PRCL-PoC Statistical Analysis Plan

A Phase 2A Study To Evaluate Safety, Tolerability, and Efficacy of PRCL-02 In Patients With Moderate To Severe Chronic Plaque Psoriasis (Version 1 Final)

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PRCL-POC

A Phase 2a Study to Evaluate Safety, Tolerability, and Efficacy of PRCL-02 in Patients with Moderate to Severe Chronic Plaque Psoriasis

Version 1 Final

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Prepared for

PRCL Research Inc.
1255 Robert Bourassa, Suite 1610,
Montreal, Quebec, H3B 3X3, Canada

Prepared by

EMB Statistical Solutions, LLC
55 Corporate Woods
9300 West 110th Street, Suite 550
Overland Park, Kansas 66210

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ABBREVIATIONS/DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoS	End-of-Study
FU	Follow-up
ITT	Intent-to-Treat
IWRS	Interactive Web-Response System
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PASI 75	A 75% improvement from baseline in the Psoriasis Area and Severity Index
PASI 90	A 90% improvement from baseline in the Psoriasis Area and Severity Index
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Standard Data Tabulation Model
SOC	System Organ Class
sPGA	static Physician Global Assessment
TEAE	Treatment Emergent Adverse Event
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION AND OBJECTIVES

1.1. Introduction

Study PRCL-POC is a multicenter, randomized, double-blinded, placebo controlled, multiple oral dose parallel design study of PRCL-02 in patients with moderate to severe chronic plaque psoriasis. Clinical evaluations are at pre-treatment, and at Day 1, Weeks 1, 2, 4, 8, 12, 14, 16, 18, and 20 after randomization.

The purpose of this statistical analysis plan (SAP) is to describe the analysis variables and statistical procedures that will be used to analyze and report the results from PRCL-POC: "A Phase 2a Study to Evaluate Safety, Tolerability, and Efficacy of PRCL-02 in Patients with Moderate to Severe Chronic Plaque Psoriasis."

This SAP is based on the protocol PRCL-POC, which was approved on 16 July 2018.

Some of the analyses detailed here may be more explicit or in some aspects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the SAP.

The formats for the tables, listings, and figures described in this SAP are provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the clinical study report (CSR).

See the study protocol for details about the study design, procedures, and schedule of assessments and see the electronic case report form (eCRF) for details about variables collected and their possible values.

The time and events schedule for this study is provided in Section 10.

EMB Statistical Solutions, LLC will have responsibility for performing these analyses.

1.2. Study Objectives and Endpoints

The aim of this study is to evaluate safety, tolerability, and efficacy of PRCL-02 in patients with moderate to severe chronic plaque psoriasis. There will be three parallel treatment arms: 2 dose levels of PRCL-02 and a placebo arm. Patients will be randomized in 1:1:1 ratio to PRCL-02 Dose 1:PRCL-02 Dose 2:Placebo.

Table 1 shows the objectives and endpoints of the study.

Table 1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of PRCL-02 after 12 weeks of once daily oral dosing in patients with moderate to severe chronic plaque psoriasis	A 75% improvement from baseline to Week 12 in the PASI (PASI 75)
Secondary	
To evaluate the safety and tolerability of PRCL-02 after 12 weeks of once daily oral dosing in patients with moderate to severe chronic plaque psoriasis	Treatment emergent adverse events
To characterize the pharmacokinetics (PK) of PRCL-02 after multiple once daily oral dosing for 12 weeks, in patients with moderate to severe chronic plaque psoriasis	$AUC_{0-\tau}$, C_{max}, t_{max} at steady state
Exploratory	
To evaluate clinical response to PRCL-02 over time using the PASI and sPGA	• PASI • sPGA
To explore the PK/PD exposure-response relationships of PRCL-02	The relationship between PRCL-02 exposure and selected PD efficacy and/or safety measures

1.3. Sample Size Determination

Approximately 27 patients will be randomized to each of the 3 treatment arms for a total of 81 patients. The sample size was chosen so that there is at least 80% power to detect an increase in response of 30% or more for the primary objective (percentage of patients reaching a PASI 75 at week 12) in any PRCL-02 treatment arm relative to placebo using a one-sided Fisher's Exact test with a 10% type 1 error rate. This assumes a placebo response of 7.5% and PRCL-02 response of 37.5% in either PRCL-02 treatment arm for the primary end point, based on available clinical data from marketed injectable and oral targeted therapies for psoriasis. The sample size was calculated assuming a 10% drop out of patients in each arm and that drop-outs would be analyzed as non-responders.

2. GENERAL STATISTICAL METHODOLOGY AND CONVENTIONS

2.1. General Considerations

All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon

completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

Before implementation of parametric methods of analysis, the distribution of analysis variables will be examined to determine if model assumptions are satisfied. Transformations or nonparametric methods of analysis may be used if warranted. However, in some cases, nonparametric analysis may be the initially proposed method due to the expected distribution of response. Whenever alternative methods of analysis are required, the description of the new method along with the rationale for its use will be documented in the CSR.

The eCRF data for all patients will be provided in Standard Data Tabulation Model (SDTM) datasets. Data listings supplied as part of the CSR will be sorted by investigative site and patient identification number, and patients will be identified in the listings by the investigator number concatenated with the patient number.

2.2. Randomization and Unblinding Plan

This is a double-blind study; both patients and investigators will be blinded. Eligible patients will be 1:1:1 randomized to one of 3 arms (2 treatment and 1 placebo) within 28 days following screening. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign blister packs containing double-blind drug product to each patient. The IWRS system will be programmed using an adaptive allocation scheme to balance the treatment arms according to the following baseline measurements:

- weight (< 95kg and ≥ 95kg), and
- prior number of failed therapies (< 3 and ≥ 3).

To preserve the blinding of the study, no study personnel will see the randomization table and treatment assignments before database lock.

Emergency unblinding for AEs may be performed through the IWRS, or other means if necessary. Emergency unblinding may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment.

Unblinding will occur after the last patient completes the study and all data management activities have been completed (i.e. data entered, coding completed, and all queries resolved).

2.3. Analysis Populations

The analysis populations are described in Table 2.

Table 2. Analysis Populations

Population	Description
Randomized	All patients who sign informed consent and were randomized.
Safety	All randomized patients who take at least 1 dose of double-blind study treatment. In the event of a treatment error, patients will be analyzed according to the treatment they actually received.

Population	Description
Intent-to-Treat (ITT)	All randomized patients with moderate to severe chronic plaque psoriasis who take at least 1 dose of double blind study treatment and have at least the Week 1 post-baseline PASI assessment. In the event of a treatment error, patients will be analyzed according to the treatment to which they were randomized.
Pharmacokinetic	All randomized patients who take at least 1 dose of double blind study treatment and provide sufficient data for pharmacokinetic assessments.

2.4. Treatment Groups

This study involves 3 parallel treatment arms: PRCL-02 Dose 1, PRCL-02 Dose 2, and placebo. All patients will receive study drug, to be administered orally once daily, for 12 weeks. The planned active doses are:

Dose 1: Loading dose of 150 mg followed by a once daily maintenance dose of 25 mg, commencing on Day 2 and continuing for 12 weeks.

Dose 2: Loading dose of 300 mg followed by a once daily maintenance dose of 50 mg, commencing on Day 2 and continuing for 12 weeks.

Doses may be revised upwards or downwards based on new safety information and exposure data becoming available during the course of the study.

2.5. Definition of Baseline Assessments

Day 1 is defined in the protocol as the first day of Visit 2. The last assessment made on or before this date will be defined as the Baseline assessment. Adverse events that occurred on Day 1 will be assumed to be treatment-emergent, unless there is evidence to the contrary.

2.6. Definition of Study Visit

Patient data will be analyzed according to the nominal visit collected in the eCRF. Unscheduled visits at which safety data is collected (e.g. labs and ECGs) may result in clinically significant findings or withdrawal, which will be included in adverse event and/or disposition summaries.

2.7. Handling of Dropouts and Missing Data

Dates

Imputation of missing or partial dates is not expected, but if a complete date is required for calculations, the following algorithms will be applied:

- For the start date:
  - If year, month, and day are missing then use the minimum of the patient's first visit date or the consent date.
  - If either only month or month and day are missing then use January 1.
  - If only day is missing, impute the first day of the month.

- For the end date:
  - If year, month, and day are missing then use the patient's last visit date.
  - If either only month or month and day are missing then use December 31.
  - If only day is missing then use the last day of the month.
  - Do not expand the record past the patient's last visit.

The original missing or partial date, the imputed complete date, and the indicator variable that indicates which dates were imputed will be retained in the database.

PASI and sPGA Response

Patients whose response to treatment cannot be determined due to missing data (including early withdrawal) will be considered non-responders in the analyses.

2.8. Adjustment for Multiplicity

There are no planned adjustments for multiple efficacy endpoints or analyses.

2.9. Adjustment for Multiple Centers

Differences between study centers will be not be incorporated into the statistical analyses for this study. There are no plans to analyze data within centers.

2.10. Adjustment for Covariates

Efficacy analyses will adjust for the baseline value of the endpoint where possible. Exploratory analyses may be performed that adjust for the strata used in the randomization.

2.11. Subgroup Analyses

There are no planned subgroup analyses.

2.12. Coding of Concomitant Medications and Adverse Events

Adverse events (AEs) and conditions/procedures from the patients' medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). The versions of the dictionaries used for reporting will be provided in the CSR.

2.13. Computation of Questionnaire Scores

Psoriasis Area and Severity Index (PASI)

The PASI scores the severity of disease on a scale from 0 to 72 (where a score of 72 indicates extreme disease severity) by combining assessments of the extent of body surface involvement (A) in the head, trunk, arms, and legs together with the severity of desquamation (D), erythema (E), and plaque induration (I). Values for the extent of body surface involvement and severity are classified according to Table 3.

Table 3. PASI Scoring

Degree of Severity	**Value**
None	0
Slight	1
Moderate	2
Marked	3
Very Marked	4
Surface area involved	**Value**
None	0
< 10%	1
10-29%	2
30-49%	3
50-69%	4
70-89%	5
90-100%	6

The PASI subscore for each region is calculated as (D+E+I)*A. The Total PASI score is then calculated as 0.1*(Head Score) + 0.3*(Trunk Score) + 0.2*(Arms Score) + 0.4*(Legs Score).

The PASI subscores will not be computed if any element of the equation is missing. The total score will not be computed if any subscore is missing.

Static Physicians Global Assessment (sPGA)

The sPGA defines the severity of disease (an average of the investigator's perception of induration, erythema, and scaling) from clear (score=0) to severe (score=5). Patients were to enter the trial with at least a score of 3 at screening and at randomization; therefore, patients with a post-baseline score less than 3 will be considered responders.

3. INTERIM ANALYSES

No interim analyses are planned for this study.

4. PATIENT CHARACTERISTICS

4.1. Patient Disposition

The disposition of all randomized patients will be presented. The number of patients in each Analysis Population will be presented overall and by treatment group. In addition, the reason for treatment discontinuation and study discontinuation will be tabulated for the overall population and by treatment group using the list of reasons provided in the eCRF.

4.2. Protocol Violations

A list of protocol violations that could potentially impact the analysis of the study will be determined during the conduct of the study by study team members who are blinded to study treatment being received. The number and percentage of patients with each violation will be tabulated overall and by randomized treatment assignment.

4.3. Demographics and Baseline Assessments

Patient's baseline age, sex, race, height, body weight, body mass index, number of previously failed therapies, and baseline efficacy measures will be summarized using descriptive statistics by treatment arm and overall. These summaries will be based on the Safety population. Patients who are missing measurements of the baseline variable being analyzed will not be included in the summary for that variable.

For the purposes of the Clinical Trial Registry, a summary will be made by age categorized as 49 or younger, 50-64, 65-84, and 85 or older.

Patient height and weight will be collected prior to randomization. Both variables will be reported in metric units (height in cm and weight in kg) and will be summarized as continuous variables along with Body Mass Index (BMI; in kg/m^2).

No statistical testing will be performed for comparisons of baseline characteristics.

4.4. Concomitant Medications

Concomitant medications will be defined as medications taken on or after the date of first dose of randomly assigned study treatment. This includes all medications initially taken prior to the date of first dose of randomly assigned study medication but with a stop date that is either missing or after the date of first dose of randomly assigned study medication. Those medications where the stop date is documented as prior to the date of first dose of randomly assigned study medication will be classified as prior medications. The prior medications will not be included in any summary reports.

The number (percent) of patients who receive each concomitant medication, based on the WHODD preferred drug name, will be tabulated. By-patient listings of all concomitant medications, including WHODD preferred drug name, will be prepared.

5. EFFICACY ANALYSES

5.1. Primary Analysis

Efficacy endpoints will be assessed using the ITT population.

The primary treatment effect will be measured as the difference between each active treatment arm and placebo in the percentage of patients with a ≥ 75% improvement from baseline in PASI (PASI 75) at 12 weeks.

A one-sided Fisher's exact test with a 10% type 1 error rate will be used to compare each PRCL-02 treatment arm to placebo. Point estimates for the treatment differences (PRCL minus placebo) will be calculated using a lower 90% exact unconditional confidence interval.

Supporting Analysis of the Primary Endpoint

The primary treatment difference may be analyzed using only those patients with a Week 12 PASI assessment; that is, no imputation made for early withdrawal.

The primary treatment differences may be analyzed using a Cochran-Mantel-Haenszel test, adjusting for the four strata used in the randomization [weight (< 95kg and ≥ 95kg), and prior number of failed therapies (< 3 and ≥ 3)] if there are a sufficient number of patients in each cell.

5.2. Secondary Analyses

Safety/tolerability and PK analyses are described in Section 6 and Section 7, respectively.

5.3. Exploratory Analyses

The percentage of patients with a ≥ 90% improvement from baseline in PASI (PASI 90) at 12 weeks will be analyzed similarly to PASI 75. PASI 75 and PASI 90 will be summarized at each scheduled visit.

Observed values of the PASI score and subscores, the sPGA score, and the change and percent change from baseline to each scheduled visit will be summarized using descriptive statistics and the treatment groups compared using analysis of variance methods.

The quantitative secondary efficacy endpoints will be assessed by analyzing the change from baseline to the 12-week time point using PROC MIXED to model the difference in the Week 12 change from baseline score between treatment groups and to handle missing assessments. The change from baseline to each scheduled post-baseline visit will be estimated using repeated measures mixed models assuming data are missing at random, with covariates for baseline and visit. The lower 95% confidence limit of the difference in mean scores at Week 12 (PRCL minus Placebo) will be estimated from the mixed model. The effects of baseline scores and treatment will be allowed to vary across visits. The following example SAS code will be used, for assessments at Weeks 1, 2, 4, 8, and 12. For patients who withdraw prior to Week 12, data from the early termination visit will be used as the next visit's assessment; for example, if a patient's last scheduled assessment is at Week 4, the early termination data will be included in the analysis as Week 8.

```
proc mixed;
  class visit treatment patient;
  model endpoint=week*baseline week*treatment;
  repeated week / type=vc subject=patient;
  random patient;
run;
```

In addition, plots of each least squares mean (± standard error) for the scores by scheduled visit will be created

If the data appear non-Normal or if a reasonable variance-covariance structure cannot be fit to the data, the treatment comparisons will be made using Wilcoxon Rank-Sum tests at each visit using the observed data.

6. SAFETY ANALYSES

All analyses of safety including the extent of exposure to study medication will be performed using the Safety population.

No statistical testing will be performed for comparisons of safety endpoints.

6.1. Study Medication Exposure and Treatment Compliance

Extent of Exposure

Time on study will be derived for each patient as:

- Time on study = Date of last visit – Date of randomization + 1.

The extent of exposure to study drug will be derived for each patient as:

- Extent of exposure = Date of last dose of study drug – Date of 1st dose of study drug + 1.

Time on study and extent of exposure will be descriptively summarized for each treatment sequence and treatment arm.

Treatment Compliance

Patient compliance with study drug will be assessed at each visit. Compliance will be assessed by counting returned tablets. The patient will be considered significantly noncompliant if he or she takes < 80% or > 120% of the dispensed tablets. Deviations from the prescribed dosage regimen should be recorded.

Treatment compliance will be calculated for each treatment phase using the formula:

- Treatment Compliance =100 ((number of capsules received)/(number of capsules intended)).

The total number of tablets intended is equal to the number of days the patient spent in the treatment phase.

Treatment compliance will be descriptively summarized for each treatment arm.

6.2. Adverse Events

Summaries of AEs will include the number of patients with at least one AE for each treatment group. When reporting by system organ class (SOC) and preferred term (PT), the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence overall. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT.

Summaries of AEs will include the number of patients with at least one AE for each treatment group. When reporting by system organ class (SOC) and preferred term (PT), the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence overall. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT.

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAE) include all adverse events that emerge or worsen after taking the first dose of study drug. TEAEs will be summarized for each treatment group by SOC and PT, and by PT in order of decreasing frequency of preferred term.

Serious Adverse Events

Treatment-Emergent SAEs will be summarized for each treatment arm by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.

Treatment-Emergent Adverse Events Resulting in Death

If there are any TEAEs that result in death, a listing of all deaths will be provided. In addition, a summary table may also be created by PT in order of decreasing frequency of preferred term.

Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

TEAEs for which the action taken with medication is 'Drug Withdrawal' will be identified as TEAEs that lead to study drug discontinuation. The TEAEs that lead to study drug discontinuation will be summarized for each treatment group by SOC and PT for the Safety population. A by-patient listing of the TEAEs that lead to study drug discontinuation will also be provided.

Treatment-Related Treatment-Emergent Adverse Events

Every AE will be assessed by the investigator for its relationship to the randomly assigned study medication. The subset of TEAEs considered by the investigator as either possibly, probably, or definitely related to study treatment will be summarized as drug-related TEAEs by SOC and PT.

Treatment-Emergent Adverse Events by Maximal Severity

Every AE will be graded by the investigator as mild, moderate, or severe, so for each patient the greatest severity observed can be obtained by comparing the severity of all of a patient's TEAEs that share the same SOC or PT. A table of TEAEs by maximal severity will be prepared for each treatment arm by SOC and PT.

Treatment-Emergent (Not Including Serious) Adverse Events

The most common non-serious TEAEs will be summarized. All PT that occur in at least 5% of the Safety Population patients in any treatment group, when not counting the serious TEAEs, will be tabulated by SOC and PT for each treatment group. These reports will also present the total number of TEAEs for each SOC and PT.

6.3. Clinical Laboratory Analyses

Blood samples for hematology and clinical chemistry and urine samples for urinalysis will be collected. Profiles for the hematology, clinical chemistry and the numeric urinalysis parameters will be summarized, and extreme values for select parameters during the on-treatment period during the study will be summarized.

6.3.1. Clinical laboratory assessments over time

Change from baseline for each of the hematology, clinical chemistry and the numeric urinalysis parameters will be derived for each of the post-dose time points using the pre-dose measurement as the baseline. Descriptive statistics for the measurement at baseline and the measurement and change from baseline at each post-dose time point will be tabulated.

6.3.2. Clinical laboratory shift tables

Each laboratory parameter will be classified as low, normal or high relative to the central laboratory's normal range. For each treatment group shift tables will be generated from the pre-dose category to the category post-dose for each laboratory parameter. The shift tables will present the number (percent) of patients who started in a category (low, normal, high) at baseline and ended in a category at the end of the study. A missing category will be included for both pre-dose and post-dose, so that all patients in the Safety population will be represented in the table. The percentages will be calculated using number of patients in the Safety population who have measurements at pre-dose and post-dose.

Shift tables comparing pre-dose to the other time points in the study may be generated if warranted after data review.

Similar shift tables for the categorical urinalysis parameter will also be produced using all categories reported for a parameter during the study.

6.4. Vital Signs and Weight

Extreme vital signs will be determined using the following criteria:

- Pulse rate either < 50 bpm or > 100 bpm,
- Systolic blood pressure either ≤ 90 mmHg or ≥ 160 mmHg,
- Diastolic blood pressure either ≤ 50 mmHg or ≥ 100 mmHg.

The number (percent) of patients having extreme vital signs will be tabulated by treatment group at each scheduled visit. The percentage will be calculated using the number of patients in the Safety population with data at each visit as the denominator. The number (percent) of patients having extreme vital signs post-baseline (including unscheduled assessments) will be calculated.

Change from baseline statistics will also be defined for the measurements of blood pressure, pulse rate and temperature using the pre-dose values as baseline. Descriptive statistics for the measurement of temperature will also be provided by treatment group.

All patients who have an extreme vital sign value will be documented in a by-patient listing. The listing will include all of the vital sign measurements from the study for the patient, and the noteworthy values will be flagged.

6.5. Electrocardiograms

At each time point, the change from baseline will be derived for each numeric parameter using the pre-dose value as baseline. Descriptive statistics for the value of each parameter at each time point and the change from baseline for each parameter at each post-dose time point will be provided by treatment group.

The number (percent) of patients who either had an abnormal ECG (regardless whether clinically significant or not) or had an extreme QTc value at any time while on-treatment will be tabulated by treatment group. Extreme QTc values will be determined using the following criteria:

- QTc ≥ 500 msec
- QTc ≥ 550 msec
- Change from baseline in QTc ≥ 30 msec
- Change from baseline in QTc ≥ 60 msec.

All on-treatment values, including unscheduled assessments, will be considered.

6.6. Other Safety Analyses

Results of physical exams will be included in listings but not summarized.

7. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Pre-dose samples are to be obtained at 1 week, 2 weeks, 4 weeks and 8 weeks after the first dose of study drug. On the last day of dosing (Day 85/Week 12), the following samples are to be collected: pre-dose and 1, 2, 4, 8, 24 (Day 86), 72 hr (Day 88), and 168 hr (1 week; Day 92) post dose. One sample should be taken at the EOS visit (at least 6 weeks after the last dose [Week 18]). One sample should be taken at the early termination visit, if applicable.

Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. PK parameters such as the maximum concentration (Cmax,ss), time of maximum concentration (Tmax,ss), area under the concentration versus time curve within a dosing interval (AUC0-τ,ss), the first-order terminal elimination rate constant (λz), the terminal elimination half-life (t1/2), apparent clearance (CL/F), and apparent volume of distribution (Vd/F) will be reported. Other parameters may be calculated as deemed appropriate. Mean and individual PRCL-02 plasma concentration-time curves will be represented graphically.

Note that for all PK parameters but Tmax, summary statistics will include geometric mean and geometric CV%. Tmax will be reported as median and range (minimum to maximum).

The PK/PD relationship of PRCL-02 with PD, efficacy, and/or safety measures may be explored.

8. REPORTING CONVENTIONS

This section details the general conventions to be used for the statistical analyses. Departures from these general conventions will be provided in the specific detailed sections of this analysis plan. The following conventions will be applied to all data presentations and analyses:

- Quantitative variables will generally be summarized by the number of patients, mean, standard deviation, median, minimum, and maximum.
- Categorical variables will be summarized by the number and percentage of patients within each category.
- All mean and median values will be formatted to one more decimal place than the measured value.

- Standard deviation values will be formatted to two more decimal places than the measured value.
- Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- The number and percent of responses will be presented in the form XX (XX %), where the percentage is in parentheses. Percentages will be rounded to the nearest percent. In the case of a frequency of zero, the frequency and percentage will be presented as 0 rather than 0 (0%).
- All summary tables will include the analysis population sample size (i.e. number of patients) in each treatment group.
- Date variables will be formatted as ddMMMYYYY for presentation.

For PK data, the geometric coefficient of variation will be calculated assuming the data follow a log-Normal distribution. That is, let X = concentration.

If Y = log[X] has a Normal distribution with

$E[Y] = \mu$ and $Var[Y] = \sigma^2$,

then X has a log-Normal distribution with

$$E[X] = \exp[\mu + .5*\sigma^2] = \exp[\mu]*\exp[.5*\sigma^2]$$

and

$$Var[X] = \exp[2\mu + 2*\sigma^2] - \exp[2\mu + \sigma^2] = \exp[2\mu]*\exp[\sigma^2]*(\exp[\sigma^2] - 1)$$

so

$$SD[X] = \exp[\mu]*\exp[.5*\sigma^2]*\text{sqrt}(\exp[\sigma^2] - 1)$$

Therefore, $CV[X] = SD[X]/E[X] = \text{sqrt}(\exp[\sigma^2] - 1)$. The log-transformed concentration values will be computed and the coefficient of variation calculated using the sample variance.

9. SCHEDULE OF ASSESSMENTS

Procedure	**Screening**									**FU**	**EoS**
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Days	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**99**	**113**	**127**	**141**
Window Period (Days)		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
Week	**-**	**-**	**1**	**2**	**4**	**8**	**12**	**14**	**16**	**18**	**20**
Informed consent	X										
Demographics	X										
Medical history	X										
Inclusion and exclusion criteria	X	X									
Pregnancy test (♀)	X	X	X	X	X	X	X	X	X	X	
Serum FSH (PMP ♀)	X										
QuantiFERON TB Test	X										
HIV/hepatitis screen	X										
Randomization		X									
Study drug dispensing		X	X	X	X	X					
Study drug accountability			X	X	X	X	X				X if ET
Safety Evaluations											
Physical examination	X	X	X	X	X	X	X				X
Height/weight	X	X	X	X	X	X	X				X
Vital signs (pulse and BP)	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X				X
Clinical laboratory tests	X	X	X	X	X	X	X				X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Efficacy and Other Evaluations											
PASI	X	X	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X	X	X
PK sampling			X	X	X	X	X	X	X	X	X
Plasma sample collection for PGx assessments		X									

See protocol for footnotes.