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1	6-Apr-2020		Original SAP
2	17-Jun-2021	Please see Section 2.2 for details.	Please see Section 2.2 for details
3	29-Aug-2021	Please see Section 2.2 for details.	Please see Section 2.2 for details

Table of Contents

Document History 2
Table of Contents 3
List of Tables 5
1. Overview 6
2. Study Objectives and Endpoints 6
2.1. Study Objectives 6
2.1.1. Efficacy Objectives 6
2.1.2. Safety Objectives 6
2.1.3. PK/PD Objectives 7
2.1.4. Exploratory Objectives 7
2.1.5. Long Term Extension Objective 7
2.2. Statistical Modifications made in the Statistical Analysis Plan 7
2.3. Study Endpoints 10
2.3.1. Safety Endpoints 10
2.3.2. Efficacy Endpoints 10
2.3.3. Pharmacokinetic/Pharmacodynamic Endpoints 12
2.3.4. Exploratory Endpoints 12
2.3.5. Long Term Extension Endpoints 12
3. Overall Study Design and Plan 13
3.1. Overall Design 13
3.2. Sample Size and Power 13
3.3. Study Population 14
3.4. Treatments Administered 14
3.5. Method of Assigning Subjects to Treatment Groups 14
3.6. Blinding and Unblinding 15
3.7. Schedule of Events 15
4. Statistical Analysis and Reporting 16
4.1. Introduction 16
4.2. Data Monitoring 16
4.3. Timing of Analyses 17
5. Analysis Populations 17
6. General Issues for Statistical Analysis 18
6.1. Statistical Definitions and Algorithms 18
6.1.1. Baseline Definitions 18
6.1.2. Study Day 18
6.1.3. Adjustments for Covariates and Subgroup Analyses 18
6.1.4. Multiple Comparisons 18

6.1.5. Handling of Dropouts or Missing Data 19
6.1.6. Analysis Visit Windows 22
6.1.7. Pooling of Sites 23
6.1.8. Derived Variables 23
6.1.9. Corticosteroid Dose Derivation for Efficacy Analyses 28
6.1.10. GTI Scores 29
6.1.11. Data Adjustments/Handling/Conventions 31
7. Study Patients/Subjects and Demographics 32
7.1. Disposition of Patients/Subjects and Withdrawals 32
7.2. Protocol Violations and Deviations 32
7.3. Demographics and Other Baseline Characteristics 32
7.4. Exposure and Compliance 33
8. Efficacy Analysis 34
8.1. Primary Efficacy Analysis 37
8.2. Key Secondary Efficacy Analyses 37
8.3. Other Secondary Analyses 38
8.4. Exploratory Analyses 40
9. Safety and Tolerability Analysis 40
9.1. Adverse Events 41
9.1.1. Adverse Events Related to Corticosteroid Use 42
9.1.2. Adverse Events Leading to Withdrawal 42
9.1.3. Deaths and Serious Adverse Events 42
9.2. Clinical Laboratory Evaluations 42
9.3. Vital Signs 43
9.4. Physical Examinations 43
9.5. Electrocardiograms 43
9.6. Prior and Concomitant Medication 43
9.7. Long Term Extension Analysis 43
10. Changes from Planned Analysis 44
11. Other Planned Analysis 44
11.1. Pharmacokinetic and Pharmacodynamic Analysis 44
11.2. Questionnaires and health economic Analysis 44
12. References 44
Appendix 1: Abbreviations 46

[redacted]

List of Tables

Table 1: Statistical analysis plan statistical changes from Version 1 7
Table 2: Analysis Visit Windows – Blinded Treatment Period..... 22
Table 3: Analysis Visit Windows – Open-Label and Long Term Period Extension Periods..... 23
Table 4: Event and Censoring Details for Time to First CR with a CS dose at or below 10 mg/day..... 24
Table 5: Event and Censoring Details for Time to First flare/relapse after initial CDA..... 26
Table 6: Efficacy Endpoints and Analysis Methods..... 34

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Principia Biopharma protocol number PRN1008-012 (A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial to Evaluate the Efficacy and Safety of Oral BTK Inhibitor PRN1008 in Moderate to Severe Pemphigus), amendment 6 version 2 dated 06-May-2021. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3] for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Principia Biopharma's study PRN1008-012.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Efficacy Objectives

- To evaluate the efficacy of PRN1008 (Rilzabrutinib) in achieving durable complete remission (CR) on low to zero doses of oral corticosteroid (CS) and on the time course of quantitative disease activity scores
    - CR is defined as the absence of new and established lesions and is intended to mean "no disease activity," as reported by study investigators.
- To assess the ability of PRN1008 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

2.1.2. Safety Objectives

- To evaluate the safety of PRN1008
- To evaluate differences in potentially CS-related adverse events

2.1.3. PK/PD Objectives

- To evaluate the population pharmacokinetics (PK) of PRN1008
- To evaluate pharmacodynamics (PD) effects of PRN1008 on anti-desmoglein (anti-dsg) autoantibody titers (anti-dsg1 and anti-dsg3)

2.1.4. Exploratory Objectives

- To examine the effects of PRN1008, if any, of the baseline covariates on PK and/or PD, and the relationship between PK, PD and efficacy
- 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
- 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

2.1.5. Long Term Extension Objective

- To evaluate the long-term safety and efficacy of PRN1008

2.2. Statistical Modifications made in the Statistical Analysis Plan

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan from Version 1 of the SAP. The table also incorporated changes made in protocol amendments since Version 1 of SAP that affect statistical analyses.

Table 1: Statistical analysis plan statistical changes from Version 1

SAP version number	Date approved	Rationale	Description of statistical changes
2	17-June-2021	Changes to key secondary endpoints following feedback from FDA dated [redacted] and protocol amendment.	The following key secondary endpoint was exchanged with 'Proportion of patients with 3 or more lesions within 1 month that do not heal spontaneously within 1 week, or by the extension of established lesions, from Baseline to Week 37' (moved to Other Secondary Endpoints): • Proportion of patients with at least one disease relapse/flare from initial control of disease activity (CDA) to Week 37 The following key secondary endpoint was added: • Cumulative duration of CR with a CS dose = 0 mg/day, from Week 37 to Week 61".

SAP version number	Date approved	Rationale	Description of statistical changes
		Changes related to secondary endpoints were made to evaluate efficacy during the LTE Periods. This change was made due to protocol amendment.	The following other secondary endpoints were revised to include evaluation during the LTE periods : • 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 • 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 from baseline to Week 109
		Changes made for correction. This change was made due to protocol amendment.	"Week 109" was added to the PD endpoint timepoints for PD assessments.
		Changes related to exploratory endpoints to evaluate efficacy during the LTE Periods. This change was made due to protocol amendment.	Exploratory endpoints were revised to include evaluation during the LTE periods as follows: • "Proportion of patients with relapse/flare after achievement of CR between Baseline and Weeks 61, and between Baseline and Week 109 • 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 from Week 61 to Week 109".
		Changes made for correction. This change was made due to protocol amendment.	"Change in TABQOL score from baseline to Weeks 5, 13, 25, 37, 61, and 109" is an exploratory endpoint. Thus, TABQOL analysis was moved from other secondary efficacy parameters analysis section to the exploratory analysis section.

SAP version number	Date approved	Rationale	Description of statistical changes
		Changes related to statistical methodology made for clarification and as per Sanofi template. This change was made due to protocol amendment.	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 made for clarification. This change was made due to protocol amendment.	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 to clarify the population of analysis in the testing order.	The statistical testing will be done in the following order: • *Primary endpoint based on PV patients in mITT population* • *Primary endpoint in mITT population (i.e. PV+PF patients)* • *Key secondary endpoints in mITT population (i.e. PV+PF patients)* The study will be declared to be a positive study if the p-value for the primary endpoint based on PV patients in the mITT population is significant at two-sided $\alpha = 0.05$ level. The test stops as soon as an endpoint is found not statistically significant at $\alpha=0.05$ (2-sided).
		Additional analysis added	Addition of subgroup analysis: disease diagnosis category (PV, PF)
		Changes were made for clarification.	CS doses for efficacy analyses will be based on the combination of the prescribed CS doses collected on the "Systemic CS Daily Dosing" eCRF form and the CS doses collected as concomitant medications on the "Other Corticosteroid Concomitant Medications" eCRF form. The following process will be used to calculate the CS doses for efficacy endpoints
		To clarify the method of assessing prednisone dose of ≤ 5 mg/day for the primary endpoint analysis .	The prednisone dose of ≤ 5 mg/day for the primary endpoint analysis will be assessed using the median daily dose between Week 29 and Week 37 with a maximum dose of ≤ 10 mg/day. Details are in Section 8.1
		The change was made for consistency purpose.	The similar missing data imputation was applied to other secondary endpoints and exploratory endpoints as the primary and key secondary endpoint for CS and CR status.

SAP version number	Date approved	Rationale	Description of statistical changes
3	29-August-2021	Changes were made based on FDA feedback on SAP [redacted]	• The primary efficacy endpoint was changed to be the proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤ 10 mg/day • The analyses of efficacy endpoints involving CR assessment for the blinded treatment period are based on on-site assessments only (i.e. not including data collected from remote visits). Details are in Section 8 • The following 3 key secondary endpoints were moved to other secondary endpoints: 1. the proportion of subjects with at least one disease flare/relapse from initial control of disease activity (CDA) to Week 37, 2. cumulative duration of CR with a CS dose ≤ 10 mg/day from Week 37 to Week 61, 3. cumulative duration of CR with a CS dose = 0 mg/day from Week 37 to Week 61 • For multiplicy control purpose, the analyses of key secondary efficacy endpoints based on PV only subjects are added to the testing sequence. Details are in section 6.1.4 • Clarified that the "time to study discontinuation" covariate is based on the blinded treatment period, in the ANCOVA model for analyzing the 1st key secondary efficacy endpoint (i.e., cumulative CS dose from baseline to Week 37). Details are in section 8.2

2.3. Study Endpoints

2.3.1. Safety Endpoints

The safety endpoints of this study include the following:

- 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)

2.3.2. Efficacy Endpoints

For efficacy endpoints, Baseline is defined as stated in Section 6.1.1. Unless specified otherwise, endpoint comparisons will be based on differences between randomized treatment groups. Week 37 visit, is the planned last assessment within the Blinded Treatment Period (as

defined in Section 3.1) over which the primary and key secondary efficacy endpoints will be evaluated. Additional endpoints may be evaluated through the Week 61 visit, or the planned last assessment within the Open-Label Extension Period, which begins after administration of the first dose of open-label PRN1008.

2.3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤ 10 mg/day.

2.3.2.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints of this study include the following, ranked in order of importance:

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

2.3.2.3. Other Secondary Endpoint(s)

The other secondary efficacy endpoints of this study include the following:

- 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 Week 61, and from baseline to Week 109
- Cumulative duration of CR with a CS dose = 0 mg/day from Baseline to Week 61, and from baseline to Week 109
- Glucocorticoid Toxicity Index (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 ≤ 10mg/day from Baseline to Week 61, and from Baseline to Week 109
- Total number of disease flares/relapses from initial CDA to Week 37
- Time to initial flare/relapse from initial CDA to Week 37
- Proportion of patients with 3 or more lesions within 1 month that do not heal spontaneously within 1 week, or by the extension of established lesions, from Baseline to Week 37.
- Proportion of patients with at least one disease flare/relapse from initial control of disease activity (CDA) to Week37.

- 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

2.3.3. Pharmacokinetic/Pharmacodynamic Endpoints

The pharmacokinetic (PK) endpoints of the study include plasma concentrations of PRN1008 as follows:

- Plasma concentrations of PRN1008 at approximately the time of maximum concentration at Day 1 and at varied subsequent time points.

The pharmacodynamic (PD) endpoints of the study include

- the 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.

The calculation of parameters for population PK analysis will be described and reported separately.

2.3.4. Exploratory Endpoints

Exploratory endpoints and analyses include the following:

- 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
- 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 after achievement of CR between Baseline and Week 61, and between Baseline and Week 109
- Proportion of patients initially randomized to PRN1008 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 flares/relapses from Week 37 to Week 61, and from Week 61 to Week 109
- (Optional) Blood samples for exploratory analysis of vaccine IgG response during treatment.

2.3.5. 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 flare/relapse from initial CDA to Week 109.

3. Overall Study Design and Plan

3.1. Overall 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 Long Term Extension Period of 48 weeks and a Follow-up Period of 4 weeks.

Patients with moderate to severe pemphigus will be randomized in a 1:1 allocation ratio to receive either PRN1008 400 mg twice daily (bid) or placebo bid during a Blinded Treatment Period (Week 1 to Week 37). At screening, patients will be initiated on a daily dose of prednisone depending on disease severity. During the study, patients will undergo a moderately rapid CS taper regimen with the goal to reduce the CS dose to 5 mg/day by no later than Study Week 29, as appropriate.

From Week 37, all patients will receive active drug in the Open-Label Extension Period for 24 weeks. 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. During the Open-Label Extension Period, further tapering of CS will be attempted to 0 mg for patients with CR.

After completing the Open-Label Extension Period, eligible patients (patients who are responding to PRN1008 treatment) 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. During the Long Term Extension Period, patients will continue to receive open-label PRN1008 400 mg bid for 48 weeks.

3.2. Sample Size and Power

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

[redacted]

[redacted]

3.3. Study Population

The study population is comprised of male and female patients with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]).

3.4. Treatments Administered

Patients will be randomized to one of two treatments in a 1:1 allocation ratio:

- 400 mg of PRN1008
- matching placebo

Study investigational product (IP) taken twice daily by mouth starting on 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, but the dose should not be reduced below the required minimum initial dose levels.

Thereafter, CS will be managed per the Corticosteroid and Rituximab Management protocol detailed in Appendix 1 of the protocol.

Rituximab treatment may also be administered during the Blinded Treatment Period after the Week 5 visit, unless contraindicated, after a second or subsequent, clinically significant "qualifying relapse" occurs. Full details on Rituximab treatment can be found in Appendix 1 of the protocol.

3.5. Method of Assigning Subjects to Treatment Groups

Patients who meet study criteria will be randomly assigned to placebo or PRN1008 in an approximately 1:1 allocation ratio. The randomization scheduled will be computer generated using a permuted block algorithm stratified by PV/PF disease type and by relapsing/newly diagnosed disease history (newly diagnosed defined as within 6 months of Screening).

The randomization schedule will be prepared by Premier Research before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignment. No subject will be randomized into this study more than once.

3.6. Blinding and Unblinding

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment, and a specified unblinded statistician and programmer from [redacted], and as part of the integration of Principia Biopharma to Sanofi an independent programmer from Sanofi will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the interactive web response system (IWRS). In all cases that are not emergencies, the investigator should discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised.

3.7. Schedule of Events

A detailed schedule of events for the blinded treatment period, open label portion, open label extension and Long Term Extension of the study are provided in the protocol.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value.

Analyses will be presented by the treatment group assigned at randomization for the Blinded Treatment Period of the study and by double-blind treatment group and overall for the Open Label Phase and Long-Term Extension Phase of the study, unless stated otherwise.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *P* values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests.

Statistical testing will be performed at the 0.05 level using two-tailed tests.

To control for the overall type I error rate, hierarchical testing based on a fixed sequence procedure will be used. If statistical significance is declared for the primary analysis, formal hypothesis testing will be done for the key secondary endpoints in sequence until a non-significant result is reached. All other *p* values from key secondary and other secondary endpoints, after a non-significant *p* value is reached, will be considered nominal.

4.2. Data Monitoring

A Data Safety Monitoring Board (DSMB) will be established to conduct reviews of subject safety. The DSMB reviews will occur approximately quarterly throughout the study unless the DSMB decides otherwise. Details of the operation of the DSMB are detailed in the DSMB charter. They can be modified as required. The unblinded analyses are performed by independent statisticians at Axio Research and the treatment codes are revealed to that party only. The unblinded DSMB listings will not be seen by anyone except the DSMB and the performing statistician.

No interim analyses are planned.

4.3. Timing of Analyses

Three sets of analyses are planned for this study.

1. After all patients have completed the week 37 (or early termination) study visit.
2. After all patients have completed the week 65 (or early termination) study visit.
3. At the end of the long term extension.

The first planned analysis will be performed after all enrolled subjects have completed the Week 37 (or Early Termination) study visit and will include subject activity occurring during the Blinded Treatment portion from Screening through Week 37. At this time, all data will be cleaned through Week 37 and the database will be locked prior to unblinding. A full set of analyses will be provided including disposition, demographics, protocol deviations, medical history, exposure and compliance through Week 37, all safety data summaries through Week 37, and all primary, secondary and exploratory efficacy endpoints through Week 37.

The second planned analysis will be performed after all subjects who have elected to participate in the Open-Label Extension Period have completed the Week 65 (or Early Termination) study visit. A full set of TLFs will be provided after the database has been cleaned and locked which will include all data collected during the open label potion of the study including disposition, demographics, protocol deviations, exposure and compliance between Week 37 and Week 61, all safety data summaries between Week 37 and Week 65.

In the above planned analyses, data collected after the target visit will also be presented either separately or combined with those prior to the target visit to have an overall assessment when appropriate (eg, exposure).

A third analysis will be conducted similarly following the end of the Long-term Extension period.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population includes all patients who receive at least one dose of study medication. Safety analyses will be based on the safety population. Analyses of the SAF population will be presented based on actual treatment received. When a patient is exposed to both PRN1008 and placebo in the double blind period, the patient will be analyzed in the treatment group that the patient was exposed longer in the blinded treatment period.
- **Intent-to-Treat (ITT) Population**: The ITT Population includes all randomized patients.
- **Modified Intent-To-Treat (mITT) Population:** The mITT Population includes all patients who are randomized and receive at least one dose of study medication. Patients will be analyzed for efficacy according to the treatment group to which they were randomized.

Pharmacokinetic and Pharmacodynamic Populations (PK and PD): The PK and PD Populations include all subjects in the Safety Population who have sufficient data for PK and/or PD analysis.

Analyses of the mITT Population will be presented based on the assigned treatment including cases in which a subject is randomized incorrectly or is administered the incorrect IP.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline Definitions

Baseline values will be the last observation recorded prior to first dose of randomized treatment. Baseline value derivations will include evaluations specified to have been collected Pre-Dose on Day 1 as specified in study schedule. For patients from the ITT Population who are randomized but not treated, baseline will be based on their randomization date.

6.1.2. Study Day

Day 1 is defined as the date of first dose of randomized treatment. Study day is calculated relative to the date of Day 1.

6.1.3. Adjustments for Covariates and Subgroup Analyses

6.1.3.1. Covariates

Disease history (newly diagnosed or relapsing) will be taken into account by including as a stratification variable or covariate in all of the analyses except for the Chi-Square analyses. Due to the small number of PF subjects expected to be enrolled in the study, the randomization strata of disease type will not be included as a covariate in any of the analyses.

6.1.3.2. Subgroup Analyses

Subgroup analyses of the primary endpoint will be conducted by

- race (White, Non-White),
- age group (< 40, 40-64, >64),
- gender (male, female)
- disease history (newly diagnosed, relapsing),
- disease diagnosis category (PV, PF)
- disease severity (moderate [PDAI 9-45], severe [PDAI>=46])

Key secondary endpoints will also be analyzed by the above subgroups.

6.1.4. Multiple Comparisons

The type I error rate of $\alpha = 0.05$ will be maintained for the study by using sequential (hierarchical) testing for the primary and key secondary endpoints.

The testing will be done in the following order:

1. Primary endpoint based on PV patients in mITT population

2. Primary endpoint in mITT population (ie, PV+PF patients)

3. Key secondary endpoints based on PV patients in mITT population (in the order presented in Section 2.3.2.2)

4. Key secondary endpoints in mITT population (ie, PV+PF patients) (in the order presented in Section 2.3.2.2)

The study will be declared to be a positive study if the p-value for the primary endpoint based on PV patients in the mITT population is significant at two-sided $\alpha = 0.05$ level. The test stops as soon as an endpoint is found not statistically significant at $\alpha=0.05$ (2-sided). The nominal p-values for subsequent tests without adjustment will be provided in the summary tables for information purpose.

All other endpoints will be considered exploratory, and no adjustments will be made for multiple comparisons.

6.1.5. Handling of Dropouts or Missing Data

All possible efforts will be made to ensure that subjects stay in the study and all data is collected as scheduled. Any subject who withdraws from the study or misses a scheduled visit will have their primary and secondary efficacy analyses missing data imputed prior to analysis according to criteria described in this section. Safety data (with the exception of AE and concomitant medication date/times as described in Section 6.1.10) will not be imputed and will be analyzed as observed.

6.1.5.1. Imputation Procedures for the Primary Efficacy Endpoint

For the primary efficacy endpoint (the proportion of patients who are in CR from Week 29 to Week 37 with a prednisone dose of ≤ 10 mg/day), patients with missing data due to study withdrawal will be considered as non-responders. A patient who received a rituximab dose prior to Week 37 will also be counted as a non-responder. [redacted]

- [redacted]
- [redacted]

[redacted]

Tipping point analyses (Yan, 2009) will be done to investigate the impact of missing data and lost to follow-up (LTF). The tipping point analysis will look at all possible combination of

converting missing data to a responder, starting at 0 and ending at all are responders. The cases where the statistical significance tips from significance to non-significance (defined as a two sided p-value >0.05) will be listed. A complete list of all combinations will also be presented. If the imbalances that leads to a change in interpretation are clinically implausible then the results of the primary analysis will be deemed reliable

6.1.5.2. Imputation Procedures for Secondary Endpoints

[redacted]

Responder analyses:

If a patient received a rituximab dose prior to Week 37, the patient will be counted as a non-responder starting from the date of first dose of rituximab for following responder analyses:

- 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

For the derivation of the following parameters:

- proportion of patients having three or more lesions within 1 month or extension of established lesions that do not heal within 1 week from Baseline to Week 37
- proportion of patients with at least one disease flare/relapse from initial control of disease activity (CDA) to Week 37,

A missing value will be considered as Yes with exception of the following:

- A 'No' can be inferred if adjacent visits are complete and reflect this same outcome. No more than one disease assessment can be imputed for this endpoint (i.e. this imputation is not applicable to consecutive missing visits). Note that, this imputation is not applicable at Week 37 when the study treatment a patient receives before and after the visit could be different.

If a patient received a rituximab dose prior to Week 37, the patient will be counted as Yes for the analyses of these two parameters.

Time to event analyses:

For the analyses of following parameters,

- Time to first CR with a CS dose ≤ 10 mg/day CS, from Baseline to Week 37
- Time to first CR with a CS dose ≤ 10mg/day, from Baseline to Week 61
- Time to initial flare/relapse from initial CDA to Week 37.

If a patient receives a rituximab therapy, the study data will be censored at the date of first rituximab administration for the above time to event analyses.

Cumulative CS dose:

- Cumulative CS dose from Baseline to Week 37

If a patient receives a rituximab therapy, the CS dose up to the date of the first dose of rituximab (including CS dose on the date of the first dose of rituximab) will be included in the analyses.

Other analyses:

For analyses of following parameter,

- Change in PDAI score from baseline to Weeks 5, 13, 25, 37 and 61
- Total number of disease flares/relapses from initial CDA to Week 37
- Glucocorticoid Toxicity Index (GTI) score at Week 37
- Change in Autoimmune Bullous Disease Quality of Life (ABQOL) score from baseline to Weeks 5, 13, 25, 37, and 61

- 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 and 61.

If a patient receives a rituximab therapy, the study data up to the date of the first dose of rituximab (but not including data from the date of the first dose of rituximab) will be included in the analyses.

Other responder analysis:

- Proportion of patients with ABQOL Score of zero at Weeks 5, 13, 25, 37, and 61

the patient will be counted as a non-responder starting from the date of first dose of rituximab for the responder analysis.

6.1.6. Analysis Visit Windows

For all analyses presented by study week, unscheduled and/or repeated measurements will only be included if a scheduled measurement is not available and the unscheduled/repeated measurement falls within the analysis visit windows as described below (Table 2 and Table 3). Otherwise, visits will be analyzed as scheduled.

Table 2: Analysis Visit Windows – Blinded Treatment Period

Analysis Visit Name	Target Day of Planned Visit	Assessment Window (Days)
Week 3	15	Post-dose ─ Day 21
Week 5	29	22 ─ 42
Week 9	57	43 ─ 70
Week 13	85	71 ─ 98
Week 17	113	99 ─ 126
Week 21	141	127 ─ 154
Week 25	169	155 ─ 182
Week 29	197	183 ─ 210
Week 33	225	211 ─ 238
Week 37	253	239 ─ Pre-open label dose

If more than 1 visit occurs within a single visit window, then the analysis will use the visit closest to the target day. If 2 visits within the same visit window are equidistant from the target day, then the analysis will use the later visit.

Table 3: Analysis Visit Windows – Open-Label and Long Term Period Extension Periods

Analysis Visit Name	Target Day of Planned Visit	Assessment Window (Days)
Week 39	267	Post-open label dose – 273
Week 41	281	274 ─ 294
Week 45	309	295 ─ 322
Week 49	337	323 ─ 350
Week 53	365	351 ─ 378
Week 57	393	379 ─ 406
Week 61	421	407 ─ Pre-long term extension dose
Week 65	449	Post-long term extension dose - 462
Week 69	477	463 – 490
Week 73	505	491 - 546
Week 85	589	547 - 630
Week 97	673	631 - 714
Week 109	757	715 - 770

6.1.7. Pooling of Sites

Data from all investigative sites will be pooled for all planned analyses. Analysis of individual site findings will be considered if necessary.

6.1.8. Derived Variables

Variables associated with primary or key efficacy analyses will be derived based on data imputed as identified in Section 6.1.5.

- Time from Pemphigus diagnosis to enrollment (years) = (screening date - first date of pemphigus diagnosis +1)/365.25

- Duration calculations are generally produced as: end date – start date + 1.

[redacted]

[redacted]

Table 4: Event and Censoring Details for Time to First CR with a CS dose at or below 10 mg/day

Situation	**Date of First CR/ Date of Censoring**	**Censored/ Event**
No post baseline assessments	Date of first dose	Censored
Patient in CR status and with a CS dose of ≤ 10 mg/day	First date that patient is in CR status and with a CS dose of ≤ 10 mg/day as identified in Section 6.1.9.	Event
Rituximab administered	Date of first Rituximab administration	Censored
No CR with a CS dose of ≤ 10 mg/day during the Blinded Treatment Period	Date of last efficacy assessment during blinded treatment phase (through Week 37)	Censored
Study discontinuation	Date of last efficacy assessment prior to or on the date of treatment discontinuation	Censored
Death before CR	Date of death	Censored

Note: Patients will be censored prior to a CR event at the earliest date of the censored events above should a censoring reason occur. Censoring reasons may be categorized for reporting (eg, by discontinuation reason).

- Three or more lesions within 1 month that do not heal spontaneously within 1 week or extension of established lesions = Yes if any of the following conditions are satisfied:

    - eCRF entry "Have new lesions appeared within a month that did not heal spontaneously within 1 week? OR Have there been extension of established lesions?" = Yes for any visits from Baseline up to Week 37.

    - At this visit, Has a Relapse occurred or is continuing?

The number of instances with investigator assessments of disease worsening will also be derived and categorized for reporting as 0, 1, 2, and ≥ 3. After the first worsening, a patient can have additional worsening, but only after the patient returns to CDA first, and then the next worsening can happen.

- PDAI score <3 from Week 29 to Week 37 with a CS dose of ≤ 10 mg/day = Yes if the following conditions are both satisfied:

    - PDAI <3 = Yes for all visits from Week 29 through Week 37

    - Daily prednisone dose is ≤ 10 mg/day from Week 29 through Week 37 as defined in Section 6.1.9.

    - No Rituximab therapy prior to Week 37.

After applying the CS dose imputation as described in Section 6.1.5.2, a patient with partial missing data (missing PDAI assessment or CS dose) or complete missing data at any scheduled visit will be considered as a non-responder.

- Change from baseline = value at current time point – value at Baseline.

- PDAI Total Score = the Total PDAI activity score as reported on the PDAI Total Score CRF (possible range of 0 to 250) as the sum of the individual skin activity, scalp activity and mucosal activity scores, higher score corresponding to worsening.

- PDAI activity subscores for skin (range 0 to 120), scalp (range from 0 to 10) and mucosal (range from 0 to 120)

- ABQOL Score of zero, = Yes if zero; = No if ABQOL is present and nonzero; missing otherwise.

- TABQOL = Sum of the 17 items of the ABQOL Questionnaire. Each item is scored on a scale of 0-3 for each of the 4 options (all the time, sometimes, occasionally and never), with 0 being the least severe and 3 being the most severe. No imputation will be done for missing item, therefore the total score will be missing if any item is missing[10].

- EQ-5D-5L: The EQ-5D-5L comprises the EQ-5D 5 dimensions (mobility, self-care, usual activities, paint/discomfort and anxiety/depression) and a visual analogue scale (VAS).

Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Overall health state is then defined as a 5-digit number. The health utility index value will be calculated using the crosswalk value sets provided in the EQ-5D-5L Index Value Calculator created by the EuroQol Group and using mapping function developed by Van Hout et al.[11]. The values sets based on UK population[12] will be used for all countries. The health utility score will be missing if response to one or more dimension is missing.

- The EQ VAS records the respondent's self-rated health on a 20 cm vertical VAS with endpoints labelled 0 ('the worst health you can imagine') to 100 ('the best health you can imagine'). This information can be used as a quantitative measure of health as judged by the individual respondents. EQ VAS will be described as given by patient. Missing data will not be imputed.

- At least one relapse/flare after initial CDA to Week 37 = Yes if the following condition is satisfied:

    - eCRF entry "At this visit, Has a Relapse occurred or is continuing?" = Yes for any visits from CDA to Week 37.

    - If a patient received a rituximab dose prior to Week 37, the patient will be counted as Yes.

  Relapse/flare can only happen following an initial CDA, subjects never achieve CDA prior to Week 37 will not be included in analysis. After the first initial flare, a patient can have additional relapse/flares, but only after the patient returns to CDA first, and then the next relapse/flare can happen. A similar method will be used to identify the number of relapses/flares from Week 37 to Week 61.

- Time to initial flare/relapse after initial CDA: Outcomes and durations for specific cases will be based on Table 5. The date of the event/censoring is considered the end date and the date of initial CDA is considered the start date, for duration calculations.

Table 5: Event and Censoring Details for Time to First flare/relapse after initial CDA

Situation	**Date of First flare/relapse or Date of Censoring**	**Censored/ Event**
No assessments after first CDA	Date of first CDA	Censored
Flare/relapse before Week 37	Date of first relapse	Event

Situation	Date of First flare/relapse or Date of Censoring	Censored/ Event
Rituximab administered	Date of first Rituximab administration	Censored
No flare/relapse during the Blinded Treatment Period	Date of last efficacy assessment during blinded treatment phase (through Week 37)	Censored
Study discontinuation	Date of last efficacy assessment prior to or on the date of treatment discontinuation	Censored
Death before flare/relapse	Date of death	Censored

- Note: Patients will be censored prior to a flare/relapse event should a censoring reason occur. Censoring reasons may be categorized for reporting (e.g. by discontinuation reason). A patient must have a CDA in order to be included in this analysis.

- Complete remission for ≥8 weeks on zero CS at Week 61 = Yes if complete remission status is achieved at Weeks 53, 57, and 61 with no recorded CS usage during this time; No otherwise, provided all data is complete for the specified visits. For patients with missing data at the specified visits this endpoint value will be missing unless there are a documented CR both before and after the missing visit.

- TEAE = any adverse event with an onset date on or after the first dose of study drug, having been absent pre-treatment or worsening relative to pre-treatment state.

- TEAE (Blinded Treatment Period) = any TEAE with an onset date on or after the first dose of study drug and occurring before enrollment into the open-label portion of the study. TEAEs that are ongoing at the time of enrollment into the open-label portion are considered part of the double-blind portion of the study.

- TEAE (Open-Label Extension Period) = any TEAE with an onset date on or after enrollment into the open-label extension portion of the study, having been absent during the double-blind portion or worsening relative to double-blind portion state. Since the TEAE time is not collected for the study, any AE started or worsened on the first day of the open-label period is considered a TEAE for the blinded treatment period.

- TEAE (Long Term Extension Period) = any TEAE with an onset date on or after enrollment into the long term extension portion of the study, having been absent during the double-blind/open-label extension portion or worsening relative to double-blind/open-label extension portion state. Since the TEAE time is not collected for the study, any AE

started or worsened on the first day of the long term extension period is considered a TEAE for the open-label extension period.

- Treatment duration (days) =

  Date of last dose of study drug – Date of first dose of study drug + 1

  For subjects who are missing the date of last study drug application, the last visit date will be used in the calculation of treatment duration.

- Study Drug Compliance (%) =

  (Total number of tablets taken during the treatment/Total number of tablets planned during the treatment) x 100%

  The total number of tablets taken will be calculated by subtracting the number of tablets returned from the number of tablets dispensed. The total number of tablets planned will be calculated by multiplying the total number of days of planned exposure to study drug by 2.

- Corticosteroid compliance (%) = amount (mg) of systemic corticosteroid prescription doses taken divided by amount (mg) of corticosteroid expected to be taken, as collected on the "Prednisone/Prednisolone Accountability" eCRF form.

6.1.9. Corticosteroid Dose Derivation for Efficacy Analyses

At screening, subjects will be prescribed required initial doses of oral corticosteroid (prednisone or prednisolone) at 0.5 mg/kg/day for newly diagnosed patients (diagnosed ≤6 months prior to Screening) with PDAI total activity score of ≥ 15, and 0.2 mg/kg/day for relapsing, chronic patients (diagnosed >6 months prior to Screening) with a PDAI total activity score of ≥9. Up-titration of CS during the screening period will be permitted if the starting dose had been insufficient to prevent worsening disease. During the treatment period, CS will be tapered once the subject reached End of Consolidated Phase (ECP) towards a goal of ≤5 mg/day by ≤Week 29. Once the 5 mg level is achieved, it will be kept at that level until the time of the primary endpoint at Week 37 is assessed. From Week 37, further tapering to 0 mg CS will be attempted in patients with CR unless medically contraindicated. Up-titration of CS will also be permitted during the treatment period in cases of worsening disease. Further details of the corticosteroid management plan can be found in Appendix 1 of the protocol.

[redacted]

[redacted]

6.1.10. GTI Scores

The Glucocorticoid Toxicity Index is a proprietary licensed instrument from Massachusetts General Hospital (Miloslavsky 2017). It was developed to assess glucocorticoid (GC)-related morbidity and GC-sparing ability of other therapies.

The GTI is composed of two components, the Composite GTI and the Specific List. The Composite GTI consists of nine domains (body mass index (BMI), glucose tolerance, blood pressure, lipid, bone mineral density, glucocorticoid-induced myopathy, skin toxicity, Neuropsychiatric toxicity, and infection) on common steroid-related adverse events anticipated to occur in ≥5% of patients treated in a clinical trial involving glucocorticoids. Note that for this study bone mineral density was not collected, and therefore not included in the derivation. The Specific List consists of 23 items (11 domains) that are mainly less common but serious adverse effects, serving as a complementary tool to the Composite GTI to ensure that all important elements of glucocorticoid toxicity were captured.

The domains of the Composite GTI and the specific list of the GTI will be assessed at Day 1, Week 13, Week 25, Week 37. The details on the derivations of baseline glucocorticoid toxicity score are provided in Appendix 2.

Domain-specific score for each patient at a visit is defined as the weight assigned based on the change in severity level as described for each domain in Appendix 3.

Composite GTI score for each patient at a visit is the sum of 8 domain-specific scores at each visit.

Cumulative GTI score is the sum of composite GTI score across visits. Two cumulative GTI scores, CWS and AIS, will be defined.

- **Cumulative worsening score (CWS)**

  CWS is designed to assess cumulative GC toxicity, regardless of whether the toxicity has lasting effects or is transient. New toxicities that occur are added, but toxicities that

appear to resolve on follow-up are not removed. Thus, the CWS serves as a lasting record of GC toxicity observed and can only increase or remain the same over time.

CWS will be lower in the treatment arm compared to the placebo arm at the end of trial, if the treatment is effective at decreasing GC toxicity over time.

- **Aggregate improvement score (AIS)**

  Patients are anticipated to have some GC toxicity at baseline, the AIS would be important in establishing that the new therapy is effective at diminishing any baseline GC toxicity over time. With the AIS, toxicities can be removed if improvement occurs, and added if worsening occurs.

  AIS decrease over time means that the treatment is effective in decreasing GC toxicity level, compared to placebo which may show fluctuation of CIS over time. Negative score reflects that toxicities present at baseline (or occurring during the trial) resolved over the treatment period.

The steps to calculate the CWS and AIS at Weeks 25 and 37 are described below.

Step 1: Calculate domain-specific worsening score (for computing CWS in Step 2) and improvement score (for computing AIS in Step 2) at each visit.

For Domains without sub-items (Body Weight, Glucose Metabolism, Blood Pressure, Lipid Metabolism, Steroid Myopathy),

a) For worsening score, only consider positive domain-specific score at each visit. For domain with a negative domain-specific score, the worsening score will be 0.

b) For improvement score, all domain-specific scores (could be positive or negative) at each visit will be considered.

The Skin and Neuropsychiatric domains both have sub-items. For the Skin domain, these are Acneiform Rash, Easy Bruising, Hirsutism, Atrophy/Striae, and Erosions/tears/ulcerations. For the Neuropsychiatric domain, these are Insomnia, Depression, Mania, and Cognitive Impairment.

a) For worsening score, only the item with the highest weight is scored for any GTI interval (typically three months) with the CWS. As an example, if neither insomnia nor depression were present at the baseline visit but there is now mild Insomnia and moderate depression present at follow-up, then only the moderate depression is scored (+63 points).

b) For improvement score, improvement as well as worsening can be recorded. Because it is conceivable that one item might improve while another worsens, the item of greatest improvement (highest absolute weight) and the item of greatest worsening (highest weight) are recorded for given GTI interval.

For Infection Domain, the worsening score and improvement score handle the scoring of infections differently, because the CWS and AIS reflect reciprocal measures of GC toxicity.

a) For worsening score, the most severe infection in every GTI interval is scored.

b) For improvement score, only the most severe infection occurring among Week 13, Week 25, and Week 37 is scored.

Step 2: Calculate composite worsening score and improvement score at each visit by summing the 8 domain-specific score.

a) For composite worsening score, sum the 8 domain-specific worsening scores.

b) For composite improvement score, sum the 8 domain-specific improvement scores.

Step 3: Calculate cumulative GTI scores by summing composite scores across visits.

a) For CWS at Week 37, summing composite GTI worsening score at Week13, Week 25 and Week 37.

b) For AIS at Week 37, summing composite GTI improvement score at Week 13, Week 25 and Week 37.

The detailed information for the derivation of Glucocorticoid Toxicity Index are presented in Appendix 3.

6.1.11. Data Adjustments/Handling/Conventions

All p-values will be displayed in four decimals and rounded using standard scientific notation (eg, 0.XXXX). If a p-value is less than 0.0001 occurs it will be shown in tables as <0.0001.

If a patient has both non missing screening value and re screening value for a parameter, then the re screening value will be used in the analyses as the screening value.

Adverse events will be coded using the MedDRA Version 24.0.

For CS medications recorded as concomitant medications on "Other Corticosteroid Concomitant Medications" eCRF form, partial end date recorded will be imputed to a date as late as possible based on the available partial date information, but no later than the date of last dose of study drug. This date imputation will be applied prior to implementation of the imputation method described in Section 6.1.5.2.

Other than the above CS dose end date imputation, no actual imputation of other medication start/end dates will be performed. If a medication start date or end date is missing or partially missing , and available information is not enough to determine whether CM was taken prior to first dose of study drug or only concomitantly with study drug, the CM will assumed to be both a prior and concomitant medication, and across as many treatment period as possible based on the available information. These data imputations are for categorization purpose only and will not be used in listings.

Missing or partial AE onset dates will be imputed so that if the partial date information is not sufficient enough to determine whether or not the AE started prior to first dose of study drug, the AE will be classified as treatment-emergent. However, if the question "Did this AE occur before the first dose of study drug?" in the AE eCRF form has the answer of "Yes", then the AE will be counted as pre-treatment AE instead of TEAE. If the partial date information is not sufficient enough to determine during which period the AE stared, the AE will be counted in the earlier period. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date of adverse event resolution.

7. Study Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

The number and percentage of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, and included in each population will be tabulated overall and by treatment group. The number of screened subjects will also be reported. This summary will be presented by trial Phase (Blinded Treatment Period, Open-Label Extension Period, and Long Term Extension separately). A summary of the number of patients enrolled, randomized, and treated at each site will also be produced.

Disposition and analysis population data will be listed. A listing of randomization codes and treatment values will also be provided.

7.2. Protocol Violations and Deviations

Protocol violations will be identified and finalized prior to database lock. The number and percentage of subjects with any important protocol deviations will be tabulated by treatment group and overall for the mITT population. Important protocol deviations will be further broken down by category. Subjects with one or more important deviations within each category will only be counted once.

All protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics variables will include age, sex, ethnicity, race, BMI, disease category, disease status (newly diagnosed/relapsing), Total PDAI Activity score, Total PDAI Activity Score category (<15, 15-45, ≥46), Total Anti-DSG1, Total Anti-DSG1 category (<100, ≥100), Total Anti-DSG, Total Anti-DSG category (<100, ≥100), and time since Pemphigus diagnosis (years). Summary statistics for demographic and baseline characteristics will be presented separately by treatment group as well as overall.

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

The number and percentage of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v24.0), will be tabulated by treatment group. Pemphigus procedure history will be presented separately from non-pemphigus medical history.

These analyses will be conducted for ITT population.

7.4. Exposure and Compliance

The following parameters will be summarized by treatment group for the safety population, and for blinded treatment period and open-label extension period:

- Treatment exposure
- Study drug compliance
- Corticosteroid compliance
- Number of times that CS was not returned during blinded and open-label periods,

Study exposure will also be summarized for long term extension period.

For subjects who are missing the date of last study drug administration, for any reason, the last study visit date will be used in the calculation of treatment duration, and exposure will be calculated up to that date. Study drug compliance will not be calculated for those subjects whose date of last study drug administration is unknown. The number and percentage of patients with compliance between 80% and 125% will be tabulated for both study drug and CS.

The compliance for CS is based on systemic prescription doses collected on "Prednisone/Prenisoline Accountability" eCRF form. CS doses collected as concomitant medications on "Other Corticosteroid Concomitant Medications" eCRF form are not included in the compliance calculations.

For the blinded period, CS doses collected from Day 1 until Week 37 Visit (until early termination visit for patients prematurely discontinued study prior to Week 37 visit) are included in the derivation. For open label extension period, CS doses collected from beginning of open label extension period until Week 61 Visit (until early termination visit for patients prematurely discontinued study during the open label extension period) are included in the derivation. For long term extension period, CS doses collected from beginning of long term extension period until Week 109 Visit (until early termination visit for patients prematurely discontinued study during the open label extension period) are included in the derivation.

8. Efficacy Analysis

A summary of the study endpoints and their corresponding analysis methods are presented in Table 6. Further details of each analysis are presented in the following sections.

Table 6: Efficacy Endpoints and Analysis Methods

	Endpoint	Analysis Method
Primary	Proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤ 10 mg/day	Cochran-Mantel-Haenszel test stratified by disease history (newly diagnosed or relapsing).
Secondary Endpoints (in hierarchy)	Cumulative CS dose from Baseline to Week 37	Analysis of covariance, with CS dose duration (in days) during the blinded treatment period time to study discontinuation as the covariate, with terms for treatment group, and disease history.
	Cumulative duration of CR with CS dose ≤ 10 mg/day from Baseline to Week 37 (days)	Zero-inflated negative binomial with terms for treatment group and disease history with an offset term based on the number of days on study during the Blinded Treatment Period
	Time (Days) to first CR with a dose of ≤ 10 mg/day from Baseline to Week 37	Log rank test stratified by disease history
	Proportion of patients with at least one disease flare/relapse from initial control of disease activity (CDA) to Week 37	Cochran-Mantel-Haenszel test stratified by disease history
	Cumulative duration of CR with CS dose ≤ 10 mg/day from Week 37 to Week 61 (days)	Zero-inflated negative binomial with terms for treatment group and disease history with an offset term based on the number of days on study during the Blinded and unblinded Treatment Period
	Cumulative duration of CR with CS dose = 0 mg/day from Week 37 to Week 61 (days)	Zero-inflated negative binomial with terms for treatment group and disease history with an offset term based on the number of days on study during the Blinded and unblinded Treatment Period

	Endpoint	Analysis Method
Secondary Endpoints (not in hierarchy, family-wise error rate not controlled)	The proportion of patients who are in CR from Week 29 to Week 37 with a CS dose of ≤ 5 mg/day	Cochran-Mantel-Haenszel test stratified by disease history
	The proportion of patients who have PDAI score < 3 from Week 29 to Week 37 with CS ≤10 mg/day	Cochran-Mantel-Haenszel test stratified by disease history
	Cumulative duration of CR with a CS dose of ≤ 10 mg/day (days) from Baseline to Week 61	Zero-inflated negative binomial with terms for treatment group and disease history with an offset term based on the number of days on study during the Open-Label Extension Period
	Cumulative duration of CR with a CS dose = 0 mg/day (days) from Baseline to Week 61	Zero-inflated negative binomial with terms for treatment group and disease history with an offset term based on the number of days on study during the Open-Label Extension Period
	GTI scores at Week 37	Analysis of covariance, with treatment, disease history as fixed effects, and baseline GTI score, baseline CS dose as covariates
	Change from Baseline in PDAI Score at Weeks 5, 13, 25, 37, and 61	MMRM with terms for treatment, week, baseline score, disease history, and treatment by week interaction
	Change from Baseline in ABQOL Score at Weeks 5, 13, 25, 37, and 61	MMRM with terms for treatment, week, baseline score, disease history, and treatment by week interaction
	Proportion of patients with ABQOL Score of zero at Weeks 5, 13, 25, 37, and 61	Cochran-Mantel-Haenszel test stratified by disease history at each visit
	Change from Baseline in EQ-5D-5L visual analog scale [VAS] results and individual dimension score categories at Weeks 5, 13, 25, 37 and 61	Continuous outcomes: MMRM with terms for treatment, week, baseline score, disease history, and treatment by week interaction. Categorical outcomes: Cochran-Mantel-Haenszel test stratified by disease history

	Endpoint	Analysis Method
	Time to first flare/relapse from initial CDA to Week 37	Log rank test stratified by disease history
	Time to first CR with a CS dose ≤ 10mg/day, from Baseline to Week 61	Log rank test stratified by disease history
	Proportion of patients with 3 or more lesions within 1 month or extension of established lesions that do not heal spontaneously within 1 week from Baseline to Week 37	Cochran-Mantel-Haenszel test stratified by disease history
	Total number of disease flares/relapses from initial CDA to Week 37	Zero-inflated negative binomial with terms for treatment group and disease history with an offset term based on the number of days on Post initial CDA

To ensure the overall type I error rate of $\alpha = 0.05$ will be maintained for the study, hierarchical testing, based on a fixed sequence procedure, will be used for the primary endpoint and continuing for the key secondary endpoints. The CMH primary analysis, as described in Section 8.1, will be the starting point for the hierarchical testing. If statistical significance is declared for the primary analysis, formal hypothesis testing will continue for the key secondary endpoints in sequence (see Section 6.1.3 for sequence of testing) until a non-significant result is reached. All other p-values from secondary and exploratory endpoints, after a non-significant p-value is reached, will be considered nominal. All statistical tests will be performed using two-tailed tests.

For Cochran-Mantel-Haensel tests, if stratum cell sizes are too small based on the Mantel-Fleiss criterion (Mantel, 1980) a Pearson Chi-square test will be used instead without stratification for disease history. If expected cell counts for the unstratified test are less than 5, a Fisher's Exact test will be used.

Analysis of covariance model residuals for the key secondary endpoint evaluated graphically for normality (e.g. quantile-quintile plot) and variance homogeneity (residual plots); additionally, a Kolmogorov-Smirnov test will be performed. A non-parametric will be considered appropriate if the two-sided p-value for the test is significant at the 0.01 level. If a parametric analysis is indicated, a rank analysis of covariance (Stokes, Davis, and Koch, 2000) will be used.

All analyses will be performed on the mITT Population as described in Section 5. Due to the small number of PF subjects expected to be enrolled in the study, the randomization strata of disease type (PV, PF) will not be included as a covariate in any of the analyses.

The analyses for efficacy endpoints involving clinical assessment CR in the blinded treatment period will be performed based on data collected on on-site visits (i.e., not including data collected from remote visits) as the primary analyses. Supportive analysis will be performed by using data collected from all visits including visits performed remotely.

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of patients who are in CR from Week 29 to Week 37 with a prednisone dose of ≤ 10 mg/day in patients treated with PRN1008 compared with placebo.

Allow p_0 to represent the proportion of responders in the placebo group; p_1 will represent the proportion of responders in the PRN1008 group. The null and alternative hypotheses are:

H_0: $p_1 - p_0 = 0$

The proportion of patients who are in CR from Week 29 to Week 37 with a prednisone dose of ≤ 10 mg/day does not differ between the two treatment groups.

H_1: $p_1 - p_0 \neq 0$

The proportion of patients who are in CR from Week 29 to Week 37 with a prednisone dose of ≤ 10 mg/day differs between the two treatment groups.

The primary endpoint will be analyzed using a CMH test, stratified by disease history. The observed number and proportion of subjects meeting the primary endpoint as well as the proportion difference (PRN1008 – placebo), estimated standard error (SE), 95% CI and the associated p-value will be reported.

Descriptive summaries of patients who are in CR with a CS dose of ≤ 10 mg/day will also be provided by visit through Week 37.

*These analyses will be performed on the mITT Population as well as in study subgroups as described in Section 6.1.3.2.*As a sensitivity analysis to the primary endpoint, disease type will be included as an additional stratification factor in the CMH test.

Tipping point analyses (Yan, 2009) will be done to investigate the impact of missing data and lost to follow-up (LTF). The tipping point analysis will look at all possible combination of converting missing data to a responder, starting at 0 and ending at all are responders. The cases where the statistical significance tips from significance to non-significance (defined as a two sided p-value > 0.05) will be listed. A complete list of all combinations will also be presented. If the imbalances that leads to a change in interpretation are clinically implausible then the results of the primary analysis will be deemed reliable.

In addition, the following endpoints will be analyzed as supportive analyses to primary endpoint:

- Time to first CDA from Baseline to Week 37
- Time to CR from Baseline to Week 37

8.2. Key Secondary Efficacy Analyses

The key secondary endpoint of Cumulative CS dose from baseline to Week 37, adjusted for time to study discontinuation will be calculated using the summation of the CS data as described in Section 6.1.9 and will be analyzed using an ANCOVA model with terms for treatment group and disease history. The estimated mean difference in cumulative CS usage (PRN1008 minus

placebo) and the associated 95% CI will be reported. Missing data for this endpoint is described in Section 6.1.5.2 . The "time to study discontinuation" covariate is up to study discontinuation, first Rituximab administration if any, or the end of the blinded treatment period whichever happens first.

If outliers or skewed data is present, sensitivity analysis will be conducted on this secondary endpoint of average weekly CS usage over 36 weeks in which the data will be rank-transformed prior to analysis.

Cumulative CS dose from Week 37 to Week 61 will be analyzed similarly.

Cumulative duration of CR with CS dose ≤10mg/day from Baseline to Week 37, will be based on a zero-inflated negative binomial model with terms for treatment group and disease history. The p-value and estimated treatment difference (parameter difference of PRN1008 minus placebo) from the negative binomial component will be reported, along with the 95% CI for the estimated parameter. The difference estimate will also be back-transformed (e.g. exponentiated) to demonstrate the relative difference in the number of pemphigus free days between treatment groups. Cumulative duration of CR with CS dose ≤10mg/day from Baseline to Week 37 will also be summarized based on descriptive statistics.

A Kaplan Meier analysis will be used to estimate the median and other quartiles for Time (Days) to first CR with a dose of ≤ 10 mg/day, along with two-sided 95% confidence intervals. The number of events and censored observations will be presented as well as graphical representations of estimated survival curves. A hazard ratio for treatment comparisons will be presented, along with its 95% confidence interval, based on a Cox regression model with terms for treatment group and disease history. The endpoint will be evaluated based on a p-value from a log-rank test stratified by disease history for treatment group comparison. In addition, a landmark analysis will be done at Week 37 in the key secondary analysis and at Week 61 for the other secondary analysis.

All key secondary endpoints will be analyzed based on the subgroups presented in Section 6.1.3.2.

8.3. Other Secondary Analyses

The following endpoints will be analyzed in a manner similar to that described for the primary endpoint in Section 8.1, with exception of the additional subgroup analyses described in Section 6.1.3.2:

- 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 CS ≤10 mg/day

Cumulative duration of CR with a CS dose ≤ 10 mg/day from Baseline to Week 61; cumulative duration of CR with a zero CS dose from Baseline to Week 61 and the cumulative duration of CR with a zero CS dose from Week 37 to Week 61 will be analyzed based on the same methods described for the cumulative duration of CR with CS dose ≤ 10mg/day from Baseline to Week 37.

Change from baseline to Weeks 5, 13, 25, 37, and 61 in PDAI will be analyzed using restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, week, baseline PDAI and treatment by week interaction. For the analysis of the differences at Weeks 5, 13, 25, and 37, only all data up to Week 37 will be included in the model. For the analyses of the difference at 61 weeks, only data collected during the Open-Label Extension Period will be included in the model (from Week 39 onward). A contrast will be written within the MMRM model to get each Week-specific treatment difference (least squares treatment means, treatment difference estimates and 95% CIs). ABQOL and EQ-5D-5L overall VAS scores will be analyzed similarly.

Descriptive summaries presenting the raw scores and change from baseline will be presented for ABQOL, PDAI, and EQ-5D-5L and EQ-5DVAS scores by treatment group at each study visit. Additionally, descriptive summaries for responses to the EQ-5D-5L dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression will be displayed as frequency counts by category and treatment group for each study visit (Week 37, as well as Weeks 5, 13, 25 and 61). Results will be analyzed using a CMH test, stratified by disease history. The observed number and proportion of subjects reporting No Problems, as well as the resulting Mantel-Haenszel risk difference (PRN1008 – placebo), estimated SE, 95% CI and the associated p-value will be reported. Descriptive summaries will be presented separately for the blinded treatment, open label, and long term extension periods of the study.

The proportion of patients with 3 or more lesions within 1 month or extension of established lesions that do not heal spontaneously within 1 week from Baseline to Week 37 will be analyzed using the same methodology as the primary endpoint as described in Section 8.1. The total number of disease flares/relapses from initial CDA to Week 37 will be analyzed based on the same methodology described for the cumulative duration of CR with CS dose ≤ 10mg/day from Baseline to Week 37 in Section 8.2.

A Kaplan Meier analysis will be used to estimate the median and other quartiles for Time to first flare/relapse from initial CDA to Week 37, along with two-sided 95% confidence intervals. The number of events and censored observations will be presented as well as graphical representations of estimated survival curves. A hazard ratio for treatment comparisons will be presented, along with its 95% confidence interval, based on a Cox regression model with terms for treatment group and disease history. The endpoint will be evaluated based on a p-value from a log-rank test stratified by disease history for treatment group comparison.

Descriptive statistics including number, mean, SD, SE, median, minimum, and maximum will be provided by treatment group and by visit for domain-specific GTI scores, composite GTI total score, CWS and AIS. For CWS and AIS at Week 37, analysis of covariance model with treatment, disease history as fixed effects, and baseline GTI score, baseline CS dose as covariates, will be used to test the difference of the least-square means (LS means) between the treatment groups. Difference in LS means and the corresponding 95% CI along with the p-value will be provided.

Proportion of patients with at least one disease flare/relapse from initial control of disease activity (CDA) to Week37 will be analyzed using the same methodology as the primary endpoint as described in Section 8.1.

Cumulative duration of CR with a CS dose ≤10 mg/day from Week 37 to Week 61, and cumulative duration of CR with a CS dose = 0 mg/day from Week 37 to Week 61 will be analyzed similarly to cumulative duration of CR with CS dose ≤ 10mg/day from Baseline to Week 37.

8.4. Exploratory Analyses

The number and percentage of patients with relapse after achievement of CR through Week 61 Yes/No) will be presented by treatment group. A similar summary will be presented for patients that reached CR with a zero CS dose by from Week 53 to Week 61 (Yes/No).

Observed values and changes from Baseline in Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) will be presented at each study visit based on summary statistics by treatment group. Descriptive summaries for the Open-Label and Long Term Extension periods will report data by treatment group in double-blinded portion and overall.

The total number of disease flares/relapses from initial Week 37 to Week 61 will be analyzed based on the same methodology described for the cumulative duration of CR with CS dose ≤10mg/day from Baseline to Week 37 in Section 8.2, using an offset term representing the time of patient participation in the Open-Label Treatment Period.

During the COVID-19 pandemic, measures to ensure continued drug supply and safety monitoring for patients were implemented. In-clinic study visits, as outlined in the protocol schedule of assessments, may be changed to a remote visit (e.g., telephone call, video call) as needed to address the COVID-19 restrictions. As a result, statistical analyses of efficacy endpoints involving CR assessment for the blinded treatment period will not include data collected from these remote visits. The incidence of remote visits and the corresponding reason for missing the onsite visits will be summarized by visit. Supportive analysis will be performed by including data collected remotely.

The analyses of the following endpoints will be documented and reported separately:

- 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
- the temporal relationship of change in PDAI with changes in quality of life and health economic variables.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported TEAEs, changes in clinical laboratory values, changes in vital signs and physical exam results. All safety analyses will be performed on the Safety population. All summaries of safety will be presented for the blinded treatment potion of the study separately from the open-label portion of the study. The long term extension period will also be separately reported. All safety and tolerability data summaries will be reported by treatment group in double-blinded portion and overall. No statistical tests will be performed for any of the safety assessments.

9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary version 24.0.

A TEAE is defined as any AE with an onset date/time on or after the first dose of study drug, having been absent pre-treatment or worsening relative to pre-treatment state. TEAEs will be broken down into Blinded Treatment Period TEAEs; Open-Label Extension Period TEAEs; and Long Term Extension TEAEs. A double-blind TEAE is defined as any TEAE with an onset date on or after the first dose of study drug and occurring before enrollment into the open-label portion of the study. TEAEs that are ongoing at the time of enrollment into the open-label portion are considered part of the double-blind portion of the study. An open-label TEAE is defined as any TEAE with an onset date on or after enrollment into the open-label portion of the study, having been absent during the double-blind portion or worsening relative to double-blind portion state. TEAEs for the long-term extension study will be determined similarly, based on the relative timing and severity of an event with respect to the end of the open-label period and start of the long term extension.

All summaries of TEAEs will be presented separately for the double-blind and open-label portions of the study for the Safety Population.

An overall summary of TEAEs will be presented including the total number of events, frequency counts, and percentages for:

- Any TEAEs
- Any treatment-related TEAEs
- Any TEAE leading to study discontinuation
- Any SAEs
- TEAEs resulting in death
- TEAEs by Grade (severity)
- Action Taken with Study Drug for all TEAEs (Study Drug Dose Not Changed, Study Drug Dose Interrupted, Study Drug Discontinued)
- TEAEs related to Corticosteroids

Summaries of the incidence of TEAEs and SAEs will be displayed by:

- SOC and PT
- SOC, PT, and maximum severity grade
- SOC, PT, and maximum causality (not related, related) to the study drug

In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once a preferred term. In the summaries showing severity and relationship to study medication the event with the maximum severity grade or strongest relationship (not related < related) will be reported. If an event is missing the severity, then severe will be used in the summary analyses (severity = severe); If an event is missing the relationship, then related

will be assumed for summary analyses (relationship = related). These data imputations are for categorization purpose only and will not be used in listings.

All TEAEs summarized by system organ class (SOC) and preferred term (PT) will be sorted in order of descending frequency of the SOC and then by descending frequency order (total across treatment groups) of the PT within each SOC.

In addition, summaries of TEAEs will be displayed by:

- SOC, HLGT, HLT and PT

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

9.1.1. Adverse Events Related to Corticosteroid Use

A summary of incidence rates (frequencies and percentages) of TEAEs related to CS use, SOC, and preferred term will be prepared for the Safety Population.

9.1.2. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by SOC, and preferred term will be prepared for the Safety Population.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.3. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented.

9.2. Clinical Laboratory Evaluations

Absolute values and changes from baseline will be summarized for clinical laboratory chemistry, hematology and coagulation results using descriptive statistics. The number of subjects with clinical laboratory values below, within, or above the normal range by time point will be tabulated for each clinical laboratory analyte. Shift tables for each clinical laboratory test will cross-tabulate the number of subjects with values below the laboratory reference range (low), values within the laboratory reference range (normal) or above the laboratory range (high) at baseline with the number of subjects with low, normal or high values at each post-baseline time point. Normal ranges and values outside the normal ranges will be identified by the central laboratory. A separate listing of out of normal range laboratory results will be provided.

A listing of all randomized subjects with pre-treatment and treatment-emergent laboratory values our of normal range will be presented.

Patients with positive urine pregnancy test results will be presented in by-subject listings.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, oral body temperature, body weight, height and BMI. Height will be presented at baseline only.

9.4. Physical Examinations

Abbreviated physical examinations will be summarized using descriptive statistics at Baseline and at each post-baseline time point. Shifts from Baseline will also be summarized.

Abnormal physical examination findings will be displayed in a by-subject listing.

9.5. Electrocardiograms

Descriptive summaries will be presented for ECG measures of PR interval, RR interval, QRS Duration interval, QTcF interval, and HR. These summaries will be presented by study visit.

Shift tables comparing baseline ECG investigator interpretation (normal; abnormal, not clinically significant; or abnormal, clinically significant) and unable to evaluate, to each study visit will be provided.

9.6. Prior and Concomitant Medication

Prior and concomitant medication use will be summarized descriptively using counts and percentages by ATC Class Level 2 and preferred term (ATC Class Level 5).

Prior medications will be presented separately from concomitant medications. Medications that started prior to Day 1 will be considered prior medications whether or not they were stopped prior to Day 1. Any medications continuing or starting after Day 1 will be considered to be concomitant. If a medication starts prior to Day 1 and continues after Day 1 it will be considered both prior and concomitant.

- Medications will be coded using the World Health Organization Drug Dictionary Version March 2021.

Medications will be summarized separately for non-corticosteroid medications and other corticosteroid (i.e. not Prednisone/Prednisolone) medications.

9.7. 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. Specifically,

- 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, will be summarized descriptively

in a manner similar to that described in Section 9.1.

- Average daily dose of CS from Week 61 to Week 113 will be summarized by treatment group in double-blinded portion and overall.
- Time to relapse from Week 61 (beginning of LTE) during the LTE will be summarized using Kaplan Meier estimates of the median and other quartiles along with two-sided 95% confidence intervals. The number of events and censored observations will be presented as well as graphical representations of estimated survival curves.

10. Changes from Planned Analysis

Not applicable.

11. Other Planned Analysis

11.1. Pharmacokinetic and Pharmacodynamic Analysis

Individual and group PK (PRN1008 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. Additional analyses may be described and reported separately.

11.2. Questionnaires and health economic Analysis

Analyses of the following two exploratory endpoints will be performed outside of CSR under the responsibility of the Health Economics Outcomes Research (HEOR) department of Sanofi.

- 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

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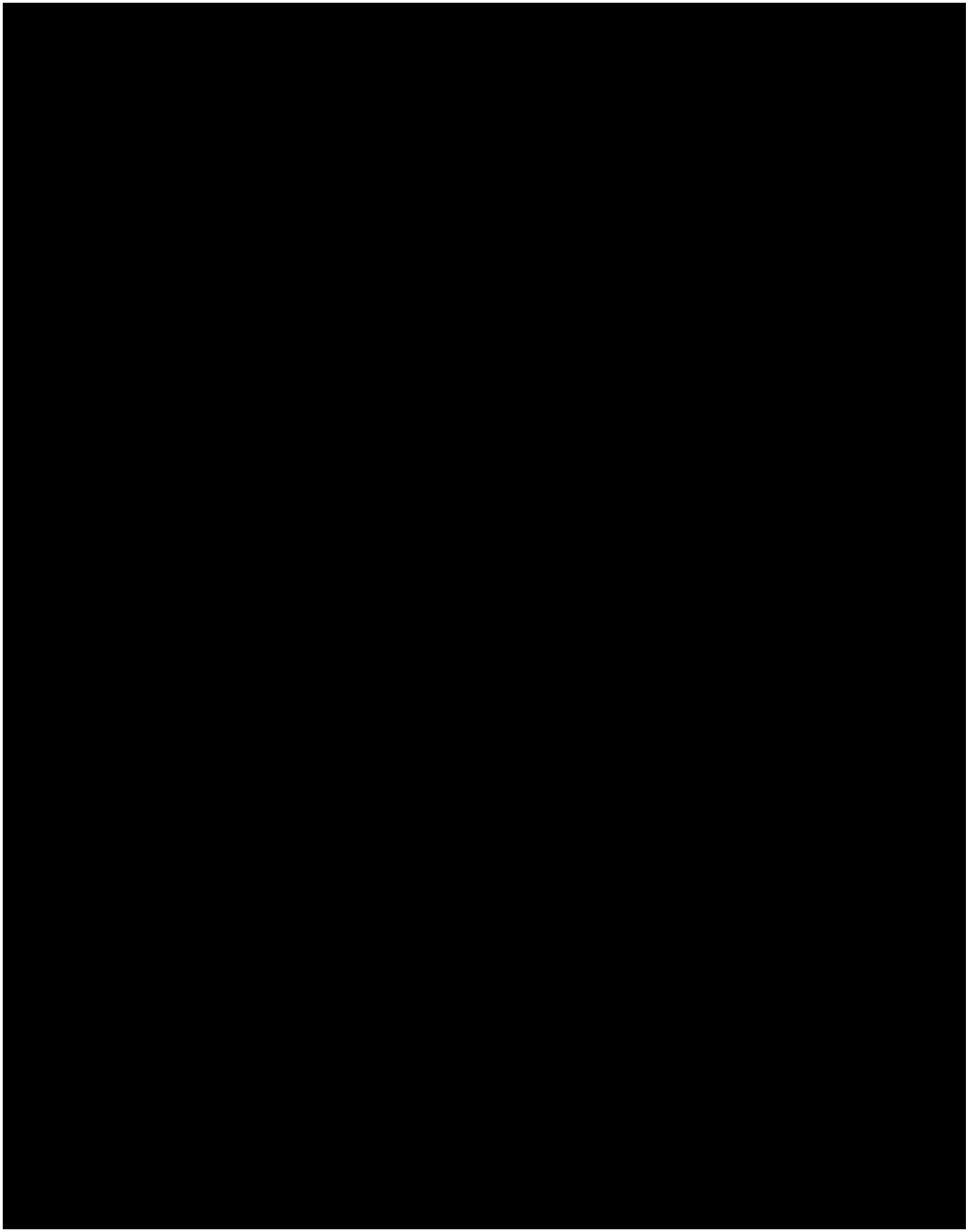
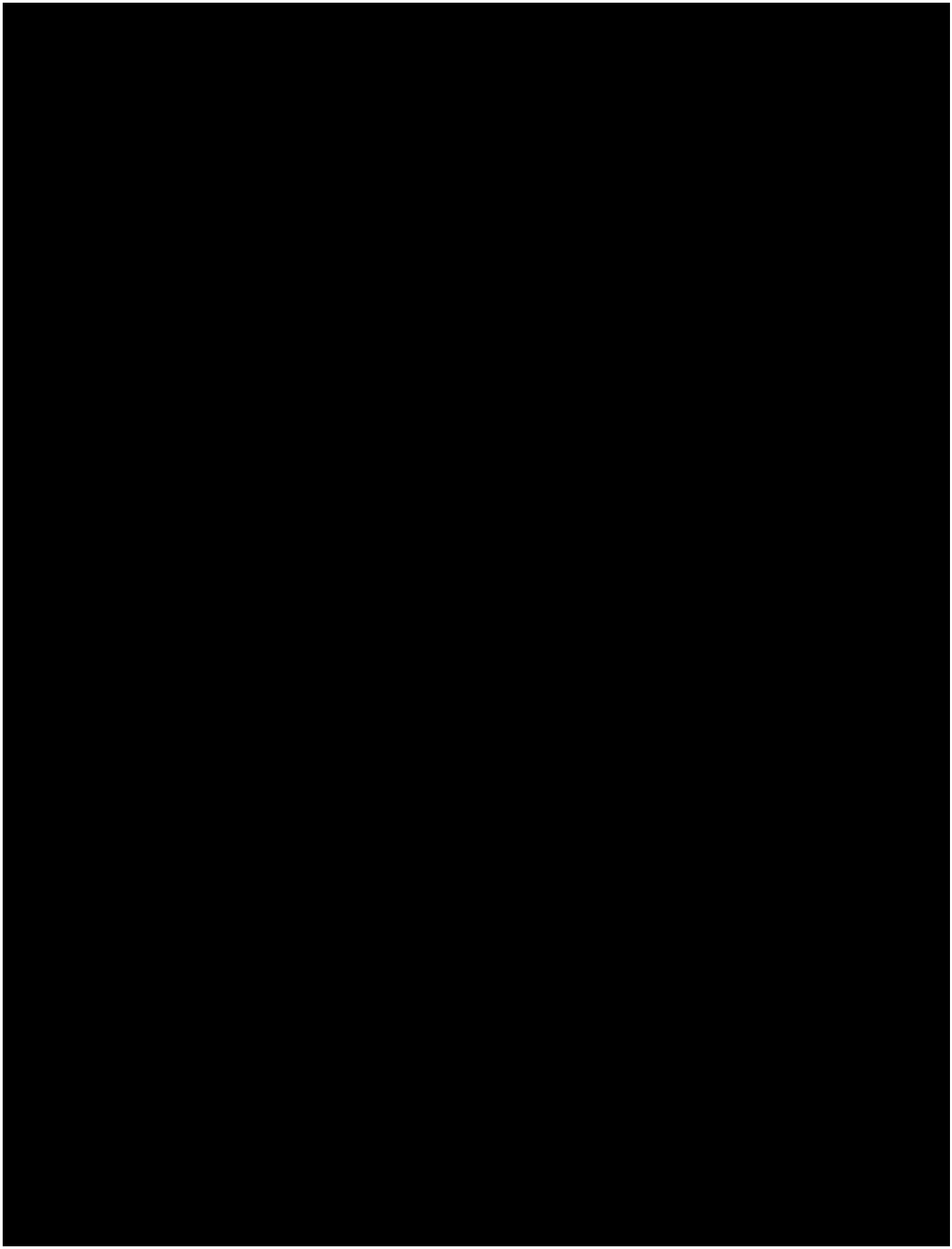
Appendix 1: Abbreviations

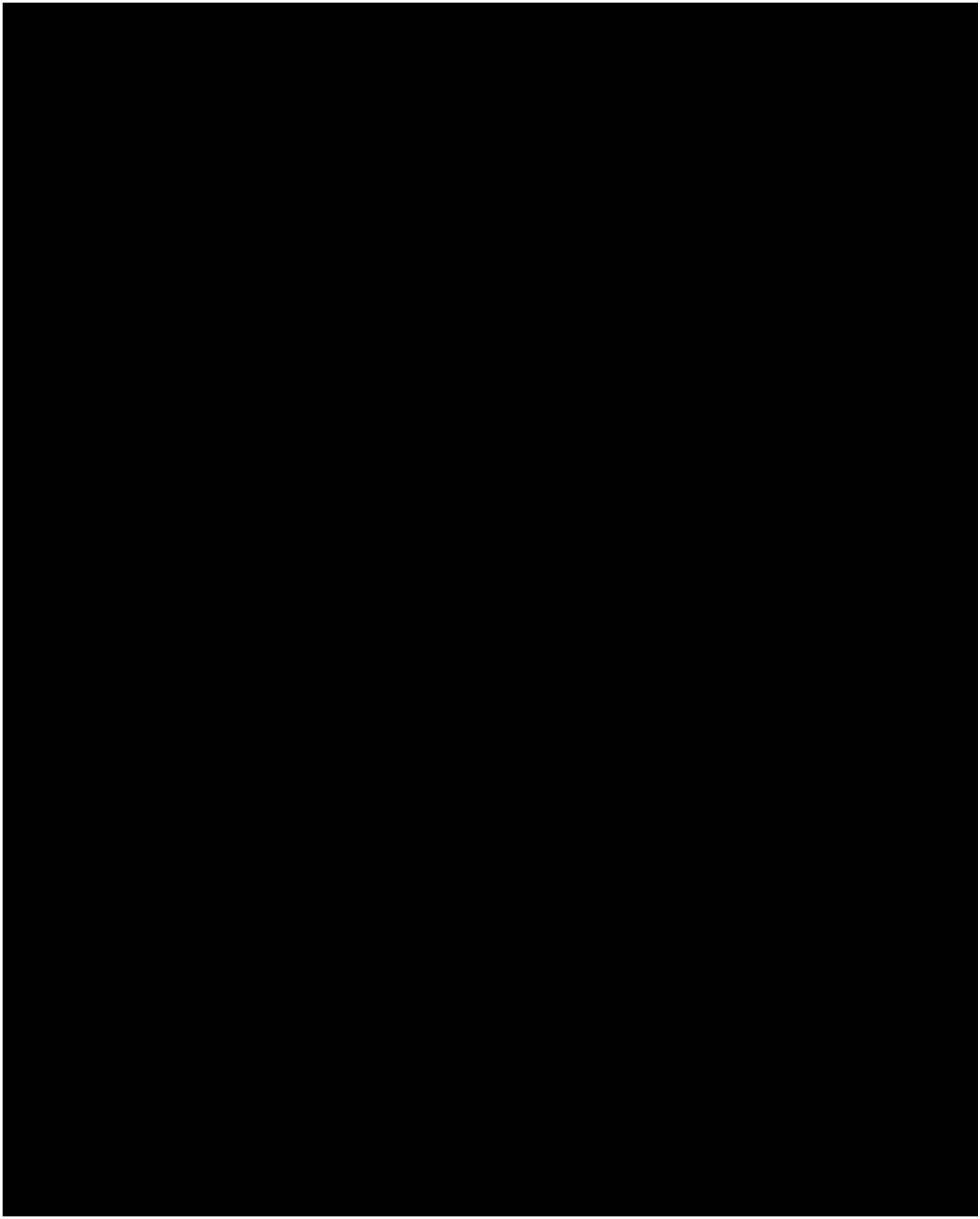
Abbreviation	Definition
ABQOL	Autoimmune Bullous Disease Quality of Life
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	asparate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
CDA	control of disease activity
CI	confidence intervals
CR	complete remission
CRF	case report form
CS	corticosteroid
CSR	clinical study report
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European medicines agency
FDA	food and drug administration
ICH	International Council for Harmonisation
IP	investigational product

Abbreviation	Definition
ITT	intent-to-treat
mITT	modified intent-to-treat
MMRM	mixed effect model repeat measurement
NA	not applicable
PD	pharmacodynamic
PDAI	Pemphigus disease area index
PF	Pemphigus foliacious
PK	pharmacokinetic
PT	preferred term
PV	Pemphigus vulgaris
SAE	serious adverse event
SAP	statistical analysis plan
SAF	safety population
SAS®	a software system used for data analysis
SD	standard deviation
SOC	system organ class
TABQOL	Treatment of Autoimmune Bullous Disease Quality of Life
TEAE	treatment-emergent adverse event

[redacted]







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