Modified Intent-to-Treat (mITT)** (efficacy) Population, and the Pharmacokinetic Population.<br><br>**Safety Population:**<br>All patients who receive at least one dose of study medication will be included in the Safety Population. **The Safety Population is the primary analysis population for safety. Patients will be analysed according to the treatment they actually received, not necessarily the treatment they were allocated to at randomization.** Results will be presented "as treated." | Clarified distinction between Intent-to-Treat Population and Modified Intent-to-Treat population for statistical analysis. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **Intent-to-Treat (ITT) Population:**<br>**All patients who are randomized will be included in the ITT Population. The ITT Population will be used for sensitivity analyses. Patients will be analyzed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented "as randomized."**<br><br>**Modified Intent-to-Treat (mITT) Population:**<br>All patients who are randomized and receive at least one dose of study medication will be included in the ~~ITT~~**mITT** Population. The ITT ~~**population**~~**mITT Population is the primary analysis population for efficacy. Patients will be analyzed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received.** Results will be presented "as randomized." | |
| Appendix 8, Efficacy Outcome Assessment Flowchart | ECP - End of Consolidation Phase<br>Is CDA confirmed (ie, no new lesions for ≥ **2 weeks**)? | Clarified in ECP, CDA confirmed is defined as no new lesions for **≥2 weeks**, per protocol. |

### 12.13.10 Clinical Study Protocol Version 5.1 for Germany (19 May 2020)

This was a local amendment to protocol Version 5 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reason for this amendment to Protocol PRN1008-012, Version 5.1 is:

- To align the content of the protocol for Germany to the global one and incorporating the same changes as the global version V5.0.

**Protocol Amendment summary of changes Table**

# PRN1008-012 Protocol V4.1 to 5.1 (19 May 2020)

The protocol Version 5.0, 22 January 2020 has been updated throughout to correct errors and to clarify or adjust study procedures and assessments. Deleted text has ~~strikethrough~~ and new text is **bolded**.

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Throughout the protocol | **19 May 2020**, Version **5.1** | Administrative change. |
| Throughout the protocol | PRN1008 **(Rilzabrutinib)** | Recommended name by the World Health Organization (WHO) International Nonproprietary Names (INN) Committee. |
| List of Abbreviations | | New entries added for clarity |
| 1.0 Synopsis<br><br>2.6 Background Trial Design Rational | Urgent Safety Measures Initiated Due to COVID-19 Pandemic<br>Each participating site, ethics committees, and the Federal Institute for Drugs and Medical Devices the (BfArM) were informed (22 April 2020) of urgent safety measures implemented to ensure continued supply of study medication and safety monitoring for patients. These measures are described in the "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" (Appendix 9). When the COVID-19 pandemic resolves, the measures will be repealed back to the previous state as government rules and benefit/risk assessment allow.<br><br>During the COVID-19 pandemic, measures to ensure continued drug supply and safety monitoring for patients are described in the "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" (Appendix 9). These measures include remote study visits, enrollment procedures, direct to patient delivery of study medication and urine pregnancy tests, as well as handling of protocol deviations and remote site monitoring. | COVID-19 pandemic procedures to aid sites for managing study subjects and study processes as outlined in the "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" Appendix 9. |

| Section(s) | Amended or New Wording | Justification of Change |
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| 6.4 Drug Management | During the COVID-19 pandemic, drug supply can be sent to patients when the patient may is not able to travel to the site or the site cannot host a patient visit. Site instructions for shipment of supplies directly to patients and procedures for conducting remote site visits inclusive of ensuring drug supply maintenance are described in Appendix 9 ("Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19"). | |
| 7.2 Trial Enrollment Procedures | During the COVID-19 pandemic, we need to assess the feasibility of implementing a plan for patient access to study drug and any additional measures required to monitor patient safety on an ongoing basis. Please notify Principia and your CRO study monitor if your site suspends patient enrollment. (Appendix 9) | |
| 7.6 Visit Overview | During the COVID-19 pandemic, remote (eg, telephone call, video call) study visits may be performed when a patient is not able to travel to the site or the site cannot host a patient visit. Procedures to be performed during remote site visits are described in Appendix 1 of "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" (Appendix 9). | |
| 9.3.1 Adverse Events | During the COVID-19 pandemic, we need to assess the feasibility of implementing a plan for patient access to study drug and any additional measures required to monitor patient safety on an ongoing basis. Please notify Principia and your CRO study monitor if your site suspends patient enrollment. (Appendix 9) | |
| 1.0 Synopsis, Study Population and<br>4.6 Study Population, and | Approximately 120 male or female patients with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]) will be enrolled with a targeted minimum of ~~45~~**90** patients with PV ~~per group~~, and a **target** maximum of ~~10~~**22** patients with PF ~~per group~~. | The targeted minimum number of enrolled PV patients was updated from a per group total (45) to a per study total (90) to ensure the number of PV patients in each group are reasonably balanced (placebo |

| Section(s) | Amended or New Wording | Justification of Change |
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| 10.1 Determination of Sample Size | Section 10.1: … Assuming a response is achieved in 50% of ITT patients treated with PRN1008 versus 15% in placebo treated patients, then, a sample size of ≥ 55 patients (there is a targeted minimum of 90 PV patients and a maximum of 22 PF patients in each treatment group) results in > 90% power at a 0.05 significance level using a 2-sided Pearson chi-square test for the analysis of PV disease type alone and PV and PF combined. Up to a total of approximately 120 patients may be enrolled, with a **targeted** cap of ~~20~~**22** PF patients. | and active) using the block randomization schedule in this study, without requiring Sponsor unblinding.<br>The text, "with a cap of 20 PF patients" changed to "targeted cap of 22 patients" to ensure the number of PF patients in each group are reasonably balanced (placebo and active) using the block randomization schedule in this study, without requiring Sponsor unblinding. |
| 1.0 Synopsis, Duration of Trial Participation<br>and<br>4.1. Duration of Trial Participation | **Long Term Extension Period**<br>**Study duration for the patients who enter the Long-Term Extension Period will be determined by the criteria described in Section 4.4** | The primary purpose of the 48-week, Long Term Extension Period (LTE) is to provide extended access to PRN1008 for patients who are receiving clinical benefit and to accrue additional long term data on the safety of PRN1008. |
| 1. Synopsis, Study Design<br>and<br><br><br><br><br>4. Study Design | This is a randomized, parallel-group, double-blind, placebo-controlled trial with 36 weeks of treatment during a Blinded Treatment Period followed by an Open-Label Extension Period of 24 weeks~~ and a follow up period of 4 weeks~~. **After completing the Open-Label Extension Period, eligible patients may continue in the Long Term Extension Period of 48 weeks. Patients will continue to have a 4 week follow-up visit after the patient's last dose of PRN1008 as detailed in the Follow-Up Period section below**.<br>This is a randomized, parallel-group, double-blind, placebo-controlled trial with 36 weeks of treatment during a Blinded Treatment Period followed by an Open-Label Extension Period of 24 weeks **After completing the Open-Label Extension Period, eligible patients may continue in the Long Term Extension Period of 48 weeks.** | Patients will be eligible for the LTE if they show adequate response to PRN1008 during the Open Label Period ie, achieve or maintain ECP (at least 80% healing of lesions and no new lesions for at least 2 weeks) while on a low CS dose (≤ 10 mg/day prednisone or equivalent) as defined in the pemphigus treatment guidelines**.** |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **Patients will continue to have a 4 week follow-up visit after the patient's last dose of PRN1008 as detailed in the** ~~and a~~ Follow-up Period **(Section 4.5) below.** ~~of 4 weeks (Figure 1~~). | |
| 1. Synopsis, Study Design<br>and<br>4.2 Blinded Treatment Period (Weeks 1 to 37)<br>and<br><br><br>7.4.1. Patient Discontinuation and Stopping Rules | If rituximab is administered, patients should **continue to take PRN1008/placebo**, remain on trial and blinded to treatment assignment, but will be considered treatment failures for all efficacy endpoints except ~~cumulative~~ for CS **dosing** and composite Glucocorticoid Toxicity Index (GTI) score. After completing the Blinded Treatment Period, patients will enter the Open-Label Extension Period to receive active treatment with PRN1008 described below. A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab course of treatment must be discontinued from the trial.<br>Mandatory termination criteria for a patient in this study include:<br>• Severe and life-threatening pemphigus disease activity<br>• Grade 4 PRN1008 -related TEAE<br>• Serious allergic reaction to PRN1008 or placebo including anaphylactic reaction<br>• A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab course of treatment or a patient in the Open-Label Extension Period **or Long Term Extension** Period requiring rituximab | Updated to clarify that patients who receive rituximab should continue to take PRN1008/placebo and remain on trial unless they meet a discontinuation criterion |
| 1. Synopsis, Open-Label Extension Period (Weeks 37 to 61)<br>and<br>4.3. Open-Label Extension Period (Weeks 37 to 61)<br>and | From Week 37, all patients will receive active drug in the Open-Label Extension Period **for 24 weeks per Table 3: Schedule of Assessments Open-Label Extension Period**. Patients who received placebo will thus receive active treatment with PRN1008 400 mg bid. Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during this period, must be discontinued from the study. **If a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period, the patient may continue in the trial. Patients that received rituximab during the Blinded Treatment Period and are continuing in the study, will complete TBNK testing (T and B and Natural Killer Lymphocyte Panel) at their Week 37 visit.** | Updated to clarify that if a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period, the patient may continue in the trial.<br>TBNK Panel is an assessment of T, B, and Natural Killer cell |

| Section(s) | Amended or New Wording | Justification of Change |
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| Table 3 Schedule of Assessments<br>and<br><br>Appendix 1 | Footnote m: **Patients that received rituximab during the Blinded Treatment Period and are continuing in the study, TBNK panel will be drawn at their Week 37 visit.**<br><br>Management during Open-Label Extension Period **and Long Term Extension Period**<br>• Patients requiring treatment by rituximab or other immunosuppressants (other than CS) for relapse during **these study periods, must be discontinued from the study. If a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period the patient may continue in the trial**~~this period, must be discontinued from the study.~~ | counts in patients who received rituximab rescue. This will establish a baseline prior to open-label PRN1008 treatment to assist in better understanding the action of PRN1008 in patients already treated with rituximab. |

| | | |
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| 1. Synopsis, Long Term Extension (LTE) Period (Week 61 to Week 109)<br>and<br>4.4. Long Term Extension (LTE) Period (Week 61 to Week 109) | **Long Term Extension (LTE) Period (Week 61 to Week 109)**<br>**After completing the Open-Label Extension Period, patients who are responding to PRN1008 treatment will be eligible to enter the Long Term Extension Period and will continue to receive open-label PRN1008 400 mg bid for 48 weeks per Table 4: Schedule of Assessments Long Term Extension Period.**<br>**Patients are eligible to participate in the LTE if:**<br>**a. they have achieved and/or maintained an ECP with ≤ 10 mg/day CS at any time between 37 and 61 weeks in the study.**<br>**Patients are not eligible to participate in the LTE if:**<br>**a. they have more than one relapse following ECP requiring treatment with> 10 mg/day CS (excluding CS taken short-term for dental work or surgery) or**<br>**b. have failed to adequately recover after a relapse despite maximal tolerated CS dose.**<br>**Failure to adequately recover is defined as: <25% decrease from peak PDAI despite treatment with maximal steroid doses (minimum of 1.5mg/kg/d unless there is a specific documented medical contraindication) for at least 2 weeks.**<br>**CS doses above refer to doses of prednisone or its equivalent.**<br>**Patients may continue in the LTE until:**<br>**a. they have had more than one relapse following ECP that requires > 10 mg/day CS (excluding CS taken short-term for dental work or surgery) or have failed to adequately recover after a relapse despite maximal tolerated CS dose (per definition of failure to adequately recover above);**<br>**b. the drug is no longer being developed by the Sponsor for this indication;**<br>**c. the program is stopped for safety reasons** | Patients will be eligible for the LTE if they show adequate response to PRN1008 during the Open Label Period ie, achieve or maintain ECP (at least 80% healing of lesions and no new lesions for at least 2 weeks) while on a low CS dose (≤10 mg/day prednisone or equivalent) as defined in the pemphigus treatment guidelines. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **Patients who have previously completed the Open-Label Extension Period prior to this amendment and were responders per the LTE requirement may enroll into the LTE.**<br><br>**Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS, but can receive site-provided CS per required standard of care. From Week 61, following CS Management Guidelines (Appendix 1) is recommended.**<br><br>**Patients requiring rituximab during the Long Term Extension Period will be discontinued from the trial.** | |
| Synopsis, Follow-up Period (4 Weeks after last Trial Visit and<br>4.5. (Follow-up Period (4 Weeks after last Trial Visit) | Follow-up Period (**4** Weeks ~~61 to 65~~**after last Trial Visit**):<br><br>End of Trial for the overall clinical trial is defined as the point at which the last patient has completed the last visit of the study.<br><br>~~End of Trial for each patient~~**For patients eligible for the Long Term Extension, the End of Trial is defined as the point at which the patient has completed their Week 113 visit (4 weeks after the patient's last dose of PRN1008).**<br><br>**For patients that are not eligible for the Long Term Extension, the End of Trial** is defined as the point at which the patient has completed their Week 65 visit (4 weeks after the patient's last dose of PRN1008).<br><br>Patients who are not able to complete the **Open-Label Extension Period or Long Term Extension Period (for patients who qualify) as** planned ~~Week 65 visit~~ and discontinue the study early should be encouraged to come back for their last visit, and this will be recorded as the End of Trial (EOT) visit. Patients that discontinue early will have the ~~ET~~**Early Termination (ET)** assessments completed as outlined in the Schedule of Assessments based upon from which phase treatment they are terminating, Table 2 (Blinded Treatment Period~~) and~~**),** Table 3 (Open-Label Extension Period), **or Table 4 (Long Term Extension Period**). | Patients will be eligible for the LTE if they show adequate response to PRN1008 during the Open Label Period ie, achieve or maintain ECP (at least 80% healing of lesions and no new lesions for at least 2 weeks) while on a low CS dose (≤ 10 mg/day prednisone or equivalent) as defined in the pemphigus treatment guidelines**.** |
| 1. Synopsis, Corticosteroid Management (Consensus Guideline, Murrell 2018) | Corticosteroid Management during **Blinded** Treatment Period ~~and~~, Open-Label Extension Period**, and Long Term Extension Period** | 1 Hydrocortisone, a short acting steroid, is often used as the preparation of choice for |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| and<br>6.1.2.2.1.Corticosteroid-Tapering (Consensus Guideline, Murrell 2018)<br>and<br>6.1.2. Corticosteroids<br>and<br>Appendix 1 Corticosteroid and Rituximab Management | CS will be tapered from ECP towards a goal of 5 mg/day by ≤ Week 29. Once the 5 mg level is achieved it will be kept at 5 mg/day until the time of the primary endpoint at Week 37 is reached. From Week 37, further tapering to 0 mg CS should be attempted in patients with CR unless medically contraindicated. **At Investigator discretion, the CS may be switched to equivalent doses of oral hydrocortisone instead of prednisone or prednisolone when tapering from 5 mg to 0 mg CS.**<br><br>Oral corticosteroids (prednisone or prednisolone) will be provided **during the Blinded Treatment Period and Open-Label Extension Period. Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS but can receive site-provided CS per required standard of care**.<br><br>During Screening or the treatment periods of the trial, where an initial induction of CDA has not been achieved and blistering continues without improvement, CS should be increased by 50 to 100% every 5 to 7 days until confirmation of ECP. After ECP is confirmed CS taper should commence. Rituximab therapy may not be used in this situation. Patients who have been treated with a minimum of 1.5 mg/kg/day of corticosteroids for 2 weeks and have not achieved control of disease activity may be eligible after discussion with Principia to receive rituximab. **For patients who are unable to escalate CS up to 1.5 mg/kg/day due to documented adverse events related to CS and cannot achieve CDA following 2 weeks of treatment with their maximally tolerated CS dose, rescue with rituximab therapy may be offered. Please consult with the medical monitor.** | graduated tapering of steroids in patients with a history of chronic use and potential dependence. Since this may be standard of care in some places, replacement of prednisone/ prednisolone with equivalent doses of oral hydrocortisone will be permitted to taper off from 5mg of prednisone.<br><br>Updated to clarify that patients who are intolerant to high doses of corticosteroid may be eligible for rescue medication |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| 1. Synopsis, Inclusion Criteria and<br>5.1. Inclusion Criteria | ~~4. Body mass index (BMI) > 17.5 (only applicable through Protocol v3.0)~~ | 2 Removed as this criterion was only applicable through Protocol v3.0. |
| 1. Synopsis, Exclusion Criteria and<br>5.2. Exclusion Criteria | 5. A history of malignancy of any type **within 5 years before Day 1**, other than surgically excised non-melanoma skin cancers or in situ cervical ~~cancer within 5 years before Day 1~~ | 3 Rephrased |
| 1. Synopsis, Exclusion Criteria and<br>5.2. Exclusion Criteria | 7. Use of proton pump inhibitor drugs such as omeprazole and esomeprazole within 3 days **of Day 1** (It is acceptable to change patient to H2 receptor blocking drugs prior to Day 1.) | 4 Clarified that the 3 days period required for stopping of proton pump inhibitors is prior to Day 1 |
| 1. Synopsis, Exclusion Criteria and<br>5.2. Exclusion Criteria | 16. Positive at Screening for human immunodeficiency virus (HIV), hepatitis B (surface **antigen** and core antibodies ~~unrelated to vaccination, surface antigen~~), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA) | 5 Clarified language on Hepatitis B positive patients to ensure that vaccinated patients can be included and patients with prior exposure to Hepatitis B are excluded from the study. |
| 1. Synopsis, Exclusion Criteria and<br>5.2. Exclusion Criteria | 17. 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~~**indeterminate for any reason** and a local blood test or TSpot TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor. | 6 Clarified that a positive central lab test for TB will satisfy the exclusion criteria. Local lab results may be used when central lab is indeterminate for any reason. |
| 2.6. Trial Design Rationale | Study PRN1008-012 is a randomized, parallel-group, double-blind, placebo-controlled trial over 36 weeks (Blinded Treatment Period) followed by an Open-Label Extension Period of 24 weeks**, Long Term Extension Period of 48 weeks,** and a follow-up period of 4 weeks, which is intended to evaluate the efficacy and safety of oral PRN1008 **(Rilzabrutinib)** in moderate to severe pemphigus.<br>…The **primary** purpose of the 24-week, Open-Label Extension Period ~~is~~**(OLE) is to allow access to study drug who were on placebo medication as well as** to evaluate | Clarified the purpose of the long term extension study |

| Section(s) | Amended or New Wording | Justification of Change |
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| | durability of clinical response and accrue additional long term data on the safety of PRN1008.<br>**The primary purpose of the 48-week, Long Term Extension Period (LTE) is to provide extended access to PRN1008 for patients who are receiving clinical benefit and to accrue additional long term data on the safety of PRN1008.** | |
| Table 2 Schedule of Assessments, Footnote e | PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Screening, Day 1 Week 1 Pre-dose, and Weeks 3, **5,** 9, ~~17~~**13**, 25, & 37. | Footnote correction to match assessments listed in Table 2. |
| Table 2 Schedule of Assessments- Open Label Extension Period Footnote n<br>and<br><br>7.6.1. Screening<br>(Day -29 to Day -1) | Footnote n: As described in Section 7.6.1, laboratory assessments delayed due to logistic considerations may be performed with an extended Screening window (up to 7 additional **business** days), upon Sponsor review and approval. Patients may be re-screened once. Any labs completed in prior Screening, within 2 weeks of re-screening will remain valid and should not be repeated. **Labs performed for a previous screening within 6 weeks, may be considered for determination of eligibility on approval of the medical monitor. In the specific cases of QuantiFERON-TB, anti desmoglein antibodies and hepatitis/HIV testing, tests may be considered for determination of eligibility if performed in a previous screen within the last 12 weeks, with the approval of the medical monitor.** However, pregnancy tests should be repeated at re-screening.<br><br>In cases where laboratory assessments are delayed due to logistic considerations, the Sponsor may permit an extension of the Screening Period for laboratory assessments up to 7 **business** days in order to determine eligibility. Week 1 Day 1 should occur as soon as possible upon evaluation of the delayed assessments and no later than 35 days after the initial Screening visit.<br>Medical history and demographic data, including sex, age, race, body weight (kg), height (cm), and body mass index (BMI), will be recorded.<br>Patients not already on the mandated CS doses for the commencement of the Screening Period will commence the protocol-mandated CS doses.<br>Patients may be re-screened once following a Screen failure. **Any labs performed in prior screening, within 2 weeks of re-screening will remain valid and should not be repeated. Labs performed for a previous screening within 6 weeks, may be** | 7 Clarified that 7 days is 7 business days to allow for adequate processing.<br>Labs done for safety screening are likely to remain stable over short periods. The medical monitor will review for any change in the patient's status that requires a repeat.<br>Anti-dsg antibodies once confirmed during screening, should not need to be repeated in most cases. This will reduce burden on patient's and avoid repeat assessments when not necessary. |

| Section(s) | Amended or New Wording | Justification of Change |
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| | **considered for determination of eligibility on approval of the medical monitor. In the specific cases of QuantiFERON-TB, anti desmoglein antibodies and hepatitis/HIV testing, tests may be considered for determination of eligibility if performed in a previous screen within the last 12 weeks, with the approval of the medical monitor. However, pregnancy tests should be repeated at re-screening.** Please see Schedule of Assessments Table 2. | |

[redacted]

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| [redacted] | | |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Table 3 Schedule of Assessments | Week 37 Visit Window: ± ~~5~~**3** days | Clarified for consistency through protocol. |
| Table 3 Schedule of Assessments | **OLE EOT** Week 65~~/EOT~~ 4 wk visit | Clarification in heading for Follow-up Period. |
| Table 3 Schedule of Assessments | Week 39 ± 3 days / **TBNK Panel Week 37: X** | Added TBNK Panel to week 37 assessments. |
| Table 3 Schedule of Assessments | Week 61 ± 5 days / 12-lead ECG: **X**<br>Week 61 ± 5 days / Urinalysis: **X**<br>Week 61 ± 5 days / HbA1c and LDL (fasting): **X**<br>Week 61 ± 5 days / GTI Index: **X**<br>Week 61 ± 5 days / PRN1008 dispensed: **X** | Week 61 is the end of the primary study and the last visit for patients not rolling over to the LTE. These tests are performed to document end of study safety. |
| Table 3 Schedule of Assessments, Footnote g deleted | ~~Online cognitive testing will be performed at designated sites.~~ | |
| Table 3 Schedule of Assessments, Footnote i<br>and<br>6.1.2. Corticosteroids | **Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS but can receive site-provided CS per required standard of care. From Week 61, following CS Management Guidelines (Appendix 1) is recommended.**<br>Oral corticosteroids (prednisone or prednisolone) will be provided **during the Blinded Treatment Period and Open-Label Extension Period. Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS but can receive site-provided CS per required standard of care.** | Clarified that during the LTE patients will no longer receive Sponsor-provided CS but can receive site-provided CS per standard of care. |
| Table 3 Schedule of Assessments - Open Label Extension Period Footnote l | **Footnote l: If patient is eligible for the Long Term Extension Period at Week 61 they will continue to receive PRN1008 per Table 4: Schedule of Assessments Long Term Extension Period. If the patient is not eligible for the Long Term Extension Period at Week 61 they will discontinue PRN1008 and complete the EOT visit at Week 65.** | 8 Edited for consistency |

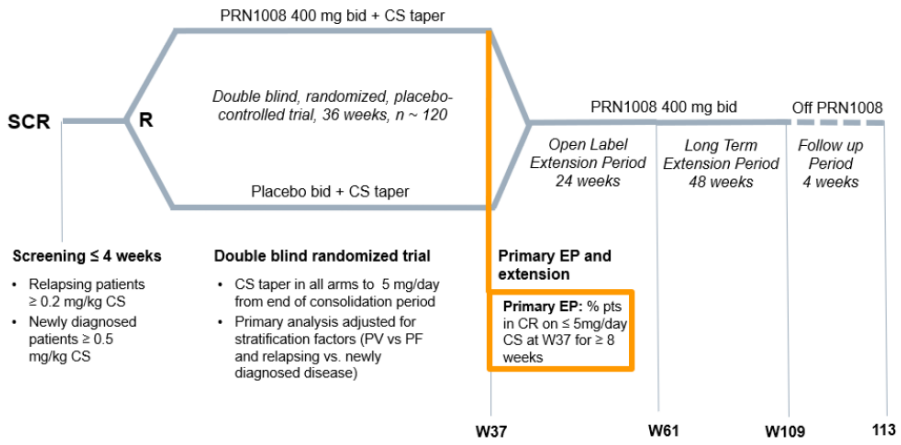
| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Table 3 Schedule of Assessments - Open Label Extension Period Footnote m | **Footnote m: Patients that received rituximab during the Blinded Treatment Period and are continuing in the study, TBNK panel will be drawn at their Week 37 visit.** | 9 Updated to clarify that if a patient has a qualifying relapse during the Blinded Treatment Period and the second infusion from the rituximab course of treatment occurs during the Open-Label Extension period, the patient may continue in the trial. TBNK Pantel is an assessment of T, B, and Natural Killer cell counts in patients who received rituximab rescue. This will establish a baseline prior to open-label PRN1008 treatment to assist in better understanding the action of PRN1008 in patients already treated with rituximab. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Table 4 Schedule of Assessments - Long Term Extension Period | **Table 4: Schedule of Assessments – Long Term Extension Period** | New table added to describe scheduled assessments to be conducted in the Long-Term Extension Period. Also contains additional pregnancy testing (once/month) |

| | Wk 61[j] ± 5 days | Wk 65 ±5 days | Wk 69 ±5 days | Wk 73 ±5 days | Wk 77 ±5 days | Wk 81 ±5 days | Wk 85 ± 10 days | Wk 89 ±5 days | Wk 93 ±5 days | Wk 97 ± 10 days | Wk 101 ±5 days | Wk 105 ±5 days | Wk 109 ± 10 days | EOT WK 113 4 wk FU Visit ± 5 days | Early Termination (ET)[a] | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Weight | X | X | X | X | | | X | | | X | | | X | X | X | X |
| Abbreviated physical examination | X | X | X | X | | | X | | | X | | | X | X | X | X |
| Fr12-lead ECG | X | | | | | | | | | | | | X | | (X)[b] | (X)[b] |
| Vital Signs | X | X | X | X | | | X | | | X | | | X | X | X | X |
| Urinalysis[c] | X | | | | | | | | | | | | X | X | X | (X)[b] |
| Urine pregnancy test[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Hematology,coagulation, and serum chemistry[c] | X | | | | | | X | | | X | | | X | X | X | (X)[b] |
| HbA1c and LDL[c] (fasting) | X | | | | | | | | | | | | X | | | |
| PK Sample[e] | X | | | X | | | X | | | | | | X | | X | (X)[b] |
| PD: anti-desmoglein -1 and -3 autoantibody titers by ELISA | X | | | X | | | X | | | X | | | X | | X | (X)[b] |
| PDAI | X | X | X | X | | | X | | | X | | | X | X | X | X |
| ABQOL and TABQOL | X | X | X | X | | | X | | | X | | | X | X | X | X |
| EQ-5D-5L | X | X | X | X | | | X | | | X | | | X | X | X | X |
| GTI Index | X | | | | | | | | | | | | X | | | |
| Efficacy Outcome Assessment[f] | X | X | X | X | | | X | | | X | | | X | X | X | X |
| Adverse events | X | X | X | X | | | X | | | X | | | X | X | X | X |
| Photography[g] | X | X | X | X | | | X | | | X | | | X | X | X | X |
| Concomitant medications | X | X | X | X | | | X | | | X | | | X | X | X | X |
| PRN1008 dispensed | X | X | X | X | | | X | | | X | | | | | | |
| Drug reconciliation[h] (PRN1008 /CS Dosing Documentation) | X | X | X | X | | | X | | | X | | | X | X | X | X |
| CS Daily Dosing[i] | X See Appendix 1 | | | | | | | | | | | | | | | X |

ABQOL = Autoimmune Bullous Disease Quality of Life; CDA = control of disease activity; CR = complete remission; CS = corticosteroids; ECG = electrocardiogram; ECP = End of consolidation phase; ELISA = enzyme-linked immunosorbent assay; EOT = End of Trial; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; FU = follow-up; HgbA1c = hemoglobin A1c; LDL = low-density lipoprotein; PD = pharmacodynamics; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetics; TABQOL = Treatment of Autoimmune Bullous Disease Quality of Life; wk = week

a. The early termination (ET) visit should also be performed for patients who are not able to complete the planned Week 113 visit and discontinue from the trial early.
b. Only if clinically indicated
c. Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Serum chemistry will include the following: 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; and glucose (random). Coagulation will include: PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Weeks 61, 85, 97, 109, ET, and EOT. Urinalysis will include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes and reflex microscopy. HbA1c and LDL level (fasting) will be collected with GTI assessment.
d. For women of childbearing potential only
e. PK sample should be taken at random timepoints during the patient visits with as much variation in time since last dose as practicable. Time of draw will be captured as well as time of the last two PRN1008 doses, and time since the patient's last meal.
f. Pemphigus Clinical Response Definitions for CDA, CR, ECP, Relapse (refer to protocol Section 3.1)
g. Any photos should be taken and stored in accordance with local regulations.
h. Subjects are required to bring all used and unused PRN1008 study drug supplies with them to every clinic visit.
i. For CS management, refer to Appendix 1. Beginning at Week 61, patients entering the LTE will no longer receive Sponsor-provided CS, but can receive site-provided CS per required standard of care. At any point if CS needs to be adjusted between required visits, the patient may return for an unscheduled visit and additional CS may be dispensed.
j. Assessments performed at the Week 61 Visit of the Open-Label Period should not be repeated at this visit.

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| 2.6. Trial Design Rationale | Study PRN1008-012 is a randomized, parallel-group, double-blind, placebo-controlled trial over 36 weeks (Blinded Treatment Period) followed by an Open-Label Extension Period of 24 weeks**, Long Term Extension Period of 48 weeks,** and a follow-up period of 4 weeks, which is intended to evaluate the efficacy and safety of oral PRN1008 **(Rilzabrutinib)** in moderate to severe pemphigus.<br><br>…The **primary** purpose of the 24-week, Open-Label Extension Period ~~is~~**(OLE) is to allow access to study drug who were on placebo medication as well as** to evaluate durability of clinical response and accrue additional long term data on the safety of PRN1008.<br><br>**The primary purpose of the 48-week, Long Term Extension Period (LTE) is to provide extended access to PRN1008 for patients who are receiving clinical benefit and to accrue additional long term data on the safety of PRN1008.** | Patients will be eligible for the LTE if they show adequate response to PRN1008 during the Open Label Period ie, achieve or maintain ECP (at least 80% healing of lesions and no new lesions for at least 2 weeks) while on a low CS dose (≤ 10 mg/day prednisone or equivalent) as defined in the pemphigus treatment guidelines. |
| 4. Figure 1: Study Design Flow Chart |  | The flow chart was replaced to include the long term extension period. |
| 6.5.2. Particular Permissible Medications | Histamine 2 (H2) receptor blocking drugs **(ranitidine or famotidine)** and antacids are permitted provided they can be given 2 hours or more after ~~doses~~**administration** of PRN1008 or placebo. | Clarified that ranitidine and famotidine are preferred H2 antagonists. When administered 2 hours or more after PRN1008, |

| Section(s) | Amended or New Wording | Justification of Change |
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| | | their effects on PK of the study drug are minimal. |
| 7.2. Trial Enrollment Procedures | Under no circumstances will participants who enroll in this trial and complete treatment as specified be permitted to re-enroll in the trial **unless in the rare case where Sponsor approval is granted (eg, for a subject who completed and exited the OLE that is eligible to participate in the LTE).** | Edited for consistency |
| 7.6.5. Long Term Extension Period | **Please refer to Table 4 for specific assessments at each visit. CS dosing is detailed in Appendix 1. Rituximab therapy is not allowed during this period unless the patient is withdrawn from the trial.** | Edited for Consistency |
| 7.7.6. Electrocardiogram Monitoring | Single 12-lead ECGs will be performed at Screening**, Week 37, Week 61,** and Week ~~37.~~**109 (for patients in the Long Term Extension).** All ECGs will be performed with the patient in a supine position. | Updated to match Schedule of Assessments and addition of LTE. |
| 9.3.1. Adverse Event Collection Period | The AE Collection Period begins at the time of the first Screening/eligibility assessment and ends at the ~~end~~ **End** of the ~~study~~**Trial** for each patient. | Rephrased |
| 10.2.1. Analysis Populations | Four populations will be defined for data analysis: the Safety Population, the Intent-to-Treat ~~(efficacy)~~Population, **the** Modified Intent-to-Treat (mITT) **(efficacy) Population**, and the Pharmacokinetic Population. | Clarified distinction between Intent-to-Treat Population and Modified Intent-to-Treat population for statistical analysis. |
| 11. Investigator Responsibilities and | By signing this protocol and the Investigator Statement (eg, national equivalent of Form FDA1572), the Investigator agrees to do the following:<br>1. Conduct the trial in accordance with the relevant current protocol and make changes only after notifying the Sponsor, except when immediate changes are necessary to protect the safety, rights, or welfare of the patients<br>2. Comply with the **currently endorsed** E6 International ~~Conference on~~ **Council for** Harmonisation Tripartite Guideline on Good Clinical Practice and applicable Food and Drug Administration (FDA) Codes of Federal Regulations (CFRs)<br>3. Personally conduct or supervise the described investigation | To reflect a change in terminology for the ICH. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | 4. Inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes<br>5. Ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval have been met<br>6. Report to the Sponsor adverse experiences that occur in the course of the investigation as specified in 21 CFR 312.64 and the E6 ~~International Conference on~~Council for Harmonisation Tripartite Guideline on Good Clinical Practice and any local regulations<br>7. Have read and understood the Investigator Brochure, including potential risks and side effects of the drug<br>8. Ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments<br>9. Maintain adequate and accurate records and make these available for inspection by the Sponsor, its designee, the FDA, the IRB/IEC, and other applicable national or local health authorities or agency authorized by law, as defined in 21 CFR 312.68 and **currently endorsed** E6 International ~~Conference on~~**Council** for Harmonisation Tripartite Guideline on Good Clinical Practice. | |
| 13.1 Patient Confidentiality and Disclosure of Data | Documents that are not for submission to the Sponsor and/or its designee (eg, signed ICFs and Patient Information Sheets) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or International ~~Conference on~~**Council for** Harmonization (ICH) and Good Clinical Practice (GCP) Guidelines. | |
| 15. References | **Rosenbach M, Murrell DF, Bystryn JC, et al. Reliability and convergent validity of two outcome instruments for pemphigus. J Invest Dermatol 2009; 129:2404-10.** | New reference for PDAI. |
| Appendix 2 Pemphigus Disease Activity: PDAI | Pemphigus Disease Area Index (PDAI) (**Rosenbach 2009**, Murrell 2018) | The PDAI form was replaced and a reference was added |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | [redacted] | |
| Appendix 6, Appendix 7, Appendix 8, Appendix 9 | ~~Appendix 6 Description of Online Cognitive Testing~~<br>~~Appendix 7~~ **Appendix 6** Glucocorticoid Toxicity Index (GTI)<br>~~Appendix 8~~ **Appendix 7** Strong to Moderate CYP3A Inhibitors and Inducers and Sensitive CYP3A Substrates<br>~~Appendix 9~~ **Appendix 8** Efficacy Outcome Assessment Flowchart | Renumbered appendices because of deletion of Appendix 6 |
| Table 4, Table 5, Table 6 | **Table 4 Schedule of Assessments - Long Term Extension Period**<br>~~Table 4~~ **Table 5** Definitions of Moderate to Severe Population and starting CS doses*<br>~~Table 5~~ **Table 6** Example Taper for a 60 mg Dose of CS | Renumbered Tables because of addition of new Table 4 |

### 12.13.11. Clinical Study Protocol Version 5.2 for Germany (30 November 2020)

This was a local amendment to protocol Version 5.1 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 5.2 are:

- To add Long Term Extension (LTE) objective and endpoints in alignment with German Central Ethics Committee request to provide LTE endpoints.,
- To add a new exclusion criterion #24 per German Central Ethics Committee requirement,
- To add COVID testing at every visit per German Central Ethics Committee requirement,
- To address measures taken due to the COVID-19 pandemic,
- To update trial stopping and discontinuation rules per German Central Ethics Committee requirement.

**Protocol Amendment summary of changes Table**

# PRN1008-012 Protocol Version 5.1 (19 May 2020) to Version 5.2 (30 November 2020)

Protocol Version 5.1 dated 19 May 2020 has been updated throughout to correct for administrative errors as well as for consistency. Deleted text has ~~strikethrough~~ and new text is **bolded**. Minor editorial changes are not included in this summary document.

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Throughout the protocol | ~~19 May 2020~~ **30 November 2020** | Administrative change to reflect new protocol date |
| Throughout the protocol | ~~Version 5.1~~ **Version 5.2** | Administrative change to reflect new protocol date |
| Synopsis: Long Term Extension Objective<br>Section 3.1.5 Long Term Extension Objective | **Long Term Extension Objective**<br>• **To evaluate the long-term safety of PRN1008** | Addition of Long Term Extension Objective in alignment with German Central Ethics Committee request to provide LTE endpoints. |
| Synopsis: Investigational Plan - Long Term Extension (LTE) Period (Week 61 to Week 109)<br>Section 4.4 Long Term Extension (LTE) Period (Week 61 to Week 109)<br>Table 3 Schedule of Assessments - Open Label Extension Period<br>Table 4 Schedule of Assessments - Long Term Extension Period | ~~Beginning at Week 61, p~~**P**atients entering the LTE will ~~no longer~~ receive Sponsor-provided CS, ~~but can receive site-provided CS per required standard of care. From Week 61,~~ following CS Management Guidelines (Appendix 1) ~~is recommended~~.<br><br>[footnote i]<br>i. …~~Beginning at Week 61, patients~~**Patients** entering the LTE will ~~no longer~~ receive Sponsor-provided CS, ~~but can receive site-provided CS per required standard of care. From Week 61,~~ following CS Management Guidelines (Appendix 1) ~~is recommended~~. | Updated to reflect that the Sponsor will be the source of corticosteroids to patients in the LTE |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| 6.1.2 Corticosteroids | 1) Oral corticosteroids (prednisone or prednisolone) will be provided during the Blinded Treatment Period and Open-Label Extension Period. ~~Beginning at Week 61, patients~~**Patients** entering the LTE will ~~no longer~~ receive Sponsor-provided CS~~, but can receive site-provided CS per required standard of care~~. | |
| Synopsis: Exclusion Criterion #24<br>Section 5.2 Exclusion Criteria - Exclusion Criterion #24 | [new exclusion criterion]<br>**Patients who have a positive test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection per local testing standards.** | Per German Central Ethics Committee requirement |
| 2) Synopsis: Outcome Measures<br>3) Section 3.2.9 Long Term Extension Endpoints | **4) Long Term Extension Endpoints**<br>• **Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects during the LTE from Week 61 to Week 113**<br>• **Average daily dose of CS from Week 61 to Week 113**<br>• **Time to relapse during the LTE** | Per German Central Ethics Committee request to provide LTE Endpoints. |
| Table 2 Schedule of Assessments - Blinded Treatment Period | [row title]<br>**SARS-CoV-2[r]**<br>**"X"** added at each visit.<br>[new footnote r]<br>• **r. Subjects must be tested for SARS-CoV-2 infection within one week prior to each visit or up to 2 days after each visit. Every effort should be made to comply with local or institutional testing procedures. If the time required for obtaining results exceeds this testing window, an extension may be granted by the Medical Monitor. The requirement for the test may be waived by the Medical Monitor (with approval from the Ethics Committee) if the local regulations change with control of the pandemic.** | Per German Central Ethics Committee requirement |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Table 3 Schedule of Assessments - Open Label Extension Period | "**X**" added for the Drug reconciliation (PRN1008/CS Dosing Documentation) at the OLE EOT Week 65 4 wk FU Visit | Updated to correct error to reflect that drug reconciliation occurs at this visit. |
| | [footnote c, final sentence]<br>c. … **At Week 37, the** HbA1c and LDL level (fasting) will be collected with GTI assessment. | Updated to provide clarity regarding laboratory samples. |
| | [row title]<br>**SARS-CoV-2[n]**<br>**"X**" added at each visit.<br>[new footnote n]<br>**n. Subjects must be tested for SARS-CoV-2 infection within one week prior to each visit or up to 2 days after each visit. Every effort should be made to comply with local or institutional testing procedures. If the time required for obtaining results exceeds this testing window, an extension may be granted by the Medical Monitor. The requirement for the test may be waived by the Medical Monitor (with approval from the Ethics Committee) if the local regulations change with control of the pandemic.** | Per German Central Ethics Committee requirement |
| Table 4 Schedule of Assessments - Long Term Extension Period | [rows for "~~HbA1c and LDL (fasting)~~" and "~~GTI Index~~" removed]<br>[footnote c, final sentence]<br>c. …~~HbA1c and LDL level (fasting) will be collected with GTI assessment.~~ | Updated to reflect that these procedures are not performed during the LTE, in line with the new LTE endpoints. |
| | "~~X~~" removed in the rows for PDAI, ABQOL and TABQOL, EQ-5D-5L, and Photography from visits at Weeks 65, 69, 73, 85, 97, 109, 113; at ET; and at the Unscheduled visit<br>[footnote g]<br>g. Any photos should be taken and stored in accordance with local regulations **(Week 61 only)**. | Updated to reflect that these procedures are not performed during the LTE, in line with the new LTE endpoints. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | [row title]<br>**SARS-CoV-2[k]**<br>**"X"** added at each visit.<br>[new footnote k]<br>**k. Subjects must be tested for SARS-CoV-2 infection within one week prior to each visit or up to 2 days after each visit. Every effort should be made to comply with local or institutional testing procedures. If the time required for obtaining results exceeds this testing window, an extension may be granted by the Medical Monitor. The requirement for the test may be waived by the Medical Monitor (with approval from the Ethics Committee) if the local regulations change with control of the pandemic.** | Per German Central Ethics Committee requirement |
| Section 4.6 Urgent Safety Measures Initiated Due to COVID-19 Pandemic | **Urgent Safety Measures Initiated Due to COVID-19 Pandemic**<br>**Each participating site, ethics committees, and the Federal Institute for Drugs and Medical Devices (BfArM) were informed (22 April 2020) of urgent safety measures implemented to ensure continued supply of study medication and safety monitoring for patients. These measures are described in the "Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" (Appendix 9). When the COVID-19 pandemic resolves, the measures will be repealed back to the previous state as government rules and benefit/risk assessment allow.** | New section added to address measures taken due to the COVID-19 pandemic that were earlier submitted as an Urgent Safety Measures letter. |
| 7.3 Trial Stopping Rules | The trial will be terminated if major safety concerns related to PRN1008 (Rilzabrutinib) or placebo emerge. Trial safety stopping criteria **in Germany** are:<br>**5. If the insurance cover cannot be adjusted to the maximum sum necessary in the event that the risk profile worsens.**<br>**6. If the approval or the positive assessment has been revoked by the State Office for Health and Social Affairs; Ethics Commission of the State of Berlin.** | Per German Central Ethics Committee requirement |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| 7.4.1 Patient Discontinuation and Stopping Rules | Mandatory termination criteria for a patient in this study **in Germany** include:<br>[new 6th bullet]<br>• **Positive SARS-CoV-2 test at any time during the study** | Per German Central Ethics Committee requirement |
| 7.6 Visit Overview | During the trial, patients will return at specified times on an outpatient basis for assessment of vital signs, physical examination, assessment of AEs and concomitant medication use, assessment of clinical benefit and for provision of blood samples for clinical safety, PK, and PD assessment. **Subjects must be tested for SARS-CoV-2 infection within one week prior to each visit or up to 2 days after each visit.**<br>… | Per German Central Ethics Committee requirement |
| 7.7.15 SARS-CoV-2 Testing Requirement | **7.7.15 SARS-CoV-2 Testing Requirement**<br>**Testing for infection with SARS-CoV-2 will be required and collected during screening and for all regular study visits. The testing for SARS-CoV-2 infection must be performed within one-week (7 days) prior to each visit or up to two (2) days after. SARS-CoV-2 tests can be performed following local or institutional guidelines in order to fulfil protocol requirements. Documentation of test results must be provided to the Investigator. If the time required for obtaining results exceeds this testing window, an extension may be granted by the Medical Monitor. The requirement for the test may be waived by the Medical Monitor (with approval from the Ethics Committee) if the local regulations change with control of the pandemic.** | Per German Central Ethics Committee requirement |
| 10.2.14 Long Term Extension Analysis | **The Long Term Extension endpoints will be summarized descriptively. Summaries of patient disposition, demographics, and baseline characteristics will be provided. The number of received doses and treatment duration will be described. Safety data including adverse events, laboratory evaluations and vital signs assessments will also be summarized.** | New analysis section added to reflect addition of LTE endpoints |

### 12.13.12. Clinical Study Protocol Version 5.1 for UK (22 June 2020)

This was a local amendment to protocol Version 5 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reason for this amendment to Protocol PRN1008-012, Version 5.1 is:

- To remove the Long Term Extension Period and all associated procedures and language.

**Protocol Amendment summary of changes Table**

# PRN1008-012 Protocol V 5.0 (22 January 2020) to 5.1 United Kingdom (24 June 2020)

Protocol Version 5.0 dated 22 January 2020 has been updated throughout to correct for administrative errors as well as for consistency. Deleted text has ~~strikethrough~~ and new text is **bolded**. Minor editorial changes are not included in this summary document.

| Section #/Name | Amended or New Wording | Justification of Change |
|---|---|---|
| Throughout the protocol | ~~22 Jan 2020~~ **24 Jun 2020** | Administrative change to reflect new protocol date |
| Throughout the protocol | ~~Version 5.0~~ **Version 5.1** | Administrative change to reflect new protocol date |
| Synopsis - Duration of Trial Participation<br>Synopsis - Study Design<br>Synopsis - Corticosteroid Management during Blinded<br>Treatment Period and Open-Label Extension Period<br>Figure 1<br>Table 4 (original) et seq.<br>5.6 Trial Design Rationale<br>6.2 Corticosteroids<br>7.2 Trial Enrollment Procedures<br>7.4.1 Patient Discontinuation and Stopping Rules<br>7.6.5 Long Term Extension Period (Beginning Week 61)<br>(original) et seq.<br>7.6.6 Early Termination Visit<br>7.7.6 Electrocardiogram Monitoring<br>Appendix 1 Corticosteroid and Rituximab Management | Removal of text related to the ~~Long Term Extension (LTE) Period~~ throughout.<br>Renumbering of subsequent table after ~~Table 4 Schedule of Assessments – Long Term Extension Period~~ removed.<br>Renumbering of subsequent sections after original ~~Section 7.6.5 Long Term Extension Period (Beginning Week 61)~~ removed. | Removal of the Long Term Extension Period pending adjustments of analysis plan and statistical assessments |

### 12.13.13. Clinical Study Protocol Version 5.2 for UK (21 December 2020)

This was a local amendment to protocol Version 5.1 and was regarded as a substantial amendment.

**Overall Rationale for the Amendment**

The primary reasons for this amendment to Protocol PRN1008-012, Version 5.2 are:

- To add Long Term Extension (LTE) objective in alignment with UK MHRA request to provide study endpoints including the LTE Period,
- To update eligibility criteria to enroll in the LTE,
- To add consent required before entering LTE,
- To reflect that the Sponsor will be the source of corticosteroids in the LTE,
- To reflect that patients requiring rituximab during the LTE must be discontinued.

**Protocol Amendment summary of changes Table**

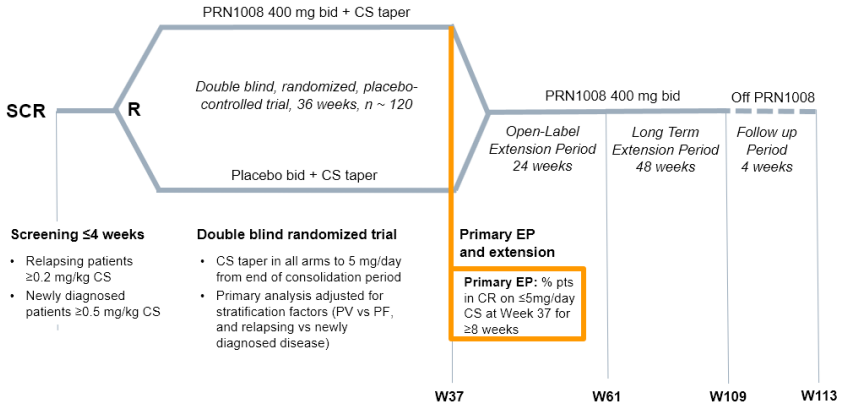
# PRN1008-012 Protocol Version 5.1 (22 Jun 2020) to Version 5.2 (21 December 2020)

Protocol Version 5.1 dated 22 Jun 2020 has been updated throughout to correct for administrative errors as well as for consistency. Deleted text has ~~strikethrough~~ and new text is **bolded**. Minor editorial changes are not included in this summary document.

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Throughout the protocol | ~~22 June 2020~~ **21 December 2020** | Administrative change to reflect new protocol date |
| Throughout the protocol | ~~Version 5.1~~ **Version 5.2** | Administrative change to reflect new protocol date |
| Protocol Signature Page | [redacted] | Administrative change to reflect new protocol signatory |
| Synopsis:<br>2.7. Duration of Trial Participation | **Long Term Extension Period**<br>**Study duration for the patients who enter the Long Term Extension Period will be determined by the criteria described in the Study Design Section 3.3.1 of the Study Synopsis.** | Updated to reflect study duration including Long Term Extension. |
| Synopsis:<br>3.2.5 Long Term Extension Objective | **Long Term Extension Objective**<br>• **To evaluate the long-term safety of PRN1008** | Addition of Long Term Extension (LTE) Objective in alignment with UK MHRA request to provide study endpoints including the LTE Period. |
| Synopsis:<br>3.3.1 Study Design<br>Long Term Extension (LTE) Period (Week 61 to Week 109) | **After completing the Open-Label Extension Period, patients who are responding to PRN1008 treatment will be eligible to enter the Long Term Extension Period and will continue to receive open-label PRN1008 400 mg bid for 48 weeks per Table 4.**<br>**Patients are eligible to participate in the LTE if:** | Addition of requirements for eligibility to enroll in the LTE. |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | **a) they have achieved and/or maintained an ECP with ≤10 mg/day CS at any time between 37 and 61 weeks in the study.**<br><br>**Patients are not eligible to participate in the LTE if:**<br>**a) they have more than one relapse following ECP requiring treatment with >10 mg/day CS (excluding CS taken short-term for dental work or surgery), or**<br>**b) have failed to adequately recover after a relapse despite maximal tolerated CS dose.**<br>**Failure to adequately recover is defined as: <25% decrease from peak PDAI despite treatment with maximal steroid doses (minimum of 1.5 mg/kg/day unless there is a specific documented medical contraindication) for at least 2 weeks.**<br><br>**CS doses above refer to doses of prednisone or its equivalent.**<br><br>**The maximum acceptable maximum acceptable duration between completing the OLE Period and entering the LTE Period is 14 days. In addition to meeting the disease response criteria defined above, eligibility to enter the LTE requires the following:**<br>• **Based on the PI's clinical assessment, the patient is able to continue the study and undertake all protocol requirements, does not have any conditions that would preclude participation and the benefit risk assessment for participation remains favorable for the patient.**<br>• **Lab evaluations (hematology, coagulation and serum chemistry) at the Week 61 visit should be within normal limits or not considered clinically significant for the purpose of the patient's participation in the study, by the Investigator.**<br>• **No currently active moderate to severe infection at Week 61 (Grade 2 or higher).**<br><br>**Patients may continue in the LTE until:**<br>**a) they have had more than one relapse following ECP that requires >10 mg/day CS (excluding CS taken short-term for dental work or surgery)** | Detail provided for maximum gap between OLE and LTE.<br><br>Detail provided for patients to discontinue when no longer |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | **or have failed to adequately recover after a relapse despite maximal tolerated CS dose (per definition of failure to adequately recover above);**<br>**b) the drug is no longer being developed by the Sponsor for this indication;**<br>**c) the program is stopped for safety reasons.**<br>**Patients who have previously completed the Open-Label Extension Period prior to this amendment and were responders per the LTE requirement may enroll into the LTE.**<br>**Patients entering the LTE will receive Sponsor-provided CS, following CS Management Guidelines (Appendix 1).**<br>**Patients requiring rituximab during the Long Term Extension Period will be discontinued from the trial.** | responding to PRN1008 within the LTE.<br>Reflects that the Sponsor will be the source of corticosteroids in the LTE and that patients who require rescue rituximab must be discontinued. |
| Synopsis: Outcome Measures<br>Section 3.8.8 Long Term Extension Endpoints | **Long Term Extension Endpoints**<br>• **Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects during the LTE from Week 61 to Week 113**<br>• **Average daily dose of CS from Week 61 to Week 113**<br>• **Time to relapse during the LTE** | Per UK MHRA request to include LTE Endpoints. |

<table>
<tr><th>Section(s)</th><th>Amended or New Wording</th><th>Justification of Change</th></tr>
<tr><td>Figure 1: Study Design Flow Chart</td><td> 
</td><td>Updated to include LTE.</td></tr>
<tr><td>Table 3. Schedule of Assessments - Open Label Extension Period</td><td><table>
<tr><th></th><th></th><th colspan="7">Open-Label Extension Period</th></tr>
<tr><th></th><th>Week 37[k]</th><th>Week 39</th><th>Week 41</th><th>Week 45</th><th>Week 49</th><th>Week 53</th><th>Week 57</th><th>Week 61[l]</th></tr>
<tr><th>Visit Windows</th><th>±3 days</th><th>±3 days</th><th>±5 days</th><th>±5 days</th><th>±5 days</th><th>±5 days</th><th>±5 days</th><th>±5 days</th></tr>
<tr><th>Informed Consent</th><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>X[n]</td></tr>
</table>
n. Patients will be asked to consent to participating in the LTE Period, prior to continuing in the LTE.</td><td>Updated to indicate that patients must be asked to provide consent prior to continuing in the LTE, per MHRA request and to be consistent with Table 4.</td></tr>
</table>

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| Table 4. Schedule of Assessments - Long Term Extension Period | | Added assessments for LTE. |

| | Long Term Extension Period | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Windows | Week 61[i] ±5 days | Week 65 ±5 days | Week 69 ±5 days | Week 73 ±5 days | Week 85 ±10 days | Week 97 ±10 days | Week 109 ±10 days | EOT/Week 113 4 wk FU Visit ±5 days | Early Termination (ET)[a] | Unscheduled Visit |
| Informed Consent | X[k] | | | | | | | | | |
| Weight | X | X | X | X | X | X | X | X | X | X |
| Abbreviated physical examination | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | | | | X | | (X)[b] | (X)[b] |
| Vital Signs | X | X | X | X | X | X | X | X | X | X |
| Urinalysis[e] | X | | | | | | X | X | X | (X)[b] |
| Urine pregnancy test[d] | X | X | X | X | X | X | X | X | X | |
| Hematology, coagulation, and serum chemistry[c] | X | | | | X | X | X | X | X | (X)[b] |
| PK Sample[e] | X | | | | | | | | | (X)[b] |
| PD: anti-desmoglein-1 and -3 autoantibody titers by ELISA | X | | | X | X | X | X | | X | (X)[b] |
| PDAI | X | | | | | | | | | |
| ABQOL and TABQOL | X | | | | | | | | | |
| EQ-5D-5L | X | | | | | | | | | |
| Efficacy Outcome Assessment[f] | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X |
| Photography[g] | X | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| PRN1008 dispensed | X | X | X | X | X | X | | | | |
| Drug reconciliation[h] (PRN1008 /CS Dosing Documentation) | X | X | X | X | X | X | X | X | X | X |
| CS Daily Dosing[i] | X See Appendix 1 | | | | | | | | | X |

**a. The early termination (ET) visit should also be performed for patients who are not able to complete the Long-Term Extension period including Week 113 visit and discontinue from the trial early.**

**b. Only if clinically indicated.**

**c. Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Serum chemistry will include the following: 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; and glucose (random). Coagulation will include: PT/INR, thrombin time, aPTT, and fibrinogen level and will be collected at Weeks 61, 85, 97, 109, ET, and EOT. Urinalysis will include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes and reflex microscopy.**

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| | **d. For women of childbearing potential only. May be performed monthly between Week 73 and Week 113 if required by local regulations.**<br>**e. PK sample required at Week 61; and after Week 61 only if the patient experiences relapse. Time of draw will be captured as well as time of the last two PRN1008 doses, and time since the patient's last meal.**<br>**f. Pemphigus Clinical Response Definitions for CDA, CR, ECP, Relapse (refer to protocol Section 3.1).**<br>**g. Any photos should be taken and stored in accordance with local regulations (Week 61 only).**<br>**h. Subjects are required to bring all used and unused PRN1008 study drug supplies with them to every clinic visit.**<br>**i. For CS management, refer to Appendix 1. Patients entering the LTE will receive Sponsor-provided CS. At any point if CS needs to be adjusted between required visits, the patient may return for an unscheduled visit and additional CS may be dispensed.**<br>**j. Assessments performed at the Week 61 Visit of the Open-Label Period should not be repeated at this visit.**<br>**k. Patients will be asked to consent to participating in the LTE Period, prior to continuing in the LTE.** | |
| 5.6 Trial Design Rationale | **The primary purpose of the 48-week, Long Term Extension Period (LTE) is to provide extended access to PRN1008 for patients who are receiving clinical benefit and to accrue additional long-term data on the safety of PRN1008.** | Added primary purpose of the LTE in line with endpoints. |
| 6.2. Corticosteroids | Oral corticosteroids (prednisone or prednisolone) will be provided during the Blinded Treatment Period and Open-Label Extension Period. **Patients entering the LTE will receive Sponsor-provided CS.** | Reflects that the Sponsor will be the source of corticosteroids in the LTE |

| Section(s) | Amended or New Wording | Justification of Change |
|---|---|---|
| 7.4.1 Patient Discontinuation and Stopping Rules | • A patient in the Blinded Treatment Period requiring an additional "top up" dose of rituximab after their initial rituximab course of treatment or a patient in the Open-Label Extension Period **or Long Term Extension Period** requiring rituximab | Reflects that patients requiring rituximab during the LTE must be discontinued. |
| 7.6.7. Early Termination Visit | Please refer to Table 2 (if terminating during double-blind treatment), Table 3 (if terminating during Open-Label Extension), **or Table 4 (if terminating during Long Term Extension)** for specific early termination assessments. An attempt should be made to have the patient return for a follow-up visit approximately 4 weeks after the last dose of PRN1008 or placebo.<br>**Patients in the OLE or LTE who are required to discontinue the study early per the rituximab receipt rules (Section 6.3) should have their Early Termination visit completed prior to rituximab infusion.** | Updated for consistency. |
| 9.4.9 Long Term Extension Analysis | **The Long Term Extension endpoints will be summarized descriptively. Summaries of patient disposition, demographics, and baseline characteristics will be provided. The number of received doses and treatment duration will be described. Safety data including adverse events, laboratory evaluations and vital signs assessments will also be summarized.** | New analysis section added to reflect addition of LTE endpoints |

### 12.13.14. Amended Clinical Trial Prototocol 06 (06 May 2021)

This was a global amendment to protocol Version 5 and was considered to be substantial.

**OVERALL RATIONALE FOR THE AMENDMENT**

The primary reasons for this amendment to Protocol PRN1008-012 were:

- To add an exploratory objective in order to evaluate the impact of the Investigational Medicinal Product (IMP) on vaccine responses,
- To revise the key secondary efficacy, other secondary endpoints, and exploratory endpoints and associated statistical analyses, in particular to provide additional clinically meaningful endpoints assessing reduction of corticosteroid (CS) use, duration of complete remission (CR) achieved with the use of minimal CS treatment, speed of action in achieving CR with minimal CS treatment, and proportion of relapses/flares as defined in consensus guidelines.
- To clarify Long Term Extension (LTE) objectives and assessments, definitions of early termination (ET)/end of trial (EOT) visits, adaptations in response to Coronavirus disease 2019 (COVID-19) pandemic, and allowing pharmacokinetic (PK) assessment of rilzabrutinib metabolites and IV CS.

**Protocol amendment summary of changes table**

## PRN1008-012 Amended Clinical Trial Protocol 06 (06 May 2021)

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Title Page, Approval of the Protocol, Sponsor Signatory name, Protocol Amendment Summary of Changes, and Section 1.1 Synopsis | Document formatting revisions were made. Signatures pages were removed. A new section including protocol amendment summary of changes and document history was added. The International Nonproprietary Name (INN) (rilzabrutinib) was added on title page and in the header. The Sanofi compound number SAR444671 and study number EFC17092 were added to the header. The brief title "PEGASUS pivotal study", NCT03762265 number, and "not applicable" for WHO, EUDAMED, and other regulatory agency identifier numbers were added on title page. | Changes made to reflect the updated amended protocol 06 and to comply with parent company Sanofi standards and processes. Protocol approval is conducted via electronic signature. |
| Section 1.1 Synopsis | The numbering of subsections was removed. | Changes made to comply with parent company Sanofi standards. |
| Section 1.1 Synopsis: Duration of Trial Participation, and Blinded Treatment Period, and Section 4.1 Overall Design, Duration of Trial Participation and Blinded Treatment Period | The duration of trial participation was changed to: "For each patient, the trial will last approximately 68 weeks including Screening Period (up to 4 weeks), the Blinded Treatment Period (Week 1 through Week 37), the Open-Label Extension Period (Week 37 to Week 61), and a 4-week end of treatment follow-up (up to Week 65)." | Changes made for clarification. |
| Section 1.1 Synopsis: Pemphigus Clinical Definitions and Section 3 Objectives and Endpoints | The definition of Relapse/Flare was revised in bold as follows: "They are defined by the appearance of 3 or more new lesions after CDA and within a month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved CDA". | Changes made for clarification. |
| Section 1.1 Synopsis: Exploratory Objectives, Exploratory Endpoints, Pharmacokinetic and Pharmacodynamic, and Section 3 Objectives and Endpoints | The following exploratory objective "To evaluate the PK of rilzabrutinib metabolites" was added with the new following endpoint "Plasma concentrations of rilzabrutinib metabolites".<br>The text was updated to "Individual and group PK (rilzabrutinib and metabolites as applicable) and PD (antidesmoglein-1 and -3) data will be | Changes related to study procedures made for consistency with the added exploratory objective and to allow PK assessment of rilzabrutinib metabolites. |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| | summarized, displayed graphically, and by descriptive statistics for each visit, where measured. Please refer to the Statistical Section 9". | |
| Section 1.1 Synopsis: Exploratory Objectives, Exploratory endpoints, and Section 3 Objectives and Endpoints | The following exploratory objective "To explore association of vaccine response with rilzabrutinib" and following exploratory endpoint: "(Optional) Blood samples for exploratory analysis of vaccine IgG response during treatment" was added. | Changes made to address the purpose of this amendment, and for consistency with the added exploratory objective. |
| Section 1.3 Schedule of activities (SoA) (Table 2, Table 3, and Table 4) | Vaccine IgG and SARS-CoV-2 (for participants in Germany only, see specific instructions in Appendix 10) were added to Table 2, Table 3, and Table 4.<br>Footnotes "r" and "s" of Table 2, footnotes "n" and "o" of Table 3 and footnotes "k" and "l" of Table 4 regarding passive collection and optional collections of blood pre-and post-vaccine dose regimen were added. | |
| Section 8.2 Trial Enrollment Procedures, Section 8.3.1 Screening (Day -29 to Day -1), Section 8.3.5 Long Term Extension Period (Beginning Week 61), Section 8.4.8.1 Vaccine IgG, Section 10.3 Informed Consent and Section 12.11 Appendix 11 Vaccine Response | Wording specifying that consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccination was required by those patients who make mid-study decisions about vaccinations was added.<br>A reference to Appendix 11 for additional details was added. Section 8.4.8.1 and Appendix 11 were added to emphasize that this exploratory vaccination testing could be conducted in participants treated with rilzabrutinib for at least 6 weeks and expected to continue in the study for at least 12 weeks in either the Open-Label Period or Long-Term Extension Period. | |
| Section 9.3.7 Pharmacokinetic and Pharmacodynamic Analysis | Concerning statistics from exploratory analyses, "will" was changed to "may" to align with the exploratory objectives. | |
| Section 9.3.8 Exploratory Analysis | The following text was added: "If collected, vaccine response parameters may be summarized by treatment group and, by disease and antigenic strain of the vaccine dose regimen". | |
| Section 1.1 Synopsis: Blinded Treatment Period (Weeks 1 to 37), Section 9.3.5 Efficacy Analysis (mITT Population), and Section | The following text was removed from Synopsis and Appendix 1: "but will be considered treatment failures for all efficacy endpoints except for CS dosing and composite Glucocorticoid Toxicity Index (GTI) score.", and relocated in Section 9.3.5. | Changes made for clarification by separating instructions to investigators on use of rituximab during the trial from treatment of rituximab use in the statistical analysis. |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| 12.1 Appendix 1 Corticosteroid and Rituximab Management | | |
| Section 1.1 Synopsis, Long Term Extension Objective, Long Term Extension Endpoints, Long Term Extension Analysis, Section 2.1 Study Rationale, Section 3 Objectives and Endpoints, Section 4.2 Scientific Rationale for Study Design, and Section 9.3.9 Long Term Extension Analysis | The following objective "To evaluate the long-term safety and efficacy of rilzabrutinib" was added with the new following endpoints:<br>• "Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects during the LTE from Week 61 to Week 113<br>• Average daily dose of CS from Week 61 to Week 113<br>• Time to initial relapse/flare from initial CDA to Week 109".<br>The section describing the analysis of LTE endpoints was added. | Changes related to study procedures to clarify objectives and endpoints to be assessed during the LTE period. |
| Section 1.1 Synopsis: Investigational Plan: Blinded treatment period (week 1 to 37), Corticosteroid Management, Section 4.1 Overall Design: Blinded treatment period (Week 1 to 37), Section 6.1.2.1 Corticosteroid Starting Doses and Management During Screening and at Day 1, and Section 12.1 Appendix 1 Corticosteroid and Rituximab management | The following wording "below the required minimum dose level" was added next to "CS taper". | Changes related to study procedures made for clarification. |
| Section 1.1 Synopsis: End of Trial (Follow-up Period, 4 Weeks after last Trial Dose), Section 4.4 End of Study Definition | "End of trial" was added next to the subtitle "(Follow-up Period, 4 Weeks after last Trial Dose)". The following text was revised as follows:<br>"Patients who are not able to complete the Blinded Treatment Period, Open-Label Extension Period or Long Term Extension Period as planned and discontinue the study early should be encouraged to come back for an Early Termination (ET) visit as soon as possible."<br>The following text was added: | Changes related to study procedures made for clarity between ET and EOT visits. |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| | "In addition to the ET Visit, patients should return for the EOT Visit 4 weeks following their last dose of rilzabrutinib/placebo or rilzabrutinib.<br>In the event the ET Visit occurs ≥4 weeks after their last dose of rilzabrutinib/placebo or rilzabrutinib, this will be recorded as the ET Visit and there is no need for the 4-week safety follow-up (EOT) visit". | |
| Section 1.1 Synopsis: Urgent Safety Measures Initiated Due to Coronavirus disease 2019 (COVID-19) Pandemic, Section 4.2 Scientific Rationale for Study Design, Section 6.2.2 Drug Management, Section 8.2 Trial Enrollment Procedures, Section 8.3 Visit Overview, Section 8.6.3.1 Adverse Event Collection Period, Section 12.9 Appendix 9 Updated Guidelines to Sites for Delayed Patient Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19 | Urgent Safety Measures Initiated Due to Coronavirus disease 2019 (COVID-19) Pandemic were added. These measures include at least remote study visits, enrollment procedures, direct to patient delivery of study medication for flexibility to continue the trial during regional or national emergency such as COVID-19 pandemic. | Include flexibility and ease of continuation of study during regional or national emergency such as COVID-19. |
| Section 1.1 Synopsis: Inclusion Criteria and Section 5.1 Inclusion Criteria | The inclusion criterion I04 was revised as follows: "Adequate hematologic, hepatic, and renal function (including but not limited to absolute neutrophil count ≥1.5 × $10^9$/L, hemoglobin [Hgb] >9 g/dL, platelet count ≥100 × 109/L, aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] ≤1.5 × upper limit of normal [ULN], albumin ≥3 g/dL, creatinine ≤1.5 × ULN)." | Changes related to study procedures made for clarification. |
| Section 1.1 Synopsis: Outcome Measures: Primary efficacy endpoint, Section 3 Objectives and Endpoints, Section 9.1 Sample size determination, and Section 9.3.5 | Week ≤ 29" was replaced by "Week 29". | Changes related to study procedures made for clarification. |

| Section # and name | Description of change | Brief rationale |
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| Efficacy Analysis (mITT Population) | | |
| Section 1.1 Synopsis: Key Secondary Efficacy Endpoints, Section 3 Objectives and Endpoints, Section 9.3.5 Efficacy Analysis (mITT Population), and Section 9.3.6 Key Secondary Efficacy Sequential Testing | Key secondary endpoints were changed to:<br>• "Cumulative CS dose from Baseline to Week 37<br>• Cumulative duration of CR with a CS dose ≤10 mg/day, from Baseline to Week 37<br>• Time to first CR with a CS dose ≤10 mg/day, from Baseline to Week 37<br>• Proportion of patients with at least one disease relapse/flare from initial control of disease activity (CDA) to Week 37<br>• Cumulative duration of CR with a CS dose ≤10 mg/day, from Week 37 to Week 61<br>• Cumulative duration of CR with a CS dose = 0 mg/day, from Week 37 to Week 61". | Changes to clarify secondary endpoints and evaluate CR during the Open Label Extension (OLE) Period. |
| Section 1.1 Synopsis: Other Secondary Endpoints, Section 3 Objectives and Endpoints, and Section 9.3.6 Key Secondary Efficacy Sequential Testing | New other secondary endpoints were added or revised as follows:<br>• "The proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤10 mg/day<br>• The proportion of patients who have a PDAI score <3 from Week 29 to Week 37 with a CS dose ≤10 mg/day<br>• Cumulative duration of CR with a CS dose ≤10 mg/day from Baseline to Weeks 61 and 109<br>• Cumulative duration of CR with a CS dose = 0 mg/day from Baseline to Weeks 61 and 109<br>• Change in PDAI score from Baseline to Weeks 5, 13, 25, 37, 61, and 109<br>• Change in Autoimmune Bullous Disease Quality of Life (ABQOL) score from Baseline to Weeks 5, 13, 25, 37, 61, and 109<br>• Proportion of patients with ABQOL Score of zero at Weeks 5, 13, 25, 37, 61, and 109 | Changes related to secondary endpoints were made to evaluate efficacy during the OLE and LTE Periods. |

| Section # and name | Description of change | Brief rationale |
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| | • Change in EuroQOL-5 Dimension 5 Level (EQ-5D-5L) results (visual analog scale [VAS] results and individual dimension) scores from Baseline to Weeks 5, 13, 25, 37, 61, and 109<br>• Time to first CR with a CS dose ≤10 mg/day, from Baseline to Weeks 61 and 109<br>• Total number of disease relapses/flares from initial CDA to Week 37<br>• Time to initial relapse/flare from initial CDA to Week 37<br>• Proportion of patients with 3 or more new lesions within 1 month that do not heal spontaneously within 1 week, or with extension of established lesions, from baseline to Week 37". | |
| Section 1.1 Synopsis: Pharmacodynamic Endpoints, and Section 3 Objectives and Endpoints | "Week 109" was added to the PD endpoint timepoints for PD assessments. | Changes made for correction. |
| Section 1.1 Synopsis: Exploratory Endpoints, Section 3 Objectives and Endpoints | New exploratory endpoints were added or revised as follows:<br>• "Proportion of patients with relapse/flare after achievement of CR between Baseline and Weeks 61 and 109<br>• Proportion of patients initially randomized to rilzabrutinib that are in CR with a zero CS dose, from Week 53 to Week 61 (no randomized treatment comparison)<br>• Proportion of patients initially randomized to placebo that are in CR with a zero CS dose, from Week 53 to Week 61 (no randomized treatment comparison)<br>• Change in Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) score from Baseline to Weeks 5, 13, 25, 37, 61, and 109<br>• Total number of disease relapses/flares from Week 37 to Weeks 61 and 109". | Changes related to exploratory endpoints to evaluate efficacy during the OLE and LTE Periods. |

| Section # and name | Description of change | Brief rationale |
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| Section 1.3 Schedule of activities (SoA) (Table 3) | • Removal of HbA1C, LDL level (fasting) and GTI Index from Week 61.<br>• Footnote “i” was updated as follows: "Patients entering the LTE will receive Sponsor-provided CS, following CS Management Guidelines (Appendix 1)”. | Changes related to study procedures made for clarification and alignment with the document. |
| Section 1.3 Schedule of activities (SoA) (Table 4) | • Removal of HbA1C, LDL level (fasting), and GTI Index.<br>• Removal of PK sample and photography after Week 61.<br>• PDAI, ABQOL/TABQOL, EQ-5D-5L assessments remained only at Week 61, Week 109, and Early termination (ET) visits.<br>• The following text was added to the footnote “d” to clarify the urine pregnancy test:“May be performed monthly between Week 73 and Week 113 if required by local regulations”.<br>• The footnote “e” was revised as follows:” PK sample required at Week 61; and after Week 61 only if the patient experiences relapse/flare”.<br>• “ (Week 61 only)” was added to the footnote “g” related to the intake of photos. | |
| Section 4.1 Overall Design | “Phase 3” was added in the design section. | Changes made to comply with parent company Sanofi standards. |
| Section 4.3 Justification for dose | Text referring “Black box” warnings and “Warnings and Precautions” in the US Product Information for RITUXAN was replaced by:<br>“For detailed safety information on rituximab or other biosimilar agents investigators should refer to the current, locally applicable, approved product information.” | Section updated to account for national variations in labeling for rituximab. |
| Section 5 Study Population | “Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted” was added. | Changes made as per Sanofi template. |
| Section 6 Study Intervention(s) and concomitant therapy | Updated text providing study intervention definition in first paragraph. | Changes made as per Sanofi template. |

| Section # and name | Description of change | Brief rationale |
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| Section 6.5.1 Prohibited Medications | “Live vaccines” was added to the list of prohibited medications. | Changes made for consistency with the exclusion criterion E19. |
| Section 6.5.2 Particular Permissible Medications and Section 6.1.2 Corticosteroids | The text was added to specify possible use of short, defined courses of intravenous corticosteroids, if deemed clinically necessary and at doses consistent with the oral regimen, after consultation with Medical Monitor, and possible use of Sponsor-provided oral prednisolone during the Blinded Treatment Period. The "patients entering the LTE will no longer receive sponsor-provided CS" text was updated to "patients entering the LTE will receive Sponsor-provided CS". | Changes related to study procedures made for clarification. |
| Section 8.3.6 OLE EOT/Week 65 and LTE EOT/Week 113 Visits (Follow-up Period, 4 Weeks after last Trial Dose) | The wording of the subtitle was revised. The following text was added “EOT Visit for safety follow-up procedures performed 4 weeks after the last dose of study drug.” | Changes related to study procedures made for clarification. |
| Section 8.3.7 Early Termination Visit | A statement was added concerning patients in the open-label extension (OLE) or LTE who should have their Early Termination (ET) Visit completed prior to rituximab infusion. | Changes related to study procedures made for clarification. |
| Section 8.4.15 SARS-CoV-2 Testing Requirement (for German participants only) | The entire section was added. | Changes related to study procedures made for clarification. |
| Section 8.5 Assessment of efficacy | The entire section was added. | Changes made for clarification and as per Sanofi template. |
| Section 8.5.1 Specification of the Efficacy Parameters, Section 9.3.6 Key Secondary Efficacy Sequential Testing, and Section 9.3.8 Exploratory Analysis | “Change in TABQOL score from baseline to Weeks 5, 13, 25, 37, 61, and 109” is an exploratory endpoint. Then, TABQOL analysis moved from other secondary efficacy parameters analysis section to the exploratory analysis section. | Changes made for correction. |
| Section 8.6.4 Pregnancy | Three bullets with information regarding reporting pregnancy AEs/SAEs, including complication or elective termination, abnormal pregnancy outcomes. and post-study pregnancy-related SAEs considered reasonably related to the study intervention by the Investigator were added. | Changes related to statistical methodology made for clarification and as per Sanofi template. |

| Section # and name | Description of change | Brief rationale |
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| Section 9.1 Sample Size Determination | The targeted minimum of PV patients changed from "45" to "90" as well as the maximum number of PF patients from "10" to "22". | Changes made for correction. |
| Section 9.3.9 Long term extension analysis | The following text "in general" was added after "The long term extension endpoints will be summarized descriptively". "More details will be provided in the SAP" was added at the end of the paragraph. | Changes made for clarification. |
| Section 9.3.5 Efficacy Analysis (mITT Population) | Text was amended to "Patients who drop out of the trial, withdraw, or who receive a rituximab dose prior to Week 37 will count as non-responders in the analysis". | Changes to separate investigator instruction from statistical analysis approach regarding use of rituximab. |
| Section 10 Investigator Responsibilities | Updated to specify that investigators will sign the separate protocol and amended protocol agreement form. | Changes made to comply with Sanofi standards. |
| Section 12.1 Appendix 1: Corticosteroid and rituximab management | The following text: "For patients that have a documented and specific medical contraindication, the maximally tolerated dose of corticosteroid may be considered for this purpose following consultation with the Medical Monitor" was changed to<br>"For patients who are unable to escalate CS up to 1.5 mg/kg/day due to documented adverse events related to CS and cannot achieve CDA following 2 weeks of treatment with their maximally tolerated CS dose, rescue with rituximab therapy may be offered. Please consult with the Medical Monitor." | Changes made for clarification. |
| Section 12.10 Appendix 10: Country-specific requirements | This entire section was added to outline country specific requirements for participants from Germany such as additional inclusion/exclusion criteria, different contraception requirements, SARS-CoV-2 testing requirements, additional trial stopping rules and patient discontinuation rules (positive COVID test). | Changes made to comply with Sanofi standards. |
| Section 12.12 Appendix 12: Abbreviations | List of abbreviations was updated by adding or removing abbreviations and moved to Appendix 12. | List of abbreviations updated for correction and clarity and to comply with Sanofi standards. |
| Section 12.13 Appendix 13: Protocol Amendment History | This entire section was added. | Changes made to comply with Sanofi standards. |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 13 References | List of references was updated and numbered. | Changes made to comply with Sanofi standards. |
| Throughout document | Document formatting revisions and other minor editorial changes have been made. Titles of sections were added. Order of sections was revised, and new sections were created. "PRN1008" has been replaced with “PRN1008 (rilzabrutinib)” or “rilzabrutinib". The wording "relapse” was changed to “relapse/flare". | Changes made for clarification and to comply with Sanofi standards. |

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