PRCL-PoC Protocol (Amendment 1)

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

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PROTOCOL PRCL-POC
A PHASE 2A STUDY TO EVALUATE SAFETY, TOLERABILITY, AND EFFICACY OF PRCL-02 IN PATIENTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

PRCL-02

Version: Amendment 1

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

PROTOCOL HISTORY

Date	Version	Description/summary of changes
28-Jun-2018	Final	Original protocol
16-Jul-2018	Amendment I	Changes were made following feedback from IRB. Text was added to Section 6.3 to indicate that male patients should avoid donating sperm while participating in this trial and for 4 months after stopping the study treatment. Text was added to Section 8.2 to indicate that patients must withdraw from the study if they become pregnant. Text was added to Appendix 2. Follicle Stimulating Hormone is now included in the Clinical Laboratory Tests, as this test may be used for assessment of patient eligibility for the study.

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1. Synopsis

Title of Study:
A Phase 2a study to evaluate safety, tolerability, and efficacy of PRCL-02 in patients with moderate to severe chronic plaque psoriasis.

Rationale:
The aim of this study is to evaluate safety, tolerability, and efficacy of PRCL-02 in patients with moderate to severe chronic plaque psoriasis.

Objective(s)/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 may be explored

Abbreviations: $AUC_{0-\tau}$ = area under the concentration versus time curve from time zero to one dosing interval (24 hrs); C_{max} = maximum observed drug concentration; PASI = Psoriasis Area and Severity Index; PD = pharmacodynamics; PK = pharmacokinetics; sPGA = static physician's global assessment; t_{max} = time to reach maximum observed drug concentration.

Summary of Study Design:

This will be 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.

Eligble patients will be randomized to one of 3 arms (2 treatment and 1 placebo) within 28 days following screening. Clinical evaluations are at Day 1, weeks 1, 2, 4, 8, 12, 14, 16, 18 and 20 after randomization.

Efficacy and safety assessments will be performed at each of the study visits. Pre-dose blood samples will be collected between Week 1 and Week 8 to assess achievement of steady state PK, and pre- and post-dose serial samples will be collected at Week 12, 14, 16, 18 and 20 to evaluate steady state PK profile of PRCL-02.

Treatment Arms and Duration:

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. Study drug will be administered orally once daily for 12 weeks. A loading dose will be implemented for all treatment arms. The highest loading and maintenance doses will not exceed the maximum loading and maintenance doses administered in Part C of the previous study (SMAD) (300 mg amd 54 QD respectively).

The planned 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.

Number of Patients:

Approximately 27 patients will be targeted for enrollment in each of the 3 arms of the study (total of approximately 81 patients).

Statistical Analysis:

Efficacy: Efficacy analyses will be conducted on the Intent-to-Treat analysis set. The primary analysis will be conducted using a 1-sided, Fisher's exact test with a 10% type 1 error rate.

Safety: Safety analyses will be conducted on the Safety analysis set. Safety parameters that will be assessed include: adverse events, clinical laboratory parameters, vital signs, electrocardiogram parameters, and physical examination. The parameters will be listed and summarized using standard descriptive statistics.

Pharmacokinetics/Pharmacodynamics: Plasma PRCL-02 PK parameters after multiple dose administration will be calculated using noncompartmental methods. Pharmacokinetic parameters

will be summarized by dose level using descriptive statistics. Mean and individual PRCL-02 plasma concentration-time curves will be represented graphically.

The PK/PD relationship between PRCL-02 exposure and PD efficacy and/or safety measures may be explored.

2. Schedule of Activities

Table PRCL 1 Schedule of Activities

Procedure	Screening[a]									FU	EoS[b]
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 (♀)[c]	X	X	X	X	X	X	X	X	X	X	
Serum FSH (PMP ♀)	X										
QuantiFERON TB Test[d]	X										
HIV/hepatitis screen	X										
Randomization		X									
Study drug dispensing[e]		X	X	X	X	X					
Study drug accountability			X	X	X	X	X				X if ET
Safety Evaluations											
Physical examination[f]	X	X	X	X	X	X	X				X
Height/weight[g]	X	X	X	X	X	X	X				X
Vital signs (pulse and BP)[h]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[i]	X	X	X	X	X	X	X				X
Clinical laboratory tests[j]	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[k]			X	X	X	X	X	X	X	X	X
Plasma sample collection for PGx assessments		X									

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; EoS = end-of-study; FSH = follicle stimulating hormone; FU = Follow-up; HIV = human immunodeficiency virus; PGx = pharmacogenomics; PK = pharmacokinetics; PMP = postmenopausal; S = screening; sPGA = static physician's global assessment; TB = tuberculosis.

[a] Randomization will be within 28 days following the screening visit.

[b] In the event of early or premature discontinuation, a patient should undergo all activities per the EoS visit.

[c] Serum pregnancy test at Screening and urine pregnancy test at subsequent visits.

[d] If the result of the QuantiFERON®-TB Gold test is positive, the patient will be excluded from the study. If result is indeterminate, a single re-test will be allowed. If the result of the second test is positive or still indeterminate, the patient will be excluded from the study. Patients who have been vaccinated with BCG at any time in the past do NOT need to undergo testing. Documentation of previous vaccination is required.

[e] On days when there is pre-dose PK sampling (at 1 week, 2 weeks, 4 weeks, 8 weeks and 12 weeks after the first dose), the dosing will be at the site after pre-dose sampling (patients will be instructed to not dose at home). The patients will be required to bring to the CRU their study treatment kit with all unused tablets. On all other days, patients should take their medication at approximately the same time in the morning. It is recommended (but not required) that the dose should be taken with food.

[f] A full physical examination will be conducted at screening and on Week 4. Physical examination must include evaluation of the skin and mucus membranes. A physical examination may be performed at other visits at the investigator's discretion.

[g] Height at screening visit only.

[h] Single BP readings and other vital signs (in a seated position) on Day 1 and subsequent visits.

[i] Singe 12-lead ECG readings (in supine position, for at least 5 minutes prior to the ECG reading). The screening ECG may be repeated at the investigator's discretion. When scheduled at the same time, the following order of procedures is recommended: ECGs, vital signs, and blood collection (and/or other study procedures).

[j] Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

[k] Pre-dose samples are to be obtained at 1 week, 2 weeks, 4 weeks and 8 weeks 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 hr post last dose. One sample will also be collected on weeks 2, 4, 6 and 8 weeks post last dose. One sample should be taken at the early termination visit, if applicable. Timing of PK sample collection may be adjusted based on clinical needs. Actual sampling dates and times must be accurately recorded.

3. Introduction

3.1. Study Rationale

The aim of this study is to evaluate the safety, tolerability, and efficacy of PRCL-02 in patients with moderate to severe chronic plaque psoriasis. The study will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements.

3.2. Background

Psoriasis is one of the most common immune-mediated chronic inflammatory skin diseases, affecting about 2- 3% of the world's population. The most common variant is plaque psoriasis (psoriasis vulgaris), which affects most patients with the disease (Nestle et al. 2009; Perera et al. 2012). Psoriasis is associated with a high degree of morbidity; patients have a decreased quality of life (Rapp et al. 1999; Kimball et al. 2008; Lewis-Beck et al. 2013).

Activated T lymphocytes and several of the cytokines they produce are key drivers of pathogenesis in psoriasis. This is supported by the efficacy of several non-biologic (e.g. cyclosporine, Janus kinase inhibitors) and biologic (IL-12/23, IL-17 and TNFα inhibitors) drugs used clinically for treatment of this condition. Current approved treatment options for psoriasis include phototherapy, topical treatments, nonbiologic systemic immune modulators and biologic agents that target various functions of T cells and proinflammatory cytokines. Mild, localized psoriasis is typically treated with topical therapy while more extensive, severe disease often requires systemic, expensive, and potentially harmful treatments. There remains a need for effective treatment options that have superior long-term safety profiles to the current nonbiologic systemic treatments and with a convenient dosing regimen.

Cytoplasmic calcium (Ca^{2+}) is an important second messenger in mediating fundamental biological processes in cells (Tian et al. 2016). The Ca^{2+} release-activated Ca^{2+} (CRAC) channel is composed of two key components, STIM (STIM1 and STIM2) (Liou et al. 2005; Zhang et al. 2015) and ORAI or CRACM (ORAI1, 2 and 3; or CRACM1, 2 and 3) (Mignen 2008), with the combination of STIM1/CRACM1 prevailing in most cells and thus best characterized. Antigen stimulation of immune cells triggers Ca^{2+} entry through CRAC channels, promoting the immune response to pathogens by activating the calcineurin-NFAT signaling axis that is targeted by traditional calcineurin inhibitors, such as cyclosporine A and tacrolimus. Recent findings indicated that therapies specifically targeting CRAC channels may serve as improved immunomodulators with high selectivity and low toxicity compared with currently approved immunosuppressive agents.

PRCL-02 is a selective, potent CRACM1 inhibitor which has demonstrated inhibition of T and B cell activation, without any demonstrable effect on other immune cells, and with acceptable safety and tolerability in rats and cynomolgus monkeys after daily oral dosing up to 3 months. Due to the prominent role of T cells in psoriasis, treatment with PRCL-02 in plaque psoriasis is expected to provide clinical benefit with convenient dosing and an attractive safety profile.

3.3. Benefit/Risk Assessment

Based on PRCL-02 nonclinical and preliminary clinical data, there are no anticipated risks requiring monitoring beyond those included in the protocol. No clinically significant safety or tolerability concerns have been identified in the previous study (PRCL-SMAD) which included healthy volunteers given up to 86 mg (single dose) and 54 mg (multiple doses, after a loading dose of 300 mg) for 5 days, or in psoriasis patients who received up to 54 mg (multiple doses, after a loading dose of 300 mg) for 28 days.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of PRCL-02 can be found in the Investigator's Brochure (IB; PRCL-02 2018).

4. Objectives and Endpoints

Table PRCL 2 shows the objectives and endpoints of the study.

Table PRCL 2 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 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 PASI (Fredriksson and Pettersson 1978) and sPGA (Chaudhari et al. 2001)	• PASI • sPGA
• To characterize the PK/PD exposure-response relationships of PRCL-02	• The PK/PD relationship of PRCL-02 exposure and PD efficacy and/or safety measures may be explored

Abbreviations: $AUC_{0-\tau}$ = area under the concentration versus time curve from time zero to one dosing interval (24 hrs); C_{max} = maximum observed drug concentration; PASI = Psoriasis Area and Severity Index; PD = pharmacodynamics; PK = pharmacokinetic; sPGA = static physician's global assessment; t_{max} = time to reach maximum observed drug concentration.

5. Study Design

5.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel design Phase 2a study in patients with moderate to severe chronic plaque psoriasis.

Screening (up to 28 days prior to first dose of study drug) allows for evaluation of inclusion and exclusion criteria. Following Screening, all eligible patients will be randomly assigned (in 1:1:1 ratio) to PRCL-02 Dose 1, PRCL-02 Dose 2, or placebo and will receive study drug for 12 weeks. Following completion of 12-week treatment, all patients will attend Follow-Up Visits at 2, 4, 6 and 8 weeks after the last dose of study drug.

Efficacy and safety assessments will be performed as defined in the Schedule of Activities (Section 2).

Figure PRCL 1 illustrates the study design.

Study governance considerations are described in detail in Appendix 3.

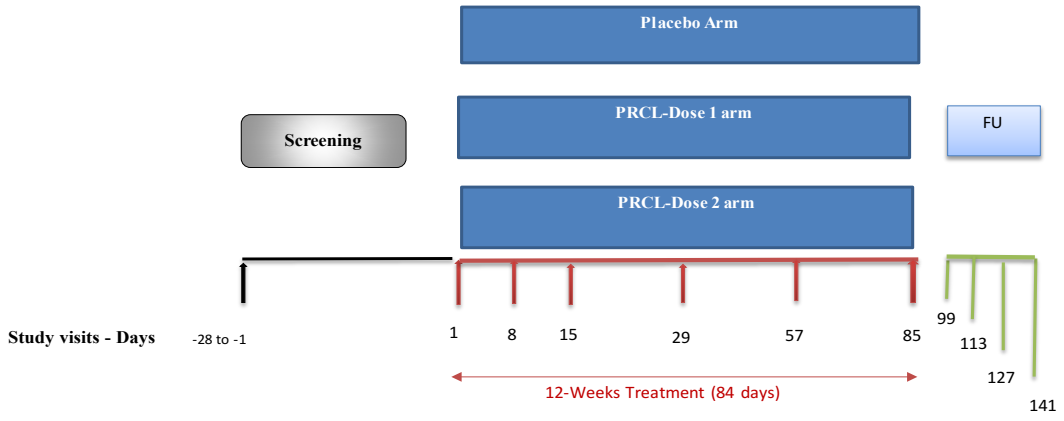

Figure PRCL 1 Illustration of study design for Clinical Protocol PRCL-PoC

5.2. Number of Participants

Approximately 27 patients will be enrolled in each of the 3 treatment arms; planned total enrollment is approximately 81 patients.

5.3. End of Study Definition

End of the study is the date for the last patient to complete or discontinue the study.

End of trial is the date of the last visit or last scheduled procedure for the last patient in the study.

5.4. Scientific Rationale for Study Design

The parallel design is a standard design used to assess efficacy in psoriasis. The study is patient- and investigator-blinded to minimize the potential bias.

5.5. Justification for Dose

The planned doses are designed to ensure the evaluation of an exposure range that encompasses the anticipated pharmacologically active exposure range, while being safe and tolerable for this population.

The lower dosing regimen: a 150 mg loading dose followed by a maintenance dose of 25 mg QD for 12 weeks (starting on Day 2) is intended to achieve an efficacious exposure, based on the IC50 for IFNγ in the human whole blood cell assay (40.3 nM or 15.7 ng/mL) (IB Table 4.7).

The higher dosing regimen: a 300 mg loading dose followed by a maintenance dose of 50 mg QD for 12 weeks (starting on Day 2) is anticipated to achieve a maximum efficacious exposure. Both doses are within the dosing range that was safe and well tolerated in the SMAD Part C study, after once daily dosing of up to 54 mg QD (after a loading dose of 300 mg) for 28 days in a psoriasis patient population.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria. The timeframes included in the below criteria are relative to screening unless otherwise noted.

1. Male and female between 18 to 75 years of age inclusive.
2. Present with moderate to severe psoriasis vulgaris based on the disease diagnostic criteria defined as:
    - Chronic psoriasis vulgaris for at least 6 months prior to randomization.
    - Plaque psoriasis involving at least 10% body surface area (BSA) at both screening and baseline (randomization).
    - Psoriasis Area and Severity Index (PASI) total score of at least 12 at both screening and baseline (randomization).
    - Static Physician's Global Assessment (sPGA) score of ≥3 at screening and at randomization (randomization).
3. Are candidates for systemic therapy.
4. Have a body mass index (BMI) within the range of 18 to 40 kg/m^2, inclusive.
5. Are able and willing to make themselves available for the duration of the study and are willing to follow study restrictions/procedures.
6. Women who are of childbearing potential, who must agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception for the entirety of the study (Appendix 5).
   Women of non-childbearing potential are defined as women who are:
    - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
    - Post-menopausal, defined as either:
        - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who had had either:
            - Cessation of menses for at least 1 year; or
            - At least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
        - A woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
    - A woman at least 55 years of age with a diagnosis of menopause prior to staring hormone replacement therapy.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria. The timeframes included in the below criteria are relative to screening unless otherwise noted.

7. Are Eli Lilly and Company, PRCL Research Inc., or Contract Research Organization employees, investigator or site personnel directly affiliated with this study and the immediate families of either of these. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
8. Are currently enrolled in any other clinical trial involving a study drug or off label use of a drug or device, or any other type of medical research judged not to be scientifically or medically compatible with this study. Patients who participated in the previous PRCL study (SMAD) will be allowed to be included in this study, provide that they meet all inclusion and none of the exclusion criteria.
9. Participated in a clinical study within 30 days (defined as the last dose of study drug), prior to first dosing in this study.
10. Present with pustular, erythrodermic psoriasis, generalized pustular psoriasis or acute guttate psoriasis.
11. Have current serious or unstable illnesses including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including a history of ischemic or structural heart disease, conduction system disease or history of clinically significant arrhythmia), endocrinologic, neurologic, psychiatric, immunologic, hematologic, or dermatologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses of safety and efficacy in this study.
12. Have a history of clinically significant severe drug allergies or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
13. Have received inactivated vaccine within 4 weeks prior to dosing in this study, or a live vaccine within 3 months prior to dosing in this study.
14. Present with a history of clinically significant opportunistic infection (e.g., invasive candidiasis or Pneumocystis pneumonia).
15. Had symptomatic herpes zoster within 3 months of randomization, other recent or ongoing infection that, in the opinion of the investigator, poses an unacceptable risk to participate in the study.
16. Present with any of the following laboratory test results;

    - Positive QuantiFERON®-tuberculosis test at screening AND have not been vaccinated for tuberculosis. If result is indeterminate, a single retest will be allowed. If the result of the second test is still indeterminate, the subject will be excluded. Patients who have been vaccinated with BCG at any time in the past do NOT need to undergo testing. Documentation of previous vaccination is required.
    - For women, positive serum pregnancy test.
    - Evidence of HIV infection or are positive for HIV antibodies based on history or point-of-care testing (POCT) at screening

- Postive test for active hepatitis B as defined as:
  - Positive for hepatitis B surface antigen (HBsAg), or
  - Positive for anti-hepatitis B core antibody (HbcAb) and positive for hepatitis B deoxyribonucleic acid (HBV DNA).
- Positive of anti-hepatitis C antibody with confirmed presence of hepatitis C virus by RNA testing, or chronic liver disease with the most recent available aspartate transaminase (AST) or alanine transaminase (ALT) > 2X the upper limit of normal (ULN).
- Evidence of clinically significant hepatic or renal impairment, including ALT above 2 × ULN, AST above 1.5 × ULN, total bilirubin (TBL) above 2 × ULN (TBL accepted up to 2 × ULN if direct bilirubin is within normal limits), or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (based on CKD-EPI calculation method).

17. Clinically significant ECG abnormalities at screening, or clinically significant personal or family history (in a first-degree relative) of heart diseases, including:
    - Confirmed corrected QT (QTcF) interval > 450 msec for both men and women.
    - Bundle branch blocks and other conduction abnormalities other than:
      - mild first degree atrioventricular block (≤ 205 msec) or
      - QRS duration shorter than 110 msec without bundle branch block morphology.
    - Irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular ectopic beats.
    - History of unexplained syncope.
    - Family history of unexplained sudden death or sudden death due to long QT syndrome.
18. Are receiving any of the following therapies for psoriasis:

- Systemic retinoids within 12 weeks prior to dosing in this study;
- Systemic psoriasis therapy (such as psoralen and ultraviolet A [PUVA] light therapy, cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine) or phototherapy (including ultraviolet B or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to dosing in this study;
- Topical psoriasis treatment (other than moisturizing emollients) within 2 weeks prior to dosing in this study; or
- Any biologic agent within the following washout periods: 30 days for anti-TNF inhibitors and 90 days for others prior to dosing in this study.

6.3. Lifestyle Restrictions

Patients will be instructed to avoid alcohol consumption within 24 hours prior to clinical site visit until the last PK blood sample is collected at the respective visits. Patients will also be

instructed to restrict sun exposure throughout the study period. Patients are not to apply any topical hydrating agent/emollient within 24 hours of a clinic visit.

Male patients should avoid donating sperm while participating in this trial and for 4 months after stopping the study treatment.

6.4. Screen Failures

Patients who do not meet the criteria for participation in the study (screen failures) may be rescreened (up to 1 time) and the rescreen should be at the discretion of the investigator after consultation with sponsor designated medical monitor. If the rescreening is performed a week or longer after the screening visit, the patient must sign a new informed consent form and will be assigned a new identification number. Retesting may occur at the discretion of the investigator, and after consultation with the sponsor designated medical monitor, within a week of the screening visit – in such cases a new identification number will not be assigned.

7. Treatments

7.1. Treatments Administered

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 doses are:

PRCL-02 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.

PRCL-02 Dose 2: Loading dose of 300 mg followed by a once daily maintenance dose of 50 mg, commencing 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.

The drug product is composed of PRCL-02 and inactive ingredients. Matching placebo will consist of only the inactive ingredients. PRCL-02 or placebo will be provided as tablets of 25 mg or 50 mg conditioned in blister packs.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of study drug to the patient
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- at the end of the study returning all unused medication to PRCL Research Inc., or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

PRCL-02 and placebo will be provided as tablets in blister packs. The sponsor or its designee will provide sufficient quantities of PRCL-02 drug products to allow completion of this study. PRCL-02 drug products are manufactured, tested, packaged, and labeled in according with all applicable good manufacturing practice requirements, guidelines, and regulations, and will be labeled according to the country's regulatory requirements. A certificate of release confirming that study drugs are to be used "for human use in clinical study" will be supplied. PRLC-02 drug products are for investigational use only and are to be used only within the context of this study.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized in 1:1:1 to 1 of 3 treatment arms: PRCL-02 Dose 1, PRCL-02 Dose 2, or placebo. 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 to balance the treatment arms according to

weight (<95kg and ≥95kg), and prior number of failed therapies (<3 and ≥3). The purpose of the algorithm is to maintain approximately the same proportion of patients for these variables in each treatment arm.

During the patient's dispensing visits, the site will access the IWRS for the correct blister pack number to dispense. The drug product will be dispensed in a kit, which will provide amounts of treatment consistent with the dispensing plan (Section 7.1) and the allowed window period (Table PRCL 1). The patients will be provided with sufficient treatment to last until the next dispensing visit. (Table PRCL 1).

7.2.1. Selection and Timing of Doses

Patients should take their medication at approximately the same time in the morning everyday. It is recommended (but not required) that the dose should be taken with food.

On days when there is pre-dose PK sampling (at 1 week, 2 weeks, 4 weeks, 8 weeks and 12 weeks after the first dose), the dose must be administered at the site after the pre-dose sample has been obtained. On all other days, patients must take their study drug at approximately the same time in the morning. It is recommended (but not required) that the dose should be taken with food. The study drug (tablet) should be swallowed whole, and should be taken with a glass of water.

7.3. Blinding

This is a double-blind study; both patients and investigators will be blinded.

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.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study, unless there are ethical reasons for the patient to remain in the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from the sponsor designated medical monitor for the patient to continue in the study.

In case of an emergency the investigator should contact the sponsor designated medical monitor prior to unblinding a patient's treatment assignment. However, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

All PRCL-02 drug products will be stored in a secure and locked area with strictly limited access and monitored for temperature, and allocated and dispensed by appropriately trained personnel. Study drugs will be stored between 2°C to 8°C.

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. 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 dispensed tablets. Deviations from the prescribed dosage regimen should be recorded in the electronic data capture (EDC).

7.7. Concomitant Therapy

Refer to the concomitant medications listed in the exclusion criteria (Section 6.2). Treatment with concomitant psoriasis therapies during the study is permitted as outlined below.

Patients will maintain their usual medication regimen for other concomitant diseases throughout the study unless specifically excluded in Section 6.2. Patients should be on stable doses of concomitant medications at baseline, and should remain at a stable dose throughout the study, unless changes need to be made for an AE. Additional systemic drugs are to be avoided during the study, unless required to treat an AE.

Use of non-live seasonal vaccinations and/or emergency vaccination (such as rabies or tetanus vaccinations) is allowed.

The following will be allowed as needed:

- use of topical antibiotics in the event of secondary infections of lesions;
- nonprescription shampoos;
- acetaminophen or aspirin; and

- topical moisturizers/ emollients on non-target lesions, bath oils, oatmeal bath preparations, and salicylic acid preparations. These topical agents should not be used within approximately 24 hours prior to visits requiring a PASI assessment.

Use of topical steroids of any potency is prohibited throughout duration of study.

Other medications may be allowed if approved by the sponsor or its designee. Patients will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Patients discontinuing from the treatment prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 of this protocol.

Patients discontinuing from the study prematurely for any reason must complete adverse event and follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation due to a hepatic event or liver test abnormality. Patients who are discontinued from using study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via EDC. Discontinuation of the study for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the sponsor designated medical monitor:

- ALT or AST >5X ULN
- ALT or AST >3X ULN along with one or more of the following criteria:
    - sustained for more than 2 weeks or
    - TBL >2X ULN or
    - prothrombin time >1.5X ULN or
    - the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

In addition, patients will be discontinued from the study drug in the following circumstances:

- White blood cell count ≥1.5X ULN or an increase in white blood cells above ULN and >2X ULN from last predose measure
- Neutrophil or total lymphocyte count of ≥1.5X ULN or an increase in neutrophils or total lymphocytes above ULN and >2X ULN from last predose measure
- Patient received concomitant medication listed in Exclusion Criteria
- Patient's failure to comply with protocol requirements or study-related procedures
- Termination of the study by the sponsor or regulatory authorities

8.1.1. Discontinuation of Inadvertently Enrolled Patients from Study Treatment

If the Sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor designate medical monitor and the investigator to determine if the patient may continue on investigational product. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled patient to continue on investigational product.

8.2. Discontinuation from the Study

Patients may be withdrawn from the study if any of the following criteria are observed:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator's decision: the investigator may decide that the patient should be discontinued from the study if, in the investigator's opinion, continuation in the study would be detrimental to the patient's well-being, in particular in case of an AE
- Subject decision: the patient requests to be discontinued from the study.
- Subject becomes pregnant while on study

Patients who are discontinued from the study may be replaced at the discretion of the Sponsor.

8.3. Patients Lost to Follow-up

Every effort must be made to contact patients who do not return for a planned visit and the reason for withdrawal should be documented in the EDC. The patient can only be declared as 'lost to follow-up' if the investigator has had no success in contacting the patient.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessment - Psoriasis Area and Severity Index (PASI)

Primary efficacy assessments will be based on the PASI.

The PASI is a proven and widely used tool to evaluate the severity of psoriasis (Hägg et al. 2017). 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 extent of body-surface involvement in the head, trunk, arms, and legs together with the severity of desquamation, erythema, and plaque induration.

9.1.2. Exploratory Efficacy Assessments – Static Physicians Global Assessment (sPGA)

The static Physicians Global Assessment (sPGA) is a widely used scale in psoriasis clinical trials that defines the severity of disease from clear to severe.

9.2. Adverse Events

A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

The sponsor has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate healthcare option, AEs that are serious or otherwise medically important, considered related to the study drug or the study, or that caused them to discontinue the study drug before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via EDC the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or study treatment via EDC.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the study drug, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Ratings of AEs will be based on the following 3-point severity scale:

Mild	Awareness of sign or symptom, but it is easily tolerated; does not interfere with daily activities.
Moderate	Discomfort enough to slightly disrupt daily activities. Medical intervention and/or close follow-up may be considered.
Severe	Incapacitating with complete disruption of daily activities. Medical intervention and/or close follow-up likely.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's study drug is discontinued as a result of an AE, study site personnel must report this to sponsor or its designee via EDC, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

Study site personnel must alert the sponsor or its designee of any SAE **within 24 hours** of investigator awareness of the event via a sponsor-approved method. Serious adverse event reporting to the sponsor begins after the patient has signed Informed Consent.

If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the EDC (Section 9.4.5.1).

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- Important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Previously planned (prior to the signing of ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

The following terms will be utilized to assess the relationship of the SAE to administration of study treatment:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probably, but is also not impossible.
- **Unlikely**: likely to be due to another etiology.
- **Not related**: without questions, the AE is definitely not associated with study drug.

Although all AEs are recorded in the case report form or EDC after signing informed consent, SAE reporting to the Sponsor begins after the subject has signed informed consent and has received the study drug. However, if an SAE occurs after signing informed consent, but prior to receiving the study drug, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study. Serious adverse events occurring after a patient has taken the last dose of study drug will be collected for 30 days after the last dose of the study drug. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify the sponsor and/or its designee.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

The designated medical monitor of the sponsor will monitor safety data throughout the course of the study. The sponsor and/or its designee will review SAEs within appropriate timeframes to meet reporting obligations imposed by regulatory authorities. All serious and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives, and regulations.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB (PRCL-02 2018) and that the investigator identifies as related to study drug. The sponsor has procedures that will be followed for identifying, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.2. Complaint Handling

The sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patient will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the IB (PRCL-02 2018).

9.4. Safety

9.4.1. Electrocardiograms

For each patient, single 12-lead electrocardiograms (ECGs) should be collected according to the Schedule of Activities (Section 2). Patients should be in a supine position for at least 5 minutes prior to recording of an ECG. The screening ECG may be repeated at the discretion of the investigator. Electrocardiograms should be taken prior to other scheduled study procedures taken at similar times, followed by vital signs and then any other study procedures.

Any clinically significant findings from ECGs and that occur after the patient receives the first dose of the study drug should be reported as an AE via EDC.

9.4.2. Vital Signs

For each patient, vital signs (sitting pulse and blood pressure) measurements should be conducted according to the Schedule of Activities (Section 2). Vital signs should be recorded in sitting position just after the ECG (if the ECG is recorded at the same timepoint) and before any other procedures according to the Schedule of Activities (Section 2).

Any clinically significant findings from vital signs measurement that that occur after the patient receives the first dose of study drug should be reported as an AE via EDC.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

With the exception of laboratory test results that may unblind the study, the sponsor or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of study drug should be reported to the sponsor or its designee as an AE via EDC.

9.4.4. Physical Examination

A complete physical examination will be conducted at screening and at Week 4. Physical examination at other scheduled visits must include evaluation of the skin and mucus membranes. Performance of other components of a physical examination at these visits will be at the investigator's discretion. Additinally, a physical examination may be performed at other unscheduled visits at the investigator's discretion, including those visits being made for evaluation of an AE.

9.4.5. Safety Monitoring

A study level safety review will be conducted quarterly.

9.4.5.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the sponsor designated medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the EDC if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

9.5. Pharmacokinetics

9.6. Sample collection and assay

At the visits and times specified in the Schedule of Activities (Section 2), blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of PRCL-02.

Sample times are provided as a guidance and should be adhered to as closely as possible. Actual sampling dates and times must be recorded.

A maximum of 2 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

9.7. Bioassay

Plasma samples will be analyzed for PRCL-02 concentrations using a validated HPLC/MS/MS method in a bioanalytical laboratory selected by the Sponsor.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Placebo samples are not planned to be assayed.

Bioanalytical samples collected to measure study drug concentration will be retained for a maximum of 1 year following last patient visit for the study.

9.8. Pharmacodynamics

9.8.1. Pharmacodynamic Assessments

Disease activity measures will include the PASI score and sPGA over the period (Refer to Section 9.1.1 for details on PASI and Section 9.1.2. for details on sPGA).

9.8.2. Exploratory Assessments

Collection of additional samples is also planned for other biomarker research, as indicated in the Schedule of Activities. The samples will only be stored for potential future exploratory analyses related to psoriasis, the drug and/or its mechanism of action.

Samples will be identified by the patient number and stored for up to 15 years after the last patient visit for the study at a facility selected by the Sponsor. The duration allows the Sponsor to respond to regulatory requests related to the study drug. The sample and any data generated can only be linked back to the patient by investigator site personnel.

Samples will be destroyed according to a process consistent with local regulation.

9.9. Pharmacogenomics

9.9.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample (10 mL) will be collected for pharmacogenetic analysis at baseline predose, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable response to study drug and to investigate genetic variants thought to play a role in psoriasis. Assessment of variable response may include evaluation of AEs or differences in efficacy.

Samples will be identified by the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by the sponsor or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of the study drug.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described in this section.

9.10. Biomarkers

Not applicable.

9.11. Health Economics or Medical Resource Utilization and Health Economics

Not applicable.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 27 patients will be randomized to each of the 3 treatment arms. The sample size was chosen so that there is at least 80% power to detect an increase in response of 30% or more in any PRCL 02 treatment arm relative to placebo using a 1 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.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Randomized	All patients who signed informed consent and are randomized.
Safety	All randomized patients who take at least 1 dose of double-blind study treatment. In the event of treatment error, patients will be analyzed according to the treatment they actually received.
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 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 were randomized.
Pharmacokinetic	All randomized patients who take at least 1 dose of double-blind study treatment and provide sufficient data for pharmacokinetic assessments.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of PRCL Research Inc. or its designee. Details of the summarization and analysis of the clinical trial data will be described in the Statistical Analysis Plan (SAP), which will be finalized prior to the database lock.

Efficacy analyses will be conducted on the Intent-to-Treat (ITT) population.

Data will be presented using summary tables by treatment arms, unless otherwise specified.

Continuous data will be summarized using the mean, standard deviation, median (for selected variables), minimum, and maximum. Categorical data will be summarized by frequency counts and percentages. Figures may be used to support the presentation of data.

All tests of treatment effects will be conducted using a 1-sided tests with a 10% type 1 error rate. The sample size was calculated assuming a 10% drop-out of patients in each arm, and assuming that early withdrawal is not influenced by the treatment effect. Secondary and any supportive analyses may be performed to explore the effect of early withdrawal on the primary endpoint.

Baseline values will be defined as the last available value prior to receiving double-blind study drug in the Treatment Period.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR).

Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be summarized by treatment arm. If known, a reason for their discontinuation will be given.

10.3.2.2. Patient Characteristics

Patient demographics (age, gender, race, ethnicity, height, weight, and BMI) and other baseline characteristics will be summarized by treatment arm using the Safety population.

10.3.2.3. Concomitant Therapy

Concomitant therapy will be summarized by treatment arm using the Safety population.

10.3.2.4. Treatment Compliance

The proportion of patients who are significantly noncompliant, as noted in Section 7.6 will be summarized by treatment arm using the Safety population.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

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.

10.3.3.2. Secondary Analyses

Safety/tolerability and PK analyses are described in Sections 10.3.4 and 10.3.5.

10.3.3.3. Tertiary/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, PASI 90, and sPGA will be summarized at each scheduled visit. Observed values of the PASI score and subscores, sPGA, 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.

10.3.4. Safety Analyses

The safety analysis will be conducted using the safety population.

The safety and tolerability of treatment will be assessed by evaluating the following:

- Treatment-emergent AEs (TEAEs) by Preferred Term and maximum severity
- SAEs
- AEs leading to discontinuation
- Vital signs
- ECGs
- Laboratory measurements
- Physical examination

Treatment-emergent adverse events are defined as the reported AEs that first occurred or worsened during the double-blind treatment phase and follow-up compared with baseline. The most recent version of Medical Dictionary for Regulatory Activities Preferred Term will be used. Treatment-emergent adverse events will be summarized by the number and percentage of patients with the event.

Other safety parameters that will be assessed include physical examinations, safety clinical laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

10.3.5.1. Pharmacokinetics

Pharmacokinetic analysis will be performed on the PK analysis set; patients dosed with PRCL-02 active that have evaluable concentrations will be included. Individual plasma PRCL-02 PK parameters will be calculated using non-compartmental analysis (NCA). Actual sampling times will be used for parameter derivations.

PRCL-02 steady state PK parameters such as the maximum concentration ($C_{max,ss}$), time of maximum concentration ($t_{max,ss}$), are under the concentration versus time curve within a dosing interval ($AUC_{0-\tau,ss}$), the first-order terminal elimination rate constant (λ_z), the terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F) and apparent volume of distribution (Vd/F) will be reported.

Other parameters may be calculated as deemed appropriate.

Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Mean and individual PRCL-02 plasma concentration-time curves will be represented graphically.

10.3.5.2. Pharmacodynamics

Pharmacodynamic analysis will be performed on the PD analysis set.

PASI and sPGA scores will be individually listed.

These parameters will be summarized, on observed values and on changes from baseline (pre-dose) values by treatment arms.

10.3.5.3. PK/PD

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

10.3.6. Evaluation of Immunogenicity

Not applicable.

10.3.7. Other Analyses

Not applicable

10.3.8. Interim Analyses

No interim analyses are planned for this study.

11. References

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12. Appendices

Appendix 1. Abbreviations

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0-\tau}$	area under the concentration versus time curve throughout a dosing interval
BSA	body surface area
Ca^{2+}	cytoplasmic calcium
C_{max}	maximum observed drug concentration
CRAC	cytoplasmic calcium release-activated cytoplasmic calcium
ECG	Electrocardiogram
EDC	electronic data capture
EoS	End-of-Study
FU	Follow-up
GCP	good clinical practice
IB	Investigator's Brochure
Ig	immunoglobulin
ICF	informed consent form
ITT	Intent-to-Treat
IWRS	interactive web-response system
PASI	Psoriasis Area and Severity Index
PASI 75	A 75% improvement from baseline to Week 12 in the Psoriasis Area and Severity Index
PK/PD	pharmacokinetics/pharmacodynamics
QD	once daily

QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
sPGA	statis physician global assessment
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
t_{max}	time to reach maximum observed drug concentratoin
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Chloride
Mean cell hemoglobin concentration (MCHC)	Bicarbonate
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented and banded	Direct bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase (ALT/SGPT)
Eosinophils	Aspartate aminotransferase (AST/SGOT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Uric acid
	Calcium
Urinalysis	Magnesium
Color	Glucose, random
Specific gravity	Albumin, total protein
pH	Lactate dehydrogenase (LDH)
Protein	Creatine kinase (CK)
Glucose	Phosphorus
Ketones	eGFR
Blood	
Urine microalbumin	**Pregnancy Test** (females only)
	Follicle-stimulating Hormone (FSH)
	Serology Tests
Coagulations Studies	Human immunodeficienty virus (HIV)
Prothrombin time/International normalized ratio (PT/INR)	Hepatitis B surface antigen (HBsAg)
Activated partial thromboplastin time (APTT)	Anti-hepatitis B core antibody (HBcAb)
	Hepatitis B deoxyribonucleic acid (HBV DNA)
	Hepatitis C antibody (HCV Ab)
	Hepatitis C virus ribonucleic acid (HCV RNA)

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

PRCL Research Inc. or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Investigators will be responsible for patient recruitment through local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to PRCL Research Inc. before the study may begin at the investigative sites. PRCL Research Inc. or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative sites. All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.5. Investigator Information

Licensed physicians with a specialty in Dermatology will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a PRLC Research Inc. representative.

Appendix 3.1.7. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, PRCL Research Inc. or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax

- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, PRCL Research Inc. or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by PRCL Research Inc. or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the PRCL Research Inc. data warehouse.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if PRCL Research Inc., the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if PRCL Research Inc. judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Monitoring Tests for Treatment-Emergent Hepatic Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the PRCL Research Inc., or its designated medical monitor.

Hepatic Monitoring Tests

Hematology	**Haptoglobin**
Hemoglobin	
Hematocrit	**Coagulation**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
AST	
GGT	**Alkaline Phosphatase Isoenzymes**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

Appendix 5. Classification of Contraceptive Methods

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini-pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total Abstinence
- Vasectomy – for men in clinical trials

Effective Methods of Contraception (must use combination of 2 methods):

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

Ineffective Forms of Contraception – not acceptable as a method for clinical trials

- Spermicide alone (please note spermicide alone is not considered a barrier method)
- Immunocontraceptives
- Periodic abstinence
- Fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal)
- Withdrawal
- Post coital douche
- Lactational amenorrhea