PRINCIPIA BIOPHARMA
A SANOFI COMPANY

AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol Title:	**A randomized, intra-patient, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of topically administered PRN473 (SAR444727) in patients with mild to moderate atopic dermatitis**
Protocol Number:	**PRN473-0005 (ACT17131)**
Amendment Number:	**Amendment 02**
Compound number (INN/Trademark):	**PRN473 (SAR444727)** **Not applicable**
Brief Title:	**Phase 2a study of the safety, tolerability, and pharmacokinetics of topically administered PRN473 (SAR444727) in patients with mild to moderate atopic dermatitis**
Study Phase:	**2a**
Sponsor Name:	**Principia Biopharma, Inc.**
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Sponsor's Medical Contact:	[redacted]
Monitoring team's representative name and contact information	

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Confidentiality Statement

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	global	01 March 2022, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01	global	15 June 2021, version 1 (electronic 2.0)
Original Protocol		19 March 2021, version 1 (electronic 2.0)

Amendment 02 (01 March 2022)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended to provide more flexibility to allow the investigational product to be administered at home or external clinic during Blinded Period, update statistical interim analysis to facilitate the internal decision making and to make other clarifications deemed necessary by the Sponsor.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated the study Sponsor's Medical Contact and study NCT numbers. Updated protocol version and date.	Administrative.
Protocol amendment summary of changes table	Included the overall rationale and protocol amendment summary of changes table for current amendment.	Administrative.
Section 1.1 synopsis; Section 3 objectives and endpoints; Section 8.6 Biomarkers	Included the RNA expression analysis in biomarker assessments.	To determine the effect of IMP on lesional transcriptional profile and its associated mechanisms on skin inflammation and barrier function.
Section 1.1 synopsis; Section 4.1 overall design; Section 6.2 Preparation/handling/storage/accountability	Added "The investigational products will be applied at the study site, at the patient's home, or at an external clinic, where available."	To provide flexibility to allow IMP administration at home by trained medical professional or external clinic during Blinded Period.
Section 1.1 synopsis; Section 4.1 overall design	Specified the STS assessment to be performed predose on Days 1, 8 (optional), 15, 29, and at Day 43 for the target lesions.	For clarity.
Section 1.1 synopsis; Section 9.5 interim analysis; Section 6.3 measures to minimize bias: randomization and blinding	Updated the language on interim analysis.	To facilitate internal decision making.

Section # and Name	Description of Change	Brief Rationale
Throughout	Adjusted the term of “at clinic” to “at study site”, where applicable.	To distinguish from “external clinic” and to align the term throughout.
	Included a trained medical professional in addition to site staff, where applicable, considering that IMP might be applied at home or external clinic.	To provide flexibility to allow IMP administration at home by trained medical professional or at external clinic during Blinded Period.
Section 1.2 schema	Updated the panel for blinded period by adding “at home or external clinic”.	To provide flexibility to allow IMP administration at home by trained medical professional or at external clinic during Blinded Period.
Section 1.2 schema, Section 1.3 schedule of activities	Updated footnote “a” by adding “The investigational products could be applied by a trained medical professional at patient’s home or an external clinic, where available, as a backup option.”	To provide flexibility to allow IMP administration at home by trained medical professional or at external clinic during Blinded Period.
Section 1.3 schedule of activities	Updated the header for blinded period from “in-clinic” to “at study site/home/external clinic”.	To provide flexibility to allow IMP administration at home by trained medical professional or at external clinic during Blinded Period.
	Updated the footnote “t” and introduced a new footnote “u” to include study intervention dosing during blinded period visits to be applied at study site, at home or an external clinic, where available.	
	Added annotation “b” to PP-NRS assessment and photographs at D15 and D29 visit.	To clarify that the PP-NRS and photography will be performed predose.
	Added study intervention dosing at D29 visit and included annotation “n”.	To correct an omission.
	Footnote "n" was modified to clarify that the dosing at D29 visit to be done after predose assessments at study site.	For clarity.
	Footnote "q" was modified to clarify that the STS assessment to be performed predose. Added annotation “b” to STS assessment at D15 and D29 visit.	For clarity.
Section 1.3 schedule of activities; Section 8.9 lesion photography	Corrected the D15 visit from Blinded Period to Open-Label Period in SoA table footnote “l” and in Section 8.9.	To correct an error.
	Specified the photographs to be taken of the 2 target lesions predose at Baseline, D8, D15, D29 and at D43.	For clarity.

Section # and Name	Description of Change	Brief Rationale
Section 6.2 preparation/handling/storage/ accountability	Defined the “study staff” who may supply or administer IMP during the Blinded Period.	For clarity.
	Clarified that the Investigator or designee is responsible for the education of “site staff” rather than “study staff”.	For clarity.
	Included text on specifying the condition when IMP application at home or external became applicable.	To provide flexibility to allow IMP administration at home by trained medical professional or at external clinic during Blinded Period.
Section 6.3 measures to minimize bias randomization and blinding	Clarified that the local tolerability assessment to be performed by another trained medical professional different than the person administering the study intervention, if the investigational products are applied at the patient’s home or at an external clinic.	Measures taken for minimize the bias.
Section 6.4 study intervention compliance	Clarified the trained medical professional, in addition to site staff, was responsible for study intervention administration and study conduct.	For clarity.
Section 7.1.1 permanent discontinuation	Added ALT >5 × ULN in the listing of events leading to permanent IMP discontinuation.	To correct an omission and align with decision chart in Section 10.3.
Section 9.4.4.5 laboratory data	Replaced the term 'vital signs' with 'laboratory data'.	To correct the error.
Section 10.5 appendix 5: Protocol Amendment History	Added the overall rationale and protocol amendment summary of changes table for amendment 01.	To include the document history.
Throughout document	Other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections).	Minor, therefore, have not been summarized.

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from zero to infinity
AUC_{0-last}	area under the plasma concentration-time curve from zero to the last measurable concentration
BCR	B cell receptor
BID	twice daily
BLQ	below the limit of quantification
BSA	body surface area
BTK	Bruton's tyrosine kinase
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL_{int}	intrinsic clearance
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CV%	percent coefficient of variation
DLQI	Dermatology Life Quality Index
DTP	direct to patient
EASI	Eczema Area and Skin Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FcγR	Fc-gamma receptor
FcεR	Fc-epsilon receptor
FDA	Food and Drug Administration

Abbreviation or Specialist Term	Explanation
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
geometric CV%	geometric coefficient of variation
IC_{50}	half maximum inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IWRS	interactive web response system
NIMP	non investigational medicinal product
NOAEL	no-observed-adverse-effect level
OD	optical density
OTC	over-the-counter
PCSA	potentially clinically significant abnormality
PK	pharmacokinetic
PO	per oral
POEM	Patient-Oriented Eczema Measure
PP-NRS	Peak Pruritus Numeric Rating Scale
QD	once daily
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation or Specialist Term	Explanation
SCORAD	SCORing atopic dermatitis
SD	standard deviation
STS	skin tape stripping
SUSAR	suspected unexpected serious adverse reaction
TCI	topical calcineurin inhibitor
TSS	total sign score
ULN	upper limit of normal
UV	ultraviolet
vIGA-AD	validated Investigator Global Assessment-Atopic Dermatitis
WHO	World Health Organization

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title: A randomized, intra-patient, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of topically administered PRN473 (SAR444727) in patients with mild to moderate atopic dermatitis

Brief Title: Phase 2a study of the safety, tolerability, and pharmacokinetics of topically administered PRN473 (SAR444727) in patients with mild to moderate atopic dermatitis

Rationale: PRN473 (also known as SAR444727), a selective Bruton's tyrosine kinase (BTK) inhibitor, is an investigational drug being developed as a topical agent for the treatment of immune-mediated dermatological diseases. This study will explore the safety, tolerability, and plasma pharmacokinetics (PK) of topically administered PRN473 in patients with mild to moderate atopic dermatitis (AD).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Safety: To assess the safety and tolerability of PRN473 Gel, 5% versus placebo administered twice daily (BID) up to 6 weeks in patients with mild to moderate atopic dermatitis (AD)	Safety: • Incidence and severity of adverse events (AEs) • Changes in vital signs, electrocardiograms (ECGs), and laboratory tests • Assessment of local cutaneous tolerability assessment: incidence and severity of application-site events such as burning/stinging, itching, and erythema
Secondary	
PK: To evaluate the plasma PK of PRN473 following administration of multiple topical doses of PRN473 Gel, 5% for 42 days in patients with mild to moderate AD	• PK: Plasma PRN473 concentrations at specified timepoints
Exploratory	
• Biomarker: To evaluate blood and skin changes in protein and RNA expression, lymphocyte infiltration, and epidermal thickness following treatment with PRN473 Gel, 5% at Days 8 and 15	• Biomarker: Change from Baseline in biomarkers using blood samples, skin tape stripping, and skin biopsy

Objectives	Endpoints
• Efficacy: To evaluate the preliminary efficacy following double-blind treatment with PRN473 Gel, 5% compared to placebo at Days 8 and 15	Efficacy During Blinded Period: • Change from Baseline in lesion total sign score (TSS) at Days 8 and 15 • Change from Baseline in daily lesional Peak Pruritus Numeric Rating Scale (PP-NRS) score up to Day 15 • Change from Baseline in lesional validated Investigator Global Assessment (IGA) score at Days 8 and 15 • Lesion validated IGA response (proportion of patients with an IGA score of 0 or 1 and ≥2-grade improvement from Baseline) at Days 8 and 15
• Efficacy: To evaluate the preliminary efficacy following open-label treatment with PRN473 Gel, 5% at Days 29 and 43	Efficacy During Open-Label Period • Change from Baseline in TSS for the 2 target lesions at Days 29 and 43. • Change from Baseline in Eczema Area and Skin Severity Index (EASI) at Days 29 and 43 • Change from Day 15 in EASI to Days 29 and 43 • Proportion of patients with EASI 50, EASI 75, and EASI 90 from Day 15 to Days 29 and 43 • Change in PP-NRS from Day 15 to Days 29 and 43 • Proportion of patients achieving at least 3-point reduction from Day 15 in PP-NRS at Days 29 and 43 • Proportion of patients achieving at least a 4-point reduction from Day 15 in PP-NRS at Days 29 and 43 • Change from Day 15 in weekly mean of PP-NRS at Days 29 and 43 • Proportion of patients achieving at least 2 grade reduction in vIGA-AD to clear (vIGA-AD 0) or almost clear (vIGA-AD 1) from Day 15 to Days 29 and 43 • Change from Day 15 in SCORing atopic dermatitis (SCORAD) at Days 29 and 43 • Change from Day 15 in percentage of treatable body surface area (BSA) at Days 29 and 43 • Change from Baseline in Patient-Oriented Eczema measure (POEM) at Days 15, 29, and 43 • Change from Baseline in Dermatology Life Quality Index (DLQI) at Days 15, 29, and 43

Overall Design:

This is a Ph2a study that consists of a double-blind, intra-patient placebo-controlled treatment period and an open-label uncontrolled treatment period with objective to evaluate the safety, tolerability, PK and preliminary efficacy of PRN473 in up to 40 patients with mild to moderate AD. All patients are required to apply an emollient (except urea-containing or medicated emollients that are regulated as medical device) daily from Day -7 to Day 1 (see Section 6.2). On Day 1 (Baseline) of the Blinded Period, 2 target lesions with a difference no greater than 1 point in TSS will be randomly assigned to treatment in an intra-patient 1:1 manner, one lesion to PRN473 Gel, 5%, and the other to matching placebo. PRN473 Gel, 5% and matching placebo are weighed and applied twice daily (BID; morning and evening) at a quantity of approximately 2.5 mg/cm^2 to a 100 cm^2 area of each target lesion on Days 1-14 (Blinded Period). The investigational products will be applied at the study site, at the patient's home, or at an external clinic, where available.

During the Blinded Period, if the target lesion is less than 100 cm^2, the application area should include surrounding nonlesional skin (note: two target lesion skin biopsy specimens on Days 1 and 15 are only on lesional skin); if the target lesion is larger than 100 cm^2, only 100 cm^2 of the lesion should be marked and treated. On Days 15-42 (Open Label Period), patients are instructed to apply PRN473 Gel, 5% BID to all AD-affected areas in a thin layer (excluding the scalp, palms, soles, and genitals) and should continue to treat the assigned areas throughout the Open Label Period.

Safety assessments include application site tolerability assessments (Appendix 4, Section 10.4.1), vital signs, ECGs, physical examination, safety labs, and AEs.

To evaluate the PK (plasma concentrations) and biomarkers of PRN473, blood samples will be collected at study visits accordingly to the SoA (Section 1.3).

Efficacy assessments of:

- The lesional PP-NRS will be administered daily predose during the Blinded Period (Days 1-14) and at predose Day 15.
- The lesional validated IGA will be performed predose at Baseline (Day 1), Days 8, and 15.
- The lesion TSS (Appendix 4, Section 10.4.3) will be performed predose at Baseline (Day 1), Days 8, 15, and 29, and at End of Study/Early Termination visit (Day 43).
- The EASI, the POEM, and the DLQI will be performed predose at Baseline (Day 1), Days 15 and 29, and at End of Study/Early Termination visit (Day 43).
- The vIGA-AD (Appendix 4, Section 10.4.2) will be performed at Screening, predose at Days 15 and 29, and at End of Study/Early Termination visit (Day 43).
- The SCORAD will be performed predose at Days 15 and 29, and at End of Study/Early Termination visit (Day 43).

- The PP-NRS will be administered daily predose before patient morning application during the Open-Label Period (Days 15-42) and at End of Study/Early Termination visit (Day 43).
- The percentage of treatable BSA will be calculated at Screening, Days 15 and 29, and at End of Study/Early Termination visit (Day 43).

To be included in the population analyzed for efficacy, the patient must have received at least 80% of prescribed study intervention in the Blinded Period and/or at least 80% of prescribed study intervention in the Open-Label Period.

Skin tape stripping (STS) will be performed predose on Days 1, 8 (optional), 15, 29, and at Day 43 for the two target lesions, and on Day 1 for the normal skin. For a minimum of 20 patients (may be reduced to 15 patients if there is an impact on enrollment from coronavirus disease 2019 [COVID-19]), a 4 or 5 mm punch skin biopsy will be collected from each target lesion on Days 1, 15, and 29 (optional) and from normal skin on Day 1. The lesional biopsy specimens at Days 15 and 29 will be collected in the vicinity of the Day 1 (Baseline lesional sample) biopsy but must be at least 1 cm away from the prior biopsy site. If the target lesion cleared after Day 1 and before Day 15, the biopsy specimen will be taken from the lesional skin location of the target area identified at Baseline.

Additional information regarding study assessments and their timing is located in the Schedule of Activities (Section 1.3).

Study Duration:

Participation will take approximately 13 weeks, including up to a 5-week screening period, a 6-week treatment period, end of study assessments 1 day after last dose, and a safety follow-up phone call 2 weeks after last dose.

Number of Patients:

Up to 40 patients with mild to moderate AD are planned to be enrolled.

Investigational Product

PRN473 Gel, 5% (w/w) and placebo to match.

Study Population:

Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria are met:

1. Male and female adults 18 to 70 years of age (inclusive) at the time of informed consent.

2. Diagnosed with mild to moderate AD, meeting at least 3 major and 3 minor criteria according to Hanifin and Rajka (Hanifin 1980; Appendix 4, Section 10.4.4) prior to or at the Screening visit.

3. History of AD for at least 6 months as determined by the Investigator through patient interview.

4. Stable disease for the 4 weeks prior to the screening visit with no significant flares in AD as determined by the Investigator.

5. Validated Investigator Global Assessment-atopic dermatitis (vIGA-AD) score of Moderate (3) or Mild (2) at Screening. The vIGA-AD is evaluated for the entire body except scalp, palms, soles, and genitals.

6. Has AD involvement (excluding scalp, palms, soles and genitals) of at least 1.0% BSA and no more than 14.0% BSA.

7. Has at least two target lesions 100cm^2 or greater with a difference no greater than 1 point in lesion TSS and at least 5 cm apart located on the trunk (excluding genitals) or upper extremities (excluding palms).

8. Male patients are eligible to participate if they agree to the following during the intervention period and for at least 2 days (eg, 5 terminal half-lives) after the last dose of study intervention,

   - Refrain from donating sperm

   PLUS, either:

   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

   OR

   - Must agree to use contraception/barrier as detailed below:

     Agree to use a male condom and an additional highly effective contraceptive method as described in Appendix 2 Contraceptive and barrier guidance Section 10.2) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

9. A female patient is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

   - Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 2 Contraceptive and barrier guidance (Section 10.2).

   OR

   - Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in

Appendix 2 Contraceptive and barrier guidance (Section 10.2) during the study intervention period and for at least 2 days (eg, 5 terminal half-lives) after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

A WOCBP must have a negative highly sensitive pregnancy test (urine and/or serum as required by local regulations) within 28 days before the first administration of study intervention, see Section 8.2.5 Pregnancy testing.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the patient must be excluded from participation if the serum pregnancy result is positive.

10. In good health as judged by the Investigator, based on medical history, physical examination, serum chemistry labs, hematology values, and urinalysis.

11. Patients are considered reliable and capable of adhering to the protocol and visit schedule, according to the judgment of the Investigator.

12. Able to provide written informed consent and agreeable to the schedule of activities.

Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met:

1. Patients who have failed 2 or more prior systemic treatments for AD (not including those who discontinued systemic treatments due to safety or tolerability issues).

2. Patients with any serious or uncontrolled medical condition or clinically significant laboratory, ECG, vital signs, or physical examination abnormality that would prevent study participation or place the patient at significant risk, as judged by the Investigator.

3. Patients who have received a live or attenuated vaccine in the last 12 weeks or intend to receive a live or attenuated vaccine during the study.

4. Patients who cannot discontinue medications and treatments prior to the Baseline visit and during the study as described in the Excluded Medications and Treatments table.

5. Has unstable AD, based on the judgement of the Investigator, or any consistent requirement for high potency topical steroids to manage AD signs or symptoms.

6. Patients who have significant active systemic or localized bacterial, viral, fungal, and helminth infection in the last 30 days (including known actively infected skin at or around a lesion of AD). Non-complicated recurrent muco-cutaneous infections such as cold sores are not considered exclusionary.

7. Patients unwilling to refrain from prolonged sun exposure or use of a tanning bed or other artificial light emitting devices for 4 weeks prior to Baseline and during the study.

8. Patients with other skin conditions that would interfere with evaluations of the effect of the study medication on AD, as determined by the Investigator. Patients with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.

9. Patients with known genetic dermatological conditions that overlap with AD, such as Netherton syndrome.

10. Patient has any state of immunodeficiency including but not limited to primary or secondary immunodeficiency syndromes, organ transplant (except corneal transplant), and previous opportunistic infections, as judged by the Investigator.

11. Known allergies to excipients in PRN473 Gel.

12. Previous use of a BTK inhibitor.

13. Women who are pregnant, wishing to become pregnant during the study, or are breastfeeding.

14. Patients currently undergoing allergy (eg, food allergy testing or skin prick testing), patch testing, or food challenges, or plan to do so during the study.

15. Patients who have undergone major surgery within 4 weeks prior to Day 1 or patients who have a major surgery planned during the study.

16. Regular use of drugs of abuse or regular alcohol consumption within 6 months prior to the study defined as: an average weekly intake of >35 units for males or >35 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 (25 mL) measure of spirits.

17. History of any malignancy except skin basal cell or squamous cell carcinomas in situ that have been removed and completely resolved at least 5 years ago.

18. Any of the following laboratory abnormalities at the screening visit (identified by the central laboratory):
    - Absolute neutrophil count $<1.5 \times 10^9$/L
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x upper limit of normal (ULN)
    - Total bilirubin >1.5 x ULN, (isolated bilirubin >1.5 x ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%)
    - Abnormal international normalized ratio (INR) test and activated partial thromboplastin time (aPTT) judged by the Investigator to be clinically significant
    - A platelet count <150 000/µL

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

20. Positive human immunodeficiency virus (HIV) antibody test.

21. Presence of Hepatitis B surface antigen (HBsAg) and/or core antibody positive at screening or within 3 months prior to first dose of study intervention.

22. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study intervention. NOTE: Patients with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

23. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest X-rays (posterior anterior and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration ≥5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) TB test such as QuantiFERON®-TB Gold Plus test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold Plus test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold Plus test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.

24. History of serious infections requiring intravenous therapy with the potential for recurrence or currently active moderate to severe infection at Screening (Grade 2 or higher) including active coronavirus disease 2019 (COVID-19).

25. Patients who have received the last dose of a COVID-19 vaccine within 14 days prior to Day 1.

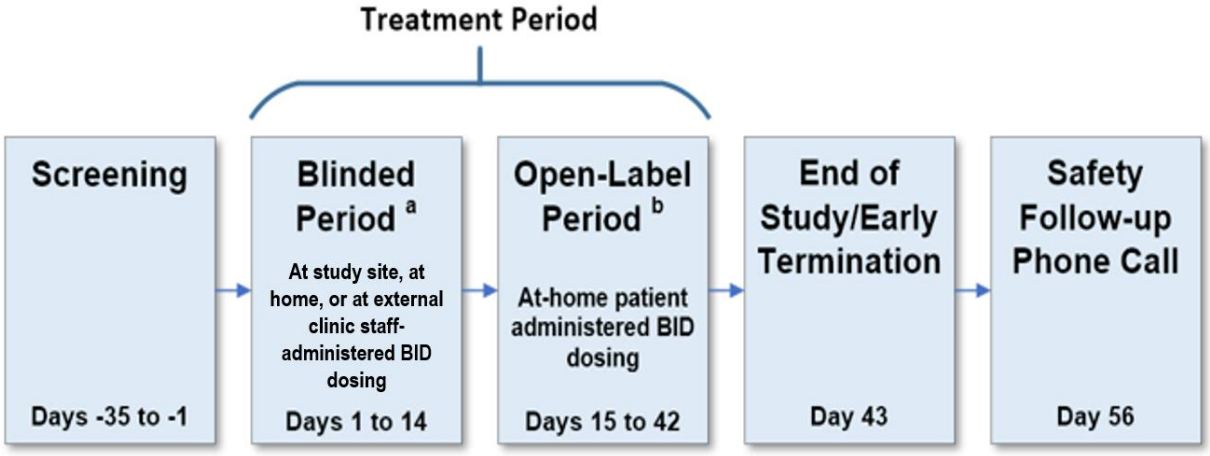
26. Patients who are family members of the clinical study site, clinical study staff, or Sponsor, or family members of enrolled patients living in the same house.

Interim Analysis

An interim analysis for internal decision making may be performed. The Sponsor team that will analyze the data will include: a Medical Monitor, a biostatistician, a programmer, and safety designee. The outcome of the Interim Analysis may lead to early termination of the study in case of unfavorable signals or continuation without any changes.

See Section 9.5 for more details.

1.2 SCHEMA



a Two target lesions with a difference no greater than 1 point in total sign scores (TSS) will be randomly assigned in an intra-patient manner 1:1 to PRN473 Gel, 5% or matching placebo. The two target lesions will be dosed twice daily at study site during the Blinded Period with the second dose application approximately 12 hours after previous dose. The investigational products could be applied by a trained medical professional at patient's home or an external clinic, where available, as a backup option.

b During the Open Label Period, patients will apply PRN473 Gel, 5% BID to the all AD-affected areas, except the scalp, palms, soles, and genitals and should continue to treat the assigned areas throughout the Open Label Period.

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening	Treatment Period (Days 1-42)						End of Study/Early Termination	Safety Follow-up Phone Call
		Blinded Period [a] (at study site/home/external clinic staff-administered BID dosing Days 1-14)		Open-Label Period (BID dosing at home by patient Days 15-42)					
Assessment	**Days -35 to -1**	**Day 1 (Baseline)**	**Days 2-14**	**Day 15 (+2 days)**	**Day 18 (±2 days)**	**Day 29 (±2 days)**	**Day 36 (±2 days)**	**Day 43 (±2 days)**	**Day 56 (±2 days)**
Informed consent	X								
Eligibility check	X	X [b]							
Medical history	X	X [b]							
Demographics	X								
Physical examination [d]	X	X [b]	X [c]	X		X		X	
Height (screening only), weight	X	X [b]							
Serum pregnancy test	X								
Urine pregnancy test [e]		X [b]				X		X	
Clinical laboratory tests	X	X [b]		X		X		X	
Serology (HIV, hepatitis B and C) and TB test	X								
FSH [f]	X								
Urinalysis	X	X [b]		X		X		X	
12-lead ECG	X	X [b]						X	
Vital signs [g]	X	X [b]	X [c]	X		X		X	
Telemedicine visit [h]					X		X		
EASI [b]		X		X		X		X	
vIGA-AD [i]	X			X [b]		X [b]		X [b]	
Evaluation of treatable BSA	X			X		X		X	
Lesional TSS	X	X [b]	X [c]	X [b]		X [b]		X [b]	

	Screening	Treatment Period (Days 1-42)						End of Study/Early Termination	Safety Follow-up Phone Call
		Blinded Period [a] (at study site/home/external clinic staff-administered BID dosing Days 1-14)		Open-Label Period (BID dosing at home by patient Days 15-42)					
Assessment	**Days -35 to -1**	**Day 1 (Baseline)**	**Days 2-14**	**Day 15 (+2 days)**	**Day 18 (±2 days)**	**Day 29 (±2 days)**	**Day 36 (±2 days)**	**Day 43 (±2 days)**	**Day 56 (±2 days)**
Randomization		X [b]							
POEM [b]		X		X		X		X	
Selection of the lesions	X								
Lesional PP-NRS [j]		Days 1-14 [b]		X [b]					
Lesional vIGA [k]		X [b]	X [c]	X [b]					
DLQI [b]		X		X		X		X	
SCORAD [b]				X		X		X	
PP-NRS [b]				Days 15-42				X	
Photographs [l]		X [b]	X [c]	X [b]		X [b]		X	
Study intervention dosing		X [u]	X [u]	X [m]		X [n]			
Study intervention distribution				X		X			
Study intervention dosing at home				Days 15-42 [n]					
Daily patient diary [o]				Days 15-42					
Study intervention collection/review						X		X	
Skin biopsy collection		X [b]		X		X [p]			
Suture removal, if applicable				X				X	
Skin tape stripping [q]		X [b]	X [c]	X [b]		X [b]		X	
PK blood sampling [r]		X	X [c]	X		X		X	
Blood biomarker levels [s]		X [b]	X [c]	X				X	
Application site tolerability assessment [t]		X	X	X		X			

	Screening	Treatment Period (Days 1-42)						End of Study/Early Termination	Safety Follow-up Phone Call
		Blinded Period [a] (at study site/home/external clinic staff-administered BID dosing Days 1-14)		Open-Label Period (BID dosing at home by patient Days 15-42)					
Assessment	**Days -35 to -1**	**Day 1 (Baseline)**	**Days 2-14**	**Day 15 (+2 days)**	**Day 18 (±2 days)**	**Day 29 (±2 days)**	**Day 36 (±2 days)**	**Day 43 (±2 days)**	**Day 56 (±2 days)**
Prior and concomitant medication review	ongoing from screening							X	X
AE reporting	ongoing from the time of consent (non-treatment- and treatment-emergent adverse events)							X	X

Abbreviations: AE = adverse event; BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Skin Severity Index; ECG = electrocardiogram; FSH = Follicle-stimulating hormone; IGA = Investigator Global Assessment; PK = pharmacokinetic; POEM = Patient-Oriented Eczema Measure; PP-NRS = Peak Pruritus Numeric Rating Scale; SCORAD = SCORing atopic dermatitis; TSS = total sign score; vIGA-AD = validated Investigator Global Assessment-Atopic Dermatitis.

Schedule of Activities (SoA), continued

a During the Blinded Period, patients will come into the study site twice daily for drug application (approximately 12 hours after the previous dose) and collection of adverse events. The investigational products could be applied by a trained medical professional at patient's home or an external clinic, where available, as a backup option.
b Procedure performed predose.
c Procedure performed prior to the morning dose on Day 8.
d A complete physical examination is to be performed at the Screening and End of Study visits. A symptom-directed physical exam is to be performed as clinically indicated at other visits.
e A positive urine pregnancy test must be confirmed by a serum test.
f For post-menopausal women of non-childbearing potential only.
g On Days 1, 8, and 15, vital signs are measured predose.
h During the telemedicine visits on Days 18 and 36, drug application, patient questions about daily diary, new or changed AEs, and new or changed concomitant medications will be reviewed with the patient.
i The vIGA-AD will be conducted predose on all treated lesions at screening, Day 15, 29 and 43 during Open Label period.
j The lesional PP-NRS will be administered predose separately on each of the 2 target lesions only during Blinded Period and predose at Day 15.
k The lesional vIGA-AD will be administered predose separately on each of the 2 target lesions only during Blinded Period and predose at Day 15.
l Photographs will be used to document change/improvement in lesions, and to document biopsy location and will not be used to evaluate adverse events. For the Blinded Period, photographs will be taken of the 2 target lesions predose at Baseline and Day 8. For the Open-Label Period, photographs of the 2 target lesions will be taken predose at Day 15, Day 29 and at Day 43.
m Study intervention dosing on the morning of Day 15 will be applied by the patient under the instruction of the site staff.
n Study intervention dosing on the evening of Day 15 and on Days 16-42 will be applied by the patient at home. Day 29 visit dosing will be done after predose assessments at study site. The EOS visit (Day 43) should occur approximately 12 hours after the previous dose.
o Daily diaries will collect the patient reported PP-NRS.
p Skin biopsy at Day 29 is optional.
q Skin tape stripping (STS) will be performed predose on Days 1, 8 (optional), 15, 29, and at Day 43 for the two target lesions, and on Day 1 for the normal skin.

r PK samples will be collected at the following timepoints relative to the morning dose: predose and at 1, 4, and 6 hours postdose on Days 1 and 15; predose on Days 8 and 29; and at the Day 43 visit, approximately 12 hours after the last dose of study intervention. The time of last application of study intervention prior to the Day 8, Day 15, Day 29, and Day 43 visits should be recorded. The allowed time deviation window before a deviation is recorded for blood sample collection post dose is 15 minutes for time points up to and including 6 hours post dose; pre-dose samples should be collected within 30 minutes prior to the next application of study intervention.

s Samples for blood biomarker levels should be drawn predose on Days 1, 8 and 15, and at the Day 43 visit approximately 12 hours after the last dose of study intervention.

t Local tolerability assessment will be performed within approximately 30 minutes of dosing by site staff using the symptom grading in Appendix 4 (Section 10.4.1) at each dosing when patients are at study site during dosing. During the blinded period in case the investigational products are applied at the patient's home or external clinic, the local tolerability assessment will be performed by a trained medical professional, different than the person administering the study intervention.

u If it becomes difficult for the patient to visit the study site, investigational products could be applied by a trained medical professional at patient's home or an external clinic, where available, as a backup option. The morning Visit of D1 and D8 must be conducted at the study site.

2 INTRODUCTION

2.1 STUDY RATIONALE

Bruton's tyrosine kinase (BTK) is an essential signaling element downstream of the B cell receptor (BCR), Fc-gamma receptor (FcγR), and Fc-epsilon receptor (FcεR). BTK is a non-receptor tyrosine kinase and is a member of the TEC tyrosine protein kinase family of kinases (Mohamed 2009). BTK activation is critical for B cell differentiation, activation, and maturation. BTK also regulates the activation of other hematopoietic cells, such as mast cells, macrophages, and neutrophils primarily through Fc receptor signaling (Rip 2018). Platelets express high levels of BTK, which is involved in collagen/glycoprotein VI (GPVI) signaling; however, alternative signaling pathways exist with bypass BTK signaling to retain normal platelet functions and thrombus formation (Futatani 2001, Byrd 2013).

BTK inhibition results in the down regulation of various immune cell activities including cell proliferation, differentiation, maturation, survival, cytokine production and the induction of apoptosis. Inhibition of BTK activity in B cells produces phenotypic changes consistent with blockade of the BCR, preventing activation, maturation, and antibody production. Inhibition of BTK in FcγR and FcεR expressing cells (such as macrophages or mast cells) blocks the inflammatory cytokine cascade driven by antibody cross-linking to the surface receptors (Chang 2011, Xu 2012). Deficiency or inhibition of BTK has been shown to reduce disease in several immune-mediated rodent models. Pertinent to the treatment of patients with immune-mediated diseases, inhibitors of BTK have been shown to be anti-inflammatory in several rodent models of arthritis (Chang 2011, Di Paolo 2011, Honigberg 2010, Kim 2011, Xu 2012), and lupus (Crofford 2016, Honigberg 2010, Hutcheson 2012) with inhibition of proteinurea, kidney histopathology, nephritis, and cutaneous endpoints. BTK inhibitors also inhibit acute skin inflammation and vasculitis in antibody induced arthus reaction model and murine passive cutaneous anaphylaxis models (Chang 2011). Several orally administered BTK inhibitors, including PRN1008, SAR442168/PRN2246, evobrutinib, and fenebrutinib, are currently in clinical development for a range of immune-mediated diseases such as pemphigus, chronic spontaneous urticaria, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis.

A topically applied BTK inhibitor could block the initiation and propagation of various immune-mediated dermatological diseases locally in the skin, with a potential clinical advantage of very limited systemic exposure. Such local skin mechanisms include inhibition of local immune cell activation, blockade of antibody-mediated Fc receptor induced inflammation, and recruitment and retention of neutrophils in the affected skin areas. Excessive and persistent infiltration of neutrophils into tissues has a role in multiple inflammatory diseases (Oliveira 2016), making neutrophil behavior a potential target for drug therapies, ideally to achieve resolution of inflammation at a specific site without causing systemic immunosuppression.

PRN473 is an investigational drug that is being developed as a topical agent for the treatment of immune-mediated dermatological diseases. PRN473 demonstrates selectivity for BTK and a small number of kinases containing a homologous cysteine with durable but reversible BTK occupancy in biochemical assays which translates into a long duration of action in cellular systems.

Atopic Dermatitis

Atopic dermatitis (AD) is a common, chronic, relapsing, pruritic, inflammatory skin disease. It is characterized by xerosis and acute (erythematous papules, vesicles, edema, exudation, crusting), subacute and chronic (scaly, erythematous papules and plaques, lichenification, excoriations, fissuring) eczematous skin lesions (Bieber 2010, Eichenfield 2014, Bieber 2017, Boguniewicz 2017, Silverberg 2017). Typically, AD presents with an age-related morphology and distribution (Eichenfield 2014, Bieber 2017).

The global prevalence of AD is estimated to be approximately 15-30% in children and approximately 2-10% in adults. In children with AD, onset occurs in 45% during the first 6 months of life, 60% during the first year, and 90% are affected before the age of 5 (Bieber 2010, Bieber 2017, Boguniewicz 2017, Silverberg 2017). Patients can experience spontaneous disease remission later in adolescence but up to 50% will live with AD throughout adulthood (Bieber 2010, Eichenfield 2014, Bieber 2017, Silverberg 2017).

The pathogenesis of AD is multifactorial and includes abnormalities of the skin barrier, defects in the innate and adaptive immune response and alterations in the resident skin microflora (Boguniewicz 2011). While there is a genetic basis for AD with loss-of-function mutations in the filaggrin gene (FLG) which leads to skin barrier abnormalities, there are a number of systemic and cutaneous immune abnormalities also present in AD. It is unclear if the abnormalities in skin barrier precedes the immune dysregulation or vice versa.

Dysregulation of the innate immune system in AD include changes in antimicrobial peptide (AMP) levels, reduced toll-like receptor (TLR) function, increased mast cells in the skin, increased levels of serum immunoglobulin E (IgE), IgE-mediated degranulation and cytokine production, increased thymic stromal lymphopoietin (TSLP) by keratinocytes, increase in eosinophil infiltrates, dermal dendritic cell involvement, and basophil recruitment and activation (Boguniewicz 2011, Werfel 2016, Weidinger 2018). In addition to the innate immune system, there are also abnormalities of the adaptive immune system in AD. Some of these abnormalities include an increase in T_H2 lymphocytes, increased T_H2 cytokine activity A (IL-4 and IL-13) which initiates B-cell IgE class switching, increase in T_H1, T_H17, and T_H22 cells and their related cytokine and chemokine production (Weidinger 2018). Topical treatments are the standard therapies for patients with mild to moderate AD. Topical steroids are typically the first line of treatment but they are used intermittently to reduce the localized adverse effects such as skin atrophy, purpura, telangiectasis, and dyspigmentation (Weidinger 2018). Topical calcineurin inhibitors (TCIs) have been used in AD as a steroid sparing treatment, however, these agents include a Food and Drug Administration (FDA) black box warning of a potential increase in the risk of lymphoma. In addition, the use of TCIs has been limited by their inferior efficacy compared to the topical steroids. The most recently FDA approved topical therapy for AD is crisaborole ointment, a cAMP-specific phosphodiesterase-4 inhibitor. Crisaborole ointment has been shown to have a modest improvement of disease (32% improvement from baseline) compared with the vehicle alone (18-25% improvement) (Ahmed 2018). In addition, crisaborole has a significant localized burning and stinging at the site of application. Moderate efficacy combined with localized adverse effects has led to the reduced use of crisaborole over TCIs and topical steroids.

Despite progress in the treatment of mild to moderate AD, there is still a need for a safe and efficacious agent that has:

- Superior or comparable efficacy to Class 1 topical corticosteroids
- Excellent safety and tolerability profile
- Safe and effective as a maintenance therapy
- No rebound effect after discontinuation

As stated above, based on the multiple roles BTK plays in adaptive and innate immunity, a topical BTK inhibitor has the potential to block the initiation and propagation of various immune-mediated dermatological diseases such as AD locally in the skin, with a potential clinical advantage of very limited systemic exposure.

2.2 BACKGROUND

2.2.1 Nonclinical studies

PRN473 has undergone an extensive nonclinical safety evaluation. All nonclinical studies conducted for PRN473 are described in detail in the PRN473 Investigator's Brochure.

PRN473 has demonstrated slow off-rate binding kinetics to the BTK enzyme; this has an advantage over fast off-rate molecules in that the longer a molecule can interact with its target, the longer the inhibition and resulting increase in efficacy. Slow off-rates also lead to longer duration of action with the potential to reduce the frequency of re-application while maximizing effective target inhibition at the topically applied target site. The potential clinical advantage of a topical PRN473 is that a longer target residence time may prolong efficacy locally with very low systemic exposures observed in the plasma.

PRN473 has been evaluated in pharmacology, PK, and toxicology studies in mice, rats, dogs, and mini pigs as an oral and topical agent. Oral PRN473 has been demonstrated to be pharmacologically active in mice and rats using collagen-induced arthritis, and in dogs with naturally occurring spontaneous pemphigus foliaceus. This is expected since the amino acid sequences of mouse, rat, dog, mini pig, and human BTK are essentially identical (99% homology), with no differences across species in the adenosine triphosphate (ATP) binding site where PRN473 binds. Topical PRN473 Gel has also been demonstrated to be pharmacologically active in mice and rats, using passive cutaneous anaphylaxis and reverse passive arthus as in vivo models of efficacy.

2.2.1.1 Nonclinical pharmacology

PRN473 is a potent, ATP-competitive, reversible inhibitor of BTK. PRN473 demonstrates rapid on and slow off-rate kinetics on BTK, as well as a few closely related TEC kinase family members: BMX, TEC, and TXK. PRN473 does not demonstrate durable target occupancy of B lymphocyte kinase or interleukin (IL)-2-inducible T-cell kinase.

PRN473 is an ATP-competitive inhibitor of BTK. Half maximal inhibitory concentration (IC_{50}) values for PRN473 were 2.1 ±0.1, 5.1 ±0.3, and 13.0 ±0.7 nM at ATP concentrations of 16, 160, 800 µM, respectively.

The binding characteristics of PRN473 to other kinases that had demonstrated cross-reactivity with PRN473 was assessed utilizing fluorescence competition (Kim 2011). These studies demonstrated that PRN473 exhibited durable occupancy on BMX, TEC, and TXK but not on BLK and ITK.

PRN473 was screened at a concentration of 10 µM in a radioligand binding assay against a panel of receptors, ion channels, and transporters. In this screen, results showing an inhibition higher than 50% were then re-evaluated with a full IC_{50} determination (A3 adenosine receptor [74.7%], dopamine D_{2s} receptor [60.4%], the gamma-aminobutyric acid [GABA]-gated Cl^- channel [69.3%], and dopamine transporter [94.8%]). Follow-up IC_{50} assays for these receptors demonstrated only weak activity (IC_{50} >1 µM) with no measurable IC_{50} for dopamine D_{2s} receptor up to 100 µM. Activity against all other receptors, transporters, and channels in this panel was less than 50%. This data reaffirms the selectivity of PRN473 for BTK and reduced potential for off target binding and signaling.

The activity of PRN473 was evaluated in several cell-based assays in which the occupancy of BTK and the resulting functional effects of the compound in primary cells was assessed. The data from the cell-based assays support the in vitro biochemical data showing that PRN473 is a potent inhibitor of BTK and inhibits the BCR mediated activation of B cells, IgE-mediated activation of mast cells and basophils, immunoglobulin G (IgG)-mediated activation of monocytes, and neutrophil migration. PRN473 demonstrated weak cytotoxicity in cell lines not expressing BTK and exhibited only weak activity on T-cell activation and epidermal growth factor receptor (EGFR) activation.

A summary of the in vitro pharmacology of PRN473 is provided Table 1. Values greater than 5000 nM or 20 000 nM indicate no activity in the assay at the limits of the concentrations tested. These data are consistent with PRN473 being a potent BTK inhibitor.

Table 1 - Summary of biochemical and cellular characterization of PRN473

Assay	Value ±SD
BTK enzymatic IC_{50}	1.8 ±0.2 nM
BTK biochemical occupancy at 24 hr	83 ±5%
Ramos B cell occupancy IC_{50}	30 ±15 nM
Occupancy of BTK in Ramos cells at 4 hr and 18 hr	91 ±3% (4 hr), 54 ±6% (18 hr)
Occupancy of BTK in WB IC_{50}	364 ±112 nM
B cell activation in HWB IC_{50}	274 ±95 nM
IgG induced TNFα production in human monocytes	76 ±40 nM
IgE induced WB human basophil CD63 activation	1130 ±510 nM
IgE mast cell degranulation β-hexaminidase release	89 nM
IgE mast cell degranulation histamine release	175 nM
EGFR signaling reporter assay IC_{50}	>5000 nM
Cytotoxicity in HCT-116 cells IC_{50}	>20 000 nM

Abbreviations: BTK = Bruton's tyrosine kinase; EGFR = epidermal growth factor receptor; IC_{50} = half maximal inhibitory concentration; IgE = immunoglobulin E; IgG = immunoglobulin G; SD = standard deviation; TNFα = tumor necrosis factor alpha.

In vivo pharmacology studies were conducted with oral PRN473 in naturally occurring pemphigus foliaceus in dogs, and experimental rodent collagen-induced arthritis models.

In all preclinical studies, PRN473 demonstrated anti-inflammatory effects with dose-dependent inhibition of clinical scores achieved as monotherapy. Both topical PRN473 Gel or oral PRN473 demonstrated similar efficacy to corticosteroids (topical betamethasone dipropionate or high dose oral prednisolone).

Topical PRN473 Gel inhibition of IgG antibody-mediated skin inflammation was studied in the rat arthus model. Topical PRN473 Gel demonstrated significant dose-dependent inhibition of passive arthus reaction, as measured by reduction in diameter of intra-dermal dye extravasation and OD_{610nm} from skin biopsy following IgG antibody challenge. A single administration of topical PRN473 Gel (over approximately 3 cm^2 area) 3 hours prior to IgG antibody challenge achieved significant inhibition at strengths greater than 0.5% (1 mg/cm^2). Similarly, multiday (3 days) application once daily (QD) also achieved significant inhibition at strengths greater than 0.5%. Complete responses equivalent to topical betamethasone dipropionate were achieved with 1% (2 mg/cm^2) and 2% (4 mg/cm^2) PRN473 Gel treatment after single day or multiday (3 days) application. Multiday (3-day) treatment with QD application of PRN473 Gel revealed that the maximal efficacy equivalent to corticosteroids could be achieved with the lower strength of topical gel compared to single day gel application. PRN473 Gel demonstrated prolonged inhibitory effect, maintaining significant dose-dependent inhibition when applied 16 hours prior to challenge.

To confirm that systemic pharmacology did not contribute to the efficacy of the topical PRN473 Gel, the systemic BTK occupancy was assessed in spleens collected terminally from the arthus rats on study (4 hours post challenge). Topically applied 2% (4 mg/cm^2) PRN473 Gel did not result in measurable systemic BTK occupancy following either single dose or multiday

(3-day) dosing, confirming that the efficacy of PRN473 Gel was driven by local skin effects and not by systemic pharmacology. Topical PRN473 Gel efficacy was equivalent to oral PRN473 (10-40mg/kg, per oral [PO], QD) and oral prednisone (10 mg/kg) treatments in a comparable rat arthus study. Taken together, these results demonstrate that topically applied PRN473 Gel can effectively inhibit IgG-mediated FcγR signaling, equivalent to topical or oral corticosteroids, and prevent downstream IgG antibody-mediated immune effects locally in the skin.

There was little impact on efficacy when a single dose of 1% PRN473 Gel was administered three hours, one hour or 10 minutes prior to challenge for the inhibition of passive arthus reaction in rats. Similarly, there was no impact on efficacy if this single dose of 1% gel was washed off prior to challenge, demonstrating that PRN473 Gel achieved a prolonged inhibitory effect without the need for continual exposure in the Rat Passive Arthus model.

Topical PRN473 Gel demonstrated significant dose-dependent inhibition of mouse passive cutaneous anaphylaxis, as measured by reduction in diameter of intra-dermal dye extravasation and optical density (OD_{610}) from skin biopsy following IgE-mediated challenge. A single administration of topical PRN473 Gel 3 hours prior to challenge achieved significant inhibition at strengths greater than 1% (0.6 mg/cm^2). Multiday (3 days) treatment with QD application achieved similar levels of inhibition. Significant responses approaching topical betamethasone dipropionate or antihistamine were achieved with 4% (2.4 mg/cm^2) PRN473 Gel treatment. These results demonstrate that topically applied PRN473 Gel (over an approximately 3 cm^2 area) can effectively inhibit IgE-mediated FcεR signaling, equivalent to corticosteroid or antihistamine treatment, and prevent downstream IgE antibody-mediated immune effects locally in the skin.

2.2.1.2 Pharmacokinetics and metabolism in animals

Metabolism was assessed in vitro with S9 liver fractions, liver microsomes, and cryopreserved hepatocytes from several species. The species-specific microsomal system the highest clearance was observed in dog (intrinsic clearance [CL_{int}] = 188 µL/min/mg protein) and the lowest clearance was observed in human (CL_{int} = 140 µL/min/mg protein).

In the S9 fractions from mouse, rat, dog, monkey, and human, a total of 8 potential metabolites from PRN473 were identified. Most of the metabolites were minor (1-10% relative peak area by mass spectrometry). Two metabolites, M6 and M7, were identified as potential major metabolites (10% relative peak area) in a subset of species.

In vivo metabolic profile studies of oral PRN473 in mice, rat, dog, monkey, and mini pig identified three major metabolites: the reduced metabolite (PRN684), the hydrolyzed metabolites (PRN834, PRN835), and the oxidation metabolite (PRN664). Overall, the metabolites observed in all animal species were similar. No unique human metabolites have been detected from studies conducted to date.

Plasma protein binding was >99% in all species and the blood to plasma ratio for distribution in evaluated species was ranged from 0.43 (in dog) to 0.66 (in monkey).

CYP450 inhibition and induction studies have also been completed. The results of the in vitro inhibition studies with 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 showed that PRN473 does not

significantly inhibit CYP450 enzymes (IC_{50} >6 μM across isoforms). In a CYP induction study no induction was seen with PRN473 at 10 μM for the tested isoforms of CYP 1A2, 2B6, and 3A4.

The in vivo PK of PRN473 was assessed in rats, dogs, and mini pigs via intravenous (IV) and PO administration. All species demonstrated good bioavailability following oral administration. Oral bioavailability was lowest in dog (7%) and comparable in mini pig (approximately 17%) and rat (21%). Following topical administration of a single dose in dogs and mini pigs, the systemic exposure was limited (<10 ng/mL for most of the samples) and lower than the exposure observed following oral administration in both rat and mini pig species, suggesting that the topical administration likely demonstrate limited systemic absorption and lower concentration levels compare to oral administration in human. Nonclinical PK studies following IV and PO administration of PRN473 are described in detail in the PRN473 Investigator's Brochure.

2.2.1.3 Nonclinical toxicology

Dermal administration of PRN473 Gel to mini pigs at 0.5% (0.05 mg/cm^2), 2% (0.2 mg/cm^2), and 10% (1 mg/cm^2), strengths for at least 28 days was well tolerated. There were no PRN473-related changes. The maximum tolerated dose was not reached even at the highest dose of 10% when administered QD over a 10 % body surface area (approximately 400 cm^2 at a gel application rate of 10 mg/cm^2/day) of mini pig. At the low dose (0.5% gel) due to the low exposure levels, the kinetic properties of PRN473 were not able to be determined, except one animal on Day 28. The maximum concentrations observed on Day 7 and Day 28, following 10% gel application were 2.32 ng/mL and 3.17ng/mL, respectively. The corresponding area under the concentration-time curve (AUC) values were 11.3 ng×hr/mL and 25.1 ng×hr/mL, respectively. Additionally, the 10% PRN473 Gel did not cause ocular irritation and the PRN473 Gel may have the potential to be a contact sensitizer as discussed in the Investigators Brochure.

In a 28-Day oral rat study, all treated animals had measurable systemic exposure following both single and repeated QD oral PRN473 administration at doses of 150 and 500 ng/mL. PRN473 mean maximum plasma concentration (C_{max}) values increased less than proportionally and area under the plasma concentration-time curve from time zero to the last measurable concentration ($AUC_{0\text{-last}}$ exposures increased proportionally with increases in dose. No significant accumulation was observed (as assessed by mean C_{max} and $AUC_{0\text{-last}}$ on Day 28 vs Day 1). A higher exposure was observed in females then males as assessed by mean C_{max} and $AUC_{0\text{-last}}$. Treatment with PRN473 was well tolerated. Liver weight changes with associated hepatocellular hypertrophy were observed following oral treatment with 500 mg/kg. Based on these findings, the no-observed-adverse-effect level (NOAEL) in rats is considered 150 mg/kg (C_{max}: female 713 ng/mL, male 308 ng/mL; AUC: female 6600 ng×hr/mL, male 3170 ng×hr/mL).

In a 28-day oral dog study, all treated animals had measurable systemic exposure. PRN473 plasma exposure (as assessed by average C_{max} and $AUC_{0\text{-last}}$) increased in a greater than dose proportional manner over the full dose range on both collection days, with the exception of Day 28 male C_{max} values. PRN-473 plasma exposure (as assessed by mean C_{max} and $AUC_{0\text{-last}}$) increased comparing Day 28 values to Day1 values. Sex differences were noted when comparing PRN473 plasma exposure on Day 1 and Day 28 values. Treatment with PRN473 was well tolerated. Based on these findings, the NOAEL is at least 400 mg/kg (C_{max}: female 2220 ng/mL, male 3390 ng/mL; AUC: female 10 600 ng×hr/mL, male 23 900 ng×hr/mL).

In a 13-week oral rat study, treatment with PRN473 was well tolerated at the dosages tested. Administration of 60 or 150 mg/kg PRN473 was associated with dose-dependent increases in liver weights for males and females with no histomorphologic correlates. Based on these findings, the NOAEL in rats following was considered to be above 150 mg/kg (C_{max}: female 726 ng/mL, male 339ng/mL; AUC: female 4590 ng×hr/mL, male 2940 ng×hr/mL).

In a 13-week oral dog study, treatment of PRN473 at the dosages tested was well tolerated. Administration of any dosage of PRN473 tested was associated with decreased activity and reduced body weight in females. Administration of 400 mg/kg in females was associated with decreased food consumption. Based on these findings, the NOAEL in dogs following oral dosing is considered to be 400 mg/kg (C_{max} 2220 ng/mL and AUC 8860ng×hr/mL) in males and 120 mg/kg (C_{max} 918 ng/mL and AUC 3110 ng×hr/mL) in females.

2.2.2 Clinical studies

First-in-human administration of PRN473 in 38 healthy volunteers occurred in completed Phase 1 Study PRN473-001 using the PRN473 liquid and tablet formulations. The results following oral dose administration up to a single dose of 600 mg (the maximum dose) demonstrated very limited systemic exposure (<10 ng/mL) of PRN473.

Due to the very low systemic exposure, PRN473 was reformulated into a topical gel and then tested in two Phase 1 studies. PRN473 topical has been administered to 42 healthy volunteers in Study PRN473-0002 and 21 patients with IgE-mediated allergies in Study PRN473-0003. Plasma concentrations of PRN473 were measured in PRN473-0002 but not in PRN473-0003. The results from PRN473-0002 showed that the majority of PK samples were not measurable (ie, below the quantitation limit). The samples that were measurable were too low to support computation of PK parameters following topical application in healthy participants.

The individual studies are summarized Table 2 in below.

Table 2 - Summary of PRN473 clinical studies

Study Number/ Formulation	Population (sample size)	Study Purpose	Dose Levels	Status
Phase 1				
PRN473-0001/ liquid and tablet	Healthy volunteer Part A (N = 38 active) Part B (N = 0)	Single and Repeat dose to assess safety, tolerability, and PK (First-in-Human Study)	50, 100, 200, 600 mg (6, 8, or 10 active; 2 PBO per group in Part A)	Completed

Study Number/ Formulation	Population (sample size)	Study Purpose	Dose Levels	Status
PRN473-0002/ topical gel	Healthy volunteer (N = 60)	Single and Repeat dose to assess safety, tolerability, and PK	0.5, 2.0, 5.0% (8 active; 2 PBO in each of 5 single-dose cohorts) 5.0% (8 active; 2 PBO in a repeat-dose cohort)	Completed
PRN473-0003/ topical gel	Patients with IgE-mediated allergies (N = 21)	Single doses to assess pharmacologic activity, safety, and tolerability	0.5, 2, 5%; or PBO	Completed

Abbreviations: MD = multiple-dose; PBO = placebo; PK = pharmacokinetic.

Available data from the Phase 1 studies are summarized in the PRN473 Investigator's Brochure.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PRN473 may be found in the Investigator's Brochure.

2.3.1 Risk assessment

No risks other than those previously mentioned in the Investigator's Brochure are known at this time.

2.3.2 Benefit assessment

Patients may benefit from having regular clinical and laboratory evaluations throughout the study. There may be no direct health benefit for patients from receipt of study intervention.

2.3.3 Overall benefit/Risk assessment

PRN473 is being developed for topical skin application for the treatment of immune-mediated dermatological diseases.

The toxicity potential of PRN473 is well characterized in in vitro assays, safety pharmacology studies, and repeat dose oral and topical toxicity studies in multiple animal species. PRN473 has also been well tolerated when orally administered in single ascending doses to healthy volunteers. The overall preclinical and clinical profile of PRN473 to date continues to favor continued investigation of PRN473.

3 OBJECTIVES AND ENDPOINTS

Table 3 - Objectives and endpoints

Objectives	Endpoints
Primary	
Safety: To assess the safety and tolerability of PRN473 Gel, 5% versus placebo administered BID up to 6 weeks in patients with mild to moderate AD	Safety: • Incidence and severity of AEs • Changes in vital signs, ECGs, and laboratory tests • Assessment of local cutaneous tolerability: incidence and severity of application-site events such as burning/stinging, itching, and erythema
Secondary	
PK: To evaluate the plasma PK of PRN473 following administration of multiple topical doses of PRN473 Gel, 5% for 42 days in patients with mild to moderate AD	• PK: Plasma PRN473 concentrations at specified timepoints
Exploratory	
• Biomarker: To evaluate blood and skin changes in protein and RNA expression, lymphocyte infiltration, and epidermal thickness following treatment with PRN473 Gel, 5% at Days 8 and 15	• Biomarker: Change from Baseline in biomarkers using blood samples, skin tape stripping, and skin biopsy
• Efficacy: To evaluate the preliminary efficacy following double-blind treatment with PRN473 Gel, 5% compared to placebo at Days 8 and 15	Efficacy During Blinded Period: • Change from Baseline in lesion TSS at Days 8 and 15 • Change from Baseline in daily lesional PP-NRS score up to Day 15 • Change from Baseline in lesional validated IGA score at Days 8 and 15 • Lesional validated IGA response (proportion of patients with a validated IGA score of 0 or 1 and ≥2-grade improvement from Baseline) at Days 8 and 15
• Efficacy: To evaluate the preliminary efficacy following open-label treatment with PRN473 Gel, 5% at Days 29 and 43	Efficacy During Open-Label Period • Change from Baseline in TSS for the 2 target lesions at Days 29 and 43. • Change from Baseline in EASI at Days 29 and 43 • Change from Day 15 in EASI to Days 29 and 43 • Proportion of patients with EASI 50, EASI 75, and EASI 90 from Day 15 to Days 29 and 43 • Change in PP-NRS from Day 15 to Days 29 and 43 • Proportion of patients achieving at least 3-point reduction from Day 15 in PP-NRS at Days 29 and 43 • Proportion of patients achieving at least a 4-point reduction from Day 15 in PP-NRS at Days 29 and 43

Objectives	Endpoints
	• Change from Day 15 in weekly mean of PP-NRS at Days 29 and 43 • Proportion of patients achieving at least 2 grade reduction in vIGA-AD to clear (vIGA-AD 0) or almost clear (vIGA-AD 1) from Day 15 to Days 29 and 43 • Change from Day 15 in SCORAD at Days 29 and 43 • Change from Day 15 in percentage of treatable BSA at Days 29 and 43 • Change from Baseline in POEM at Days 15, 29, and 43 • Change from Baseline in DLQI at Days 15, 29, and 43

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Ph2a study that consists of a double-blind, intra-patient placebo-controlled treatment period and an open-label uncontrolled treatment period with objective to evaluate the safety, tolerability, PK and preliminary efficacy of PRN473 in up to 40 patients with mild to moderate AD. All patients are required to apply an emollient (except urea-containing or medicated emollients that are regulated as medical device) daily from Day -7 to Day 1 (see Section 6.2). On Day 1 (Baseline) of the Blinded Period, 2 target lesions with a difference no greater than 1 point in TSS will be randomly assigned to treatment in an intra-patient 1:1 manner, one lesion to PRN473 Gel, 5%, and the other to matching placebo. PRN473 Gel, 5% and matching placebo are weighed and applied BID (morning and evening) at a quantity of approximately 2.5 mg/cm^2 to a 100 cm^2 area of each target lesion on Days 1- 14 (Blinded Period). The investigational products will be applied at the study site, at the patient's home, or at an external clinic, where available.

During the Blinded Period, if the target lesion is less than 100 cm^2, the application area should include surrounding nonlesional skin (note: two target lesion skin biopsy specimens on Days 1 and 15 are only on lesional skin); if the target lesion is larger than 100 cm^2, only 100 cm^2 of the lesion should be marked and treated. On Days 15-42 (Open-Label Period), patients are instructed to apply PRN473 Gel, 5% BID to all AD-affected areas in a thin layer (excluding the scalp, palms, soles and genitals) and should continue to treat the assigned areas throughout the Open Label Period.

Safety assessments include application site tolerability assessments (Appendix 4, Section 10.4.1), vital signs, ECGs, physical examination, safety labs, and AEs.

To evaluate the PK (plasma concentrations) and biomarker of PRN473, blood samples will be collected at study visits accordingly to the SoA (Section 1.3).

Efficacy assessments of:

- The lesional PP-NRS will be administered daily predose during the Blinded Period (Days 1-14) and at predose Day 15.
- The lesional validated IGA will be performed predose at Baseline (Day 1), and Days 8 and 15.
- The lesion TSS (Appendix 4, Section 10.4.3) will be performed predose at Baseline (Day 1), Days 8, 15, and 29, and at End of Study/Early Termination visit (Day 43).
- The EASI, the POEM, and the DLQI will be performed predose at Baseline (Day 1), Days 15 and 29, and at End of Study/Early Termination visit (Day 43).
- The vIGA-AD (Appendix 4, Section 10.4.2) will be performed, predose at Days 15 and 29, and at End of Study/Early Termination visit (Day 43).
- The SCORAD will be performed predose at Days 15 and 29, and at End of Study/Early Termination visit (Day 43).

- The PP-NRS will be administered daily predose before patient morning application during the Open-Label Period (Days 15-42) and at End of Study/Early Termination visit (Day 43).
- The percentage of treatable BSA will be calculated at Screening, Days 15 and 29, and at End of Study/Early Termination visit (Day 43).

To be included in the population analyzed for efficacy, the patient must have received at least 80% of prescribed study intervention in the Blinded Period and/or at least 80% of prescribed study intervention in the Open-Label Period.

Skin tape stripping (STS) will be performed predose on Days 1, 8 (optional), 15, 29, and at Day 43 for the two target lesions and on Day 1 for the normal skin. For a minimum of 20 patients (may be reduced to 15 patients if there is an impact on enrollment from COVID-19, a 4 or 5 mm punch skin biopsy will be collected from each target lesion on Days 1, 15, and 29 (optional) and from normal skin on Day 1. The lesional biopsy specimens at Days 15 and 29 will be collected in the vicinity of the Day 1 (Baseline lesional sample) biopsy but must be at least 1 cm away from the prior biopsy site. If the target lesion cleared after Day 1 and before Day 15, the biopsy specimen will be taken from the lesional skin location of the target area identified at Baseline.

Additional information regarding study assessments and their timing is located in the Schedule of Activities (Section 1.3).

Inclusive of an up to 5-week screening period, a 6-week treatment period, end of study assessments 1 day after last dose, and a safety follow-up phone call 2 weeks after last dose, the participation will take approximately 13 weeks.

Due to the COVID-19 pandemic, safety measures may be implemented to ensure continued supply of study medication and safety monitoring for patients. When the COVID-19 pandemic resolves, the measures will be repealed back to the previous state as government rules and benefit/risk assessment allow.

As required, these approaches (in accordance with local regulations) will be documented in site guidance materials.

Additionally, during the COVID-19 pandemic, drug supply may be sent to patients when the patient is not able to travel to the site or the site cannot host a patient visit. At-site study visits as outlined in the Schedule of Activities may be changed to a remote visit (eg, phone call, video call, or visiting nurse) as needed to address the COVID-19 restrictions.

If the change to remote visits is implemented due to COVID-19 to protect the safety and well-being of patients, the inability to perform/obtain protocol-specified assessments at a required study visit will be documented.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

See Section 2.1.

4.3 JUSTIFICATION FOR DOSE

The dose of PRN473 selected for topical administration during the Blinded Period on Days 1-14 in PRN473-0005 (ACT17131) is PRN473 Gel, 5% or matching placebo at approximately 2.5 mg/cm^2 over a 100 cm^2 area encompassing each target lesion BID (approximately 12 hours apart). During the Open-Label Period on Days 15-42, PRN473 Gel, 5% at 2.5 mg/cm^2 will be applied BID to all AD-affected areas excluding the scalp, palms, soles, and genitals over a body surface area of up to 14%. This dose is in the range of those associated with biological activity based on preclinical disease models and is therefore considered appropriate to evaluate in this initial assessment of PRN473 Gel efficacy in patients with AD.

The proposed dosing regimens are supported by clinical safety data from the PRN473-0002 study. The total daily dose during the Blinded Period of the study (25 mg PRN473 active pharmaceutical ingredient [API] per day) is approximately 7-fold lower than the daily dose applied in the multiple dose arm of PRN473-0002 (175 mg PRN473 API per day). This dose was safe and well-tolerated and there were no serious adverse events (SAEs) or AEs that led to discontinuation.

In the Open-Label Period, the dosing regimen of PRN473 5% (w/w) gel at 2.5 mg/cm^2 gel over 14% BSA BID will provide a daily PRN473 (API) dose of 665 mg to a patient with a total body surface area of 1.9 m^2. This is less than the dose of 700 mg PRN473 (API), which was the highest dose administered in the PRN473-0002 single ascending dose/multiple dose study in healthy participants. This dose was safe and well-tolerated and there were no SAEs or AEs that led to discontinuation.

Patients will measure the dose by the fingertip unit method and the expected dose variability when the compound is topically self-applied by this method may be up to two-fold excess of compound which is reasonably below the safety margin.

In both the Blinded and Open-Label Periods, the locally applied dose of 0.125 mg API/cm^2 is the same as that evaluated in the multiple dose arm of the PRN473-0002 study and is 4-fold lower than the highest dose that was evaluated in the single ascending dose part of PRN473-0002. In addition, this dose is approximately 8-fold lower than the maximum dose (1 mg API/cm^2) used in the 28-day mini pig dermal repeated dose study (DVR489), in which there were no PRN473-related changes, providing further support for the safety of the locally applied PRN473 dose of 0.125 mg API/cm^2.

Systemic PRN473 exposures following administration of PRN473 Gel at all dose levels in study PRN473-0002 were negligible to nonexistent, with insufficient data to estimate PK parameters as plasma PRN473 concentrations were only sporadically detectable in a few participants. However, the safety of systemic PRN473 has been characterized in dog and rat toxicity studies in which the NOAEL doses in both species were substantially higher than the exposures following oral administration to humans. On Day 28, the male and female rat (most sensitive species) mean PRN473 C_{max} values were 308 ng/mL and 713 ng/mL, respectively. At Week 13, the male and female rat mean PRN473 C_{max} values were 339 ng/mL and 726 ng/mL, respectively. These systemic exposures represent a very large safety margin compared to measured exposures of PRN473 following topical administration of a 10% gel to the mini pig and following oral administration of PRN473 in healthy volunteers (Study PRN473-001).

In summary, the totality of the clinical and preclinical data supports the evaluation of the dosing regimen of 5% (w/w) PRN473 Gel at 2.5 mg gel/cm^2 over up to 14% BSA in patients with AD.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last patient in the study.

A patient is considered to have completed the study if he/she has completed all phases of the study including the Day 43 and Day 56 safety follow up phone call.

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

Patients are eligible to be included in the study only if all the following criteria are met:

1. Male and female adults 18 to 70 years of age (inclusive) at the time of informed consent.

2. Diagnosed with mild to moderate AD, meeting at least 3 major and 3 minor criteria according to Hanifin and Rajka (Hanifin 1980; Appendix 4, Section 10.4.4) prior to or at the Screening visit.

3. History of AD for at least 6 months as determined by the Investigator through patient interview.

4. Stable disease for the 4 weeks prior to the screening visit with no significant flares in AD as determined by the Investigator.

5. Validated Investigator Global Assessment-atopic dermatitis (vIGA-AD) score of Moderate (3) or Mild (2) at Screening. The vIGA-AD is evaluated for the entire body except scalp, palms, soles and genitals.

6. Has AD involvement (excluding scalp, palms, soles and genitals) of at least 1.0% BSA and no more than 14.0% BSA.

7. Has at least two target lesions 100 cm^2 or greater with a difference no greater than 1 point in lesion TSS and at least 5 cm apart located on the trunk (excluding genitals) or upper extremities (excluding palms)

8. Male patients are eligible to participate if they agree to the following during the intervention period and for at least 2 days (eg, 5 terminal half-lives) after the last dose of study intervention,

- Refrain from donating sperm

  PLUS, either:

  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

  OR

  - Must agree to use contraception/barrier as detailed below:

    Agree to use a male condom and an additional highly effective contraceptive method as described in Appendix 2 Contraceptive and barrier guidance (Section 10.2) when

having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

9. A female patient is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a WONCBP as defined in Appendix 2 Contraceptive and barrier guidance (Section 10.2).

  OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 2 Contraceptive and barrier guidance (Section 10.2) during the study intervention period and for at least 2 days (eg, 5 terminal half-lives) after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

  A WOCBP must have a negative highly sensitive pregnancy test (urine and/or serum as required by local regulations) within 28 days before the first administration of study intervention, see Section 8.2.5 Pregnancy testing.

  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the patient must be excluded from participation if the serum pregnancy result is positive.

10. In good health as judged by the Investigator, based on medical history, physical examination, serum chemistry labs, hematology values, and urinalysis.

11. Patients are considered reliable and capable of adhering to the protocol and visit schedule, according to the judgment of the Investigator.

12. Able to provide written informed consent and agreeable to the schedule of activities.

5.2 EXCLUSION CRITERIA

Patients are excluded from the study if any of the following criteria are met:

1. Patients who have failed 2 or more prior systemic treatments for AD (not including those who discontinued systemic treatments due to safety or tolerability issues).

2. Patients with any serious or uncontrolled medical condition or clinically significant laboratory, ECG, vital signs, or physical examination abnormality that would prevent study participation or place the patient at significant risk, as judged by the Investigator.

3. Patients who have received a live or attenuated vaccine in the last 12 weeks or intend to receive a live or attenuated vaccine during the study.

4. Patients who cannot discontinue medications and treatments prior to the Baseline visit and during the study listed in the Excluded Medications and Treatments table.

5. Has unstable AD, based on the judgement of the Investigator, or any consistent requirement for high potency topical steroids to manage AD signs or symptoms.

6. Patients who have significant active systemic or localized bacterial, viral, fungal, and helminth infection in the last 30 days (including known actively infected skin at or around a lesion of AD). Non-complicated recurrent muco-cutaneous infections such as cold sores are not considered exclusionary.

7. Patients unwilling to refrain from prolonged sun exposure or use of a tanning bed or other artificial light emitting devices for 4 weeks prior to Baseline and during the study.

8. Patients with other skin conditions that would interfere with evaluations of the effect of the study medication on AD, as determined by the Investigator. Patients with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.

9. Patients with known genetic dermatological conditions that overlap with AD, such as Netherton syndrome.

10. Patient has any state of immunodeficiency including but not limited to primary or secondary immunodeficiency syndromes, organ transplant (except corneal transplant), and previous opportunistic infections, as judged by the Investigator.

11. Known allergies to excipients in PRN473 Gel.

12. Previous use of a BTK inhibitor.

13. Women who are pregnant, wishing to become pregnant during the study, or are breastfeeding.

14. Patients currently undergoing allergy (eg, food allergy testing or skin prick testing), patch testing, or food challenges, or plan to do so during the study.

15. Patients who have undergone major surgery within 4 weeks prior to Day 1 or patients who have a major surgery planned during the study.

16. Regular use of drugs of abuse or regular alcohol consumption within 6 months prior to the study defined as: an average weekly intake of >35 units for males or >35 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 (25 mL) measure of spirits.

17. History of any malignancy except skin basal cell or squamous cell carcinomas in situ that have been removed and completely resolved at least 5 years ago.

18. Any of the following laboratory abnormalities at the screening visit (identified by the central laboratory):
    - Absolute neutrophil count <1.5 x 10^9/L
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x upper limit of normal (ULN)
    - Total bilirubin >1.5 x ULN, (isolated bilirubin >1.5 x ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%)
    - Abnormal international normalized ratio (INR) test and activated partial thromboplastin time (aPTT) judged by the Investigator to be clinically significant
    - A platelet count <150 000/μL
19. Electrocardiogram (ECG) findings of QT corrected for heart rate (QTc) >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant cardiovascular abnormalities.
20. Positive human immunodeficiency virus (HIV) antibody test.
21. Presence of Hepatitis B surface antigen (HBsAg) and/or core antibody positive at screening or within 3 months prior to first dose of study intervention.
22. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study intervention. NOTE: Patients with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.
23. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest X-rays (posterior anterior and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration ≥5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) TB test such as QuantiFERON®-TB Gold Plus test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold Plus test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold Plus test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.
24. History of serious infections requiring intravenous therapy with the potential for recurrence or currently active moderate to severe infection at Screening (Grade 2 or higher) including active coronavirus disease 2019 (COVID-19).
25. Patients who have received the last dose of a COVID-19 vaccine within 14 days prior to Day 1.

26. Patients who are family members of the clinical study site, clinical study staff, or Sponsor, or family members of enrolled patients living in the same house.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

There are no dietary restrictions in this study.

5.3.2 Caffeine, alcohol, and tobacco

Patients will be excluded from the study if there is a history of chronic alcohol abuse within 6 months prior to the first study intervention administration.

5.3.3 Activity

Given that natural outdoor ultraviolet (UV) exposure can help treat AD lesions, patients must limit excessive UV exposure when possible (including refraining from suntanning) and should use sunblock SPF 30 or above when outdoor activities are planned.

Patients must keep the topical gel on the skin for at least 4 hours after application of study intervention by refraining from swimming, bathing, using a sauna, or washing the treated areas.

After applying the topical gel, patients should avoid wiping the study intervention off the area or covering the treated areas with wraps or bandages. To avoid ingestion of study intervention, wash hands immediately after application of topical gel, and avoid putting hands in mouth.

5.4 SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the study but are subsequently not enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients. Minimal information includes informed consent, demography, eligibility criteria, and any concomitant medications and AEs.

5.5 CRITERIA FOR TEMPORARILY DELAYING ADMINISTRATION OF STUDY INTERVENTION

Not applicable.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTION (S) ADMINISTERED

Table 4 - Study intervention

	PRN473	Placebo
Drug Name	PRN473 Gel, 5%	PRN473 Gel, Placebo
Type	Drug	Placebo
Dose Formulation	White to off-white gel suspension containing PRN473, inactive ingredients (propylene glycol, glycerin, polysorbate 80, medium chain triglycerides, Carbopol 980, preservatives [methylparaben and propylparaben], and water). The gel suspension is adjusted to pH 5.	White to off-white gel suspension containing the same inactive ingredients, except that titanium dioxide used to match the color of PRN473 active ingredient.
Unit Dose Strength(s)	5% (w/w)	0%
Dosage Level(s)	5% (w/w) gel at 2.5 mg gel/cm^2 over 100 cm^2 BID (Blinded Period) or up to 14% BSA BID (Open-Label Period)	Matching placebo at 2.5 mg gel/cm^2 over 100 cm^2 BID (Blinded Period)
Route of Administration	Topical	Topical
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	PRN473 Gel products are filled into aluminum tubes (approximately 30 g in each aluminum tube).	Placebo Gel products are filled into aluminum tubes (approximately 30 g in each aluminum tube).
Former Name(s) or Alias(es)	SAR444727	not applicable

Abbreviations: API = active pharmaceutical ingredient; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The Sponsor will supply the study intervention to the study site. The study intervention provided for this study was manufactured under Current Good Manufacturing Practices (CGMP) and will be suitable for human use. The Sponsor is responsible for the preparation and labelling and providing details of batch numbers, safety, and stability data. The study intervention will be labelled in accordance with local regulatory requirements and will be shipped at a temperature of 2-8ºC.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention. The recommended storage condition is 2-8°C (Investigator's Brochure).

Only patients enrolled in the study may receive study intervention, and only authorized study staff (eg, site staff, trained medical professional, home health vendor, external clinic staff, etc) may supply or administer study intervention during the Blinded Period. At the study site, all study intervention 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). When the study is completed, the Investigator will return or destroy any used and unused trial medication (eg, empty, partially used, and unused containers) to the Sponsor as requested.

The Investigator or designee is responsible for the education of site staff as to the correct administration of the study intervention.

When operationally feasible and if treating physician determines that it is appropriate and safe, administration of IMP may occur at study patient's home or at an external clinic by a trained medical professional. These approaches will only be implemented if allowed by local regulations, and agreed by the treating physician, while ensuring blinding measures are maintained.

Patients are required to apply an emollient (except urea-containing or medicated emollients that are regulated as medical device) daily from Day -7 to Day 1. Beginning on Day 1, emollient is to be applied only on untreated areas (eg, may not be used on the 2 target lesions during Days 1-14, and may not be used on any parts of the body being treated with PRN473 Gel, 5% during Days 15-42).

PRN473 Gel, 5% or matching placebo will be removed from storage at 2-8°C and held at room temperature for at least 30 minutes prior to administration. Site staff or trained medical professional will apply PRN473 Gel, 5% or matching placebo with nitrile gloves to the 2 target lesions per the randomization assignment, as follows:

- Approximately 2.5 mg gel/cm^2 to each 100 cm^2 target lesion on Days 1-14. If the target lesion is less than 100 cm^2, the application area should include surrounding nonlesional skin; if the target lesion is larger than 100 cm^2, only 100 cm^2 of the lesion should be marked and treated.
- On Days 15-42 (open-label period), patients are instructed to apply PRN473 Gel, 5% BID to all AD-affected areas in a thin layer, excluding the scalp, palms, soles, and genitals.

Under no circumstances will the Investigator supply study intervention to a third party (except for direct to patient [DTP] shipment or direct to designated clinic for home health care option if patient is not able to be dosed at home, for which a courier company has been approved by the

Sponsor), allow the study intervention to be used other than as directed by this clinical trial protocol, or dispose of study intervention in any other manner.

Intervention units are returned by the patient at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).

Further details will be outlined in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

PRN473 Gel, 5% or placebo will be randomized in a blinded fashion to be administered in each patient to 2 separate target lesions (one lesion with PRN473 Gel, 5%, the other with matching placebo) during the Blinded Period (Days 1-14). During the Open-Label Period (Days 15-42), PRN473 will be administered to all AD-affected areas in a thin layer, excluding the scalp, palms, soles, and genitals.

To minimize bias, all safety and efficacy measurements will be performed by a study staff member who is not involved in the study intervention application during the Blinded Period. If the investigational products are applied at the patient's home or at an external clinic, the local tolerability assessment will be performed by another trained medical professional, different than the person administering the study intervention.

Allocation of lesions on patients to treatment group will proceed through the use of an interactive web response system (IWRS) that is accessible 24 hours a day, 365 days a year. A randomized treatment kit number list will be generated centrally by Sanofi for the study interventions. The study interventions (PRN473 Gel, 5% or matching placebo) will be packaged in accordance with the list. All patients will be centrally assigned to randomized study intervention using an interactive response technology (IRT). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. During the Blinded Period of the study, the treatment each patient receives will not be disclosed to the Investigator, trial center personnel, patients, or the Sponsor's representatives on the clinical study team. Further details for blinding and dispensing of blinded treatment are provided in the Pharmacy Manual.

Access to the randomization code will be limited; all Sponsor personnel (and representatives), and site personnel who are directly involved in the conduct of the trial will be blinded to randomization codes.

The pharmacist or designee will be required to enter or select information that will include, but not be limited to; the user ID, and password, patient number, patient year of birth, as well as other information (as allowed locally). The pharmacist or designee will then be provided with a patient randomization number and treatment assignment. Once patient numbers and randomization numbers have been assigned, they cannot be reassigned. Specific instructions will be provided in the IWRS trial reference guide.

Study intervention will be dispensed at the study visits summarized in the Schedule of Activities. Returned study intervention should not be re-dispensed to the patients.

Sponsor safety staff may unblind the intervention assignment for any patient with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted (eg, in case of available antidote). Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a patient's intervention assignment unless this could delay emergency treatment of the patient. If a patient's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

- In case of an interim analysis, the Sponsor team that will analyze the data would be composed of a Medical Monitor, a biostatistician, a programmer, and a safety designee. Only the biostatistician and the programmer will have the access to unblinded individual data at the time of the analysis, which will not be provided to other Sponsor team members reviewing the data. They will keep the randomization schedule in a locked area, which is not accessible to the Sponsor's clinical team and will not disclose the randomization or the individual unblinded data before the official opening of the randomization (see Section 9.5).
- The bioanalyst and the pharmacokineticist responsible for the sample analysis and PK evaluation will analyze data under blinded conditions and they will not have access to the randomization schedule.

The Sponsor's clinical study team, Investigator, Medical Monitor, study personnel, and patients are not to make any effort during the Blinded Period to determine which lesions are being treated with PRN473 Gel, 5%, and which are treated with matching placebo.

Only in the case of an emergency, when knowledge of the lesion treatment assignment is essential for the clinical management or welfare of a specific patient, the Investigator may unblind a patient's lesion treatment assignment. However, prior to any unblinding, the Investigator is strongly advised to discuss options with the Medical Monitor, Sponsor, or appropriate study personnel. The Investigator will record in source documentation, the date and reason for revealing the blinded lesion treatment assignment for that patient and the names and roles of personnel unblinded.

As soon as possible, and without revealing the patient's lesion treatment assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to unblinding.

If the Investigator considers an AE to be of such severity as to require immediate specific knowledge of the identity and dose of the relevant product, the Investigator may break the study code for that patient.

6.4 STUDY INTERVENTION COMPLIANCE

Study intervention will be administered under site staff or trained medical professional supervision during the Blinded Period. The date and time of each dose administered at the study site, at patient's home, or at external clinic will be recorded. The dose of study intervention and patient identification will be confirmed at the time of dosing by site staff or trained medical professional other than the person administering the study intervention. Documentation will include the lesion identification for the patient's 2 target lesions.

During the Open-Label Period, patients will complete a daily diary to record PRN473 administered.

6.5 DOSE MODIFICATION

No dose modifications will be permitted.

6.6 CONTINUED ACCESS TO STUDY INTERVENTION AFTER THE END OF STUDY

PRN473 will not be provided to patients after completion of the study.

6.7 CONCOMITANT THERAPY

All medications, including over-the-counter (OTC) medications, vitamins, and herbal supplements, taken during the 30 days prior to the first study intervention administration will be recorded and reviewed by the Investigator to determine whether the patient is suitable for inclusion in the study.

All medications, and vaccines including OTC medications, vitamins, and herbal supplements, taken by patients during the course of the study will be recorded in the electronic case report form (eCRF) and coded using the most current World Health Organization (WHO) drug dictionary. Prior and concomitant medications will be listed by patient and summarized by anatomical therapeutic chemical (ATC) and preferred name. Any concomitant medication that the patient receives to treat an AE during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.7.1 COVID-19 vaccination

To allow for an optimal immune response as well as protection against COVID-19, it is strongly recommended that study patients receive their COVID vaccine (per local requirements) a minimum of 14 days prior to receiving the first dose of study medication. The safety profile and effectiveness of COVID-19 vaccines on people with compromised immune systems or therapies that modify or that suppress their immune response, is not yet established. While vaccination with an approved COVID-19 vaccine is widely recommended, this decision should only be made by the patient, after discussing with his/her physician as well as the investigator to assess the benefits and risks of receiving a COVID-19 vaccination during this study. If the vaccine is authorized, available, and recommended by the local regulatory health authority, it may be administered during the study and should be administered according to the label or local health authority recommendations.

6.7.2 Prohibited medications

Excluded medications and treatments with the applicable washout period prior to Baseline are listed in Table 5.

Table 5 - Excluded medications and treatments

Excluded Medications and Treatments	Washout Period Prior to Baseline
Rituximab or anti-CD-20-targeted therapies	12 months
Other biologics including dupilumab and investigational biologics	12 weeks or 5 half-lives, whichever is longer
JAK-inhibitors and investigational JAK-inhibitors	8 weeks or 5 half-lives, whichever is longer
Systemic treatments that could affect AD (eg, corticosteroids, retinoids, calcineurin inhibitors, hydroxycarbamide [hydroxyurea], methotrexate, cyclosporine, azathioprine, hydroxychloroquine, mycophenolate mofetil, or other immunosuppressive therapies, or systemic treatment with non-sedating antihistamines in a nonstable regimen). Systemic treatments with non-sedating antihistamines in a stable regimen are allowed.	4 weeks or 5 half-lives, whichever is longer
PUVA or NBUVB phototherapy	4 weeks
Topical products containing urea	1 week
Sedating antihistamines and doxepin	1 week
Topical corticosteroids, calcineurin inhibitors, or crisaborole. Topical antibacterial medications or products, including soaps, dilute bleach baths, or sodium hypochlorite-based products anywhere on the body.	4 weeks
Systemic antibiotics	2 weeks
Tanning beds, other light emitting devices	4 weeks
All other investigational drugs	4 weeks or 5 half-lives, whichever is longer
Any live vaccines	12 weeks

Note:
Topical antibiotics, topical antihistamines, or any other topical agents are not permitted to be applied to treated areas. Only study intervention should be applied to treated areas.

6.7.3 Permitted medications

Use of hormonal contraception is allowed prior to and during the study.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Non-medicated emollients, moisturizers, and sunscreens will be permitted once daily in a stable regimen as normally used by the patients and applied at least 2 hours after application of randomized study intervention to untreated areas only (topical agents are not permitted to be applied to treated areas; only study intervention should be applied to treated areas).

6.7.4 Rescue medicine

Rescue topical medications use will be at the discretion of the Investigator after discussion with the Medical Monitor if the patient is flaring above 14% treatable BSA (excluding scalp, palms, soles and genitalia) during the last two weeks of the Open Label Period. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this, if necessary. Patients who receive rescue treatment will be asked to continue with study treatment and procedures.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the Investigator must discuss with the Medical Monitor to determine if the patient will be asked to continue with PK sample collection (if applicable and depending upon the study day on which the discontinuation occurs), and have early termination safety assessments (Day 43). See the Schedule of Activities in Section 1.3.

Patients who are enrolled but who do not receive any dose of study intervention will be replaced. Patients may be replaced at the discretion of the Sponsor.

The Investigator/Sponsor must permanently discontinue dosing with study intervention in a patient if any of the following patient-level stopping rules are met:

- Pregnancy will lead to definitive study intervention discontinuation in all cases.
- Change in compliance with inclusion/exclusion criteria that is clinically relevant and affects patient's safety.
- Intake of non-permitted concomitant medications that might affect patient's safety or study assessments/objectives.
- An allergic reaction, including an anaphylactic reaction, in association with IMP administration.
- Occurrence of AEs, that, in the opinion of Investigator/Sponsor, may jeopardize patient's safety or data integrity. These include, but are not limited to
  - Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status.
  - Serum ALT >5 × ULN or ALT >3 × ULN and total bilirubin >2 ULN (see Section 10.3).

Any clinically significant abnormal laboratory value, as assessed by the investigator, will be rechecked for confirmation as soon as possible before making a decision of definitive discontinuation of the IMP for the concerned patient.

Handling of patients after permanent intervention discontinuation

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a patient meets one of the conditions outlined in Appendix 3 (Section 10.3) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the patient.

7.1.3 QTc stopping criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment, the Investigator or qualified designee will determine if the patient can continue in the study and if any change in patient management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4 Hematology stopping criteria

Discontinuation of study intervention for abnormal neutrophil or platelet tests is required by the Investigator when a patient meets one of the conditions outlined in Appendix 3 (Section 10.3) or in the presence of abnormal results not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the patient.

7.2 PATIENT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or compliance reasons.

The patient may be discontinued from the study intervention but continue in the study for PK sample collection (if applicable) and follow-up visits.

At the time of discontinuation, the patient should have early termination safety assessments (Day 43). See the Schedule of Activities in Section 1.3.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3 LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he or she is unable to be contacted by the study site, and the following actions must be taken:

- The site must attempt to contact the patient and reschedule the End of Study/Early Termination visit as soon as possible, counsel the patient on the importance of participating, and ascertain whether or not the patient wishes to participate.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of the study as a whole is described in Section 10.1.7.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities in Section 1.3. Protocol waivers or exemptions are not permitted.

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. Patients are permitted to be re-screened once. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 550 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

Efficacy assessments will be performed per the Schedule of Assessments in Section 1.3:

- Lesional PP-NRS is a patient-completed assessment to determine the intensity of lesion pruritus.
- Lesional validated IGA is an Investigator assessment of the 2 target lesions during the Blinded Period and predose at D15 during the Open-Label Period.
- Eczema Area and Skin Severity Index (EASI) is a validated Investigator-administered scoring system used to measure the severity of clinical signs in AD.
- Validated Investigator Global Assessment-Atopic Dermatitis (vIGA-AD; Appendix 4, Section 10.4.2) is an Investigator assessment of the global severity of clinical signs in AD.
- Lesion TSS (Appendix 4, Section 10.4.3) is a scale that rates the severity of each of 4 AD symptoms (erythema, induration/papulation, excoriation, and lichenification) on a 4-point scale from 0 (none) to 3 (severe), for a total score ranging from 0 to 12.

- SCORing atopic dermatitis (SCORAD) is a clinical tool used to assess AD by intensity, extent, and subjective signs.
- Peak Pruritus Numeric Rating Scale (PP-NRS) is a patient-completed assessment to determine the intensity of peak pruritus over the previous 24 hours.
- Patient-Oriented Eczema Measure (POEM) is a validated, patient-derived assessment measure for monitoring atopic eczema severity.
- Dermatology Life Quality Index (DLQI) is a validated, self-administered questionnaire designed to measure the health-related quality of life of adult patients suffering from a skin disease.
- Estimation of treatable BSA.

8.2 SAFETY ASSESSMENTS

Safety will be assessed by means of application site tolerability assessments (Appendix 4, Section 10.4.1), occurrence of AEs, clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis), vital signs measurements, 12-lead ECGs, and physical examinations.

Planned timepoints for all safety assessments are provided in the Schedule of Activities in Section 1.3.

8.2.1 Physical examinations

A complete physical examination includes, at a minimum: assessments of the abdomen, chest, ear, head and neck, heart, lower limb, upper extremity, lung, musculoskeletal, neurological, rib, skin, thoracic vertebra, lumbar spine, and cervical vertebra. Height (only at screening) and weight will also be measured and recorded.

A symptom-directed physical exam is to be performed as clinically indicated at visits when a complete examination is not specified.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

Vital signs will be measured at the timepoints specified in the study schedule with patients resting for at least 5 minutes in a supine position. When the time of vital signs measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible, ensuring the blood draw is within the window specified.

Additional vital sign measurements may be performed at other times if deemed necessary.

8.2.3 Electrocardiograms

A 12-lead ECG will be performed at the timepoints indicated in the study schedule. Additional ECG monitoring may be conducted at other times as deemed necessary. Refer to Section 7.1.3 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

The ECGs will be performed prior to vital signs with patients in a supine position. Patients must remain in this position for at least 5 minutes before the reading is taken. All ECG tracings will be reviewed by the Investigator or designee.

When the time of ECG monitoring coincides with a blood draw, the ECG will be performed before the scheduled blood draw while ensuring the blood draw is within the window specified in the protocol.

A repeat ECG can be performed if results are abnormal.

8.2.4 Clinical safety laboratory assessments

See Section 8.2.4.1 for the list of clinical laboratory tests to be performed and the Schedule of Activities in Section 1.3 for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the patient's condition.

Any treatment-emergent abnormal laboratory or ECG result that is clinically significant (ie, meeting one or more of the following conditions) should be recorded as a single diagnosis on the AE page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study intervention (eg, dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (eg, addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

Note: Any laboratory or ECG result abnormality fulfilling the criteria for a SAE must be reported as such, in addition to being recorded as an AE in the eCRF.

The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be a more severe variation in patient's disease activity than expected.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory tests, as defined in Section 8.2.4.1, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), the results must be recorded.

8.2.4.1 Clinical laboratory tests

The tests detailed in Table 6 will be performed. Investigators must document their review of each laboratory safety report. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 6 - Laboratory tests

Laboratory Test	Parameters	
Hematology	Hemoglobin Hematocrit Red blood cell (RBC) count including: • reticulocyte % Platelet Count	White blood cell (WBC) count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Coagulation	International Normalized Ratio (INR)	Activated partial thromboplastin time (aPTT)
Clinical Chemistry [a]	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-GT (GGT) Total and direct bilirubin Alkaline phosphatase (ALP) [b] Creatinine Blood urea nitrogen (BUN)/Albumin Bicarbonate	Sodium Potassium Calcium Chloride Phosphate Glucose (fasting labs only) C-reactive protein Creatine kinase (CK) w/h reflex Troponin I >ULN Lactate dehydrogenase (LDH)

Laboratory Test	Parameters
Routine Urinalysis	Specific gravity, pH, glucose, protein, occult blood, ketones, urobilinogen, nitrite, leukocytes
Pregnancy testing	Highly sensitive serum (at the Screening visit) or urine (Day 1, Day 29, End of Study visits) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) [c]
Other Screening Tests	• Follicle-stimulating hormone (as needed in post-menopausal women of non-childbearing potential only) • Serology (HIV, hepatitis B [surface antigen and core antibodies], hepatitis C [anti-HCV antibody confirmed with Hepatitis C RNA]) • Tuberculosis test (interferon-gamma release assay [IGRA])

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 Liver Chemistry Stopping Criteria and Appendix 5 Liver and other safety: suggested actions and follow-up assessments. All events which may indicate severe liver injury (possible Hy's Law) must be reported to Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

b If alkaline phosphatase is elevated, consider fractionating.

c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

8.2.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female patient with an early undetected pregnancy.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at study visits accordingly to the SoA (Section 1.3).
- Pregnancy testing (urine or serum as required by local regulations) must be conducted corresponding with the time frame for female patient contraception in Section 5.1 Inclusion criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the patient's participation in the study.

8.2.6 Local Cutaneous Tolerability

Grading of application site local tolerability symptoms will be recorded using the grading scale (Appendix 4, Section 10.4.1) following each dosing during the blinded period. Each target lesion will be graded within approximately 30 minutes after dosing by site staff or trained medical professional and a record of the worst symptom grade during time period will be recorded. During the Open Label period symptom grading will record worst symptom observed on the lesional areas treated within approximately 30 min after dosing.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Section 8.3.1.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.3.1.

8.3.1 AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

8.3.1.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease):
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to study intervention discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.3.1.2 Definition of SAE

An SAE is defined as any AE that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
- Development of drug dependence or drug abuse
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

8.3.1.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. “Severe” is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data** to the Sponsor**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

8.3.1.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the study reference manual.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the study reference manual.

8.3.2 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the follow-up visit at the timepoints specified in the Schedule of Activities (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 8.3.1. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. 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 to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.3 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.4 Follow-up of AEs and SAEs

After the initial AE /SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 8.3.1.

8.3.5 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information in the Investigator's Brochure.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

- An Investigator who receives an Investigator safety report describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.6 Pregnancy

- Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study intervention and through 30 days after the final dose of the study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female patient or female partner of male patient (after obtaining the necessary signed informed consent from the female partner) pregnancy.
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such
- The patient/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study patient/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.7 Expedited reporting requirements

The AEs below will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. Such events may require further investigation in order to characterize and understand them.

- Symptomatic overdose (serious or nonserious) with study intervention
  - An overdose (accidental or intentional) with the study intervention is an event suspected by the Investigator or spontaneously notified by the patient (not based on study intervention tube weight) and defined as greater than twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

- Elevation of liver enzymes as below (see Appendix 3, Section 10.3 for flow chart of required activities)
  - ALT >3 × upper limit of normal (ULN)
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy (see Section 8.3.6).

8.3.8 Guidelines for reporting product complaints

Any defect in the study intervention must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels, or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

Blood samples of approximately 4 mL per sample will be collected for measurement of plasma concentrations of PRN473 as specified in the Schedule of Activities in Section 1.3. Venipuncture should not occur within a treated area.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual collection time of each sample must be recorded in the source data documentation, and in the eCRF. The allowed time deviation window before a deviation is recorded for blood sample collection post dose is 15 minutes for timepoints up to and including 6 hours postdose; predose samples should be collected within 30 minutes prior to the next application of study intervention .

Samples will be used to evaluate the PK of PRN473. Samples collected for analyses of PRN473 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Pharmacokinetic endpoints are listed in Section 3.

After the blood samples are analyzed for plasma PRN473 concentrations, any residual samples may be used for analysis such as metabolite profiling and identification, interacting drug concentration measurements, ex vivo protein binding, or development of PK assays. Residual PK samples will be destroyed within 1 month of withdrawal of consent. Residual PK samples will be stored for 5 years after the final Clinical Study Report, at which point they will be destroyed.

Genetic analyses will not be performed on these samples. Patient confidentiality will be maintained.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Genetics and/or pharmacogenomics will not be evaluated in this study.

8.6 BIOMARKERS

Changes in protein and RNA expression, lymphocyte infiltration, and epidermal thickness following treatment with PRN473 will be evaluated using blood samples, skin tape stripping and skin biopsy.

Changes in blood biomarkers will be assessed following treatment with PRN473.

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For patients who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins, or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease, or its associated conditions.

In the event future research is conducted for other purposes, the study patients will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to patients in the ICF.

All study patient data and samples will be coded such that no patient direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting patient confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a patient requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws.

Study patient coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study patient who has requested the destruction of his/her samples).

The patient's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

8.7 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed as part of this study.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health Economics or Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9 LESION PHOTOGRAPHY

Photographs will be used to document change/improvement in lesions, and to document biopsy location as detailed in the lab manual and will not be used to evaluate AEs.

For the Blinded Period, photographs will be taken of the 2 target lesions at predose Baseline and Day 8. For the Open-Label Period, photographs of the 2 target lesions will be taken predose at Day 15, Day 29 and at Day 43.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No statistical hypotheses will be tested.

9.2 SAMPLE SIZE DETERMINATION

No sample size calculations were performed due to the exploratory nature of this study.

The sample size of up to 40 for this study with patients receiving both PRN473 Gel, 5% and placebo is based upon empirical clinical consideration. The sample size is considered adequate to evaluate the safety, tolerability, and PK of topically administered PRN473.

This study is signal seeking and neither aimed nor powered to provide formal inferential statistical analyses.

9.3 ANALYSIS SETS

For the purposes of analysis, the following analysis sets are defined:

Table 7 - Analysis sets

Patient Analysis Set	Description
Screened	All patients who signed the ICF.
Enrolled/Randomized	All patients from the screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Safety	All randomized patients who receive any amount of study intervention (PRN473 or placebo) will be included in the Safety population. The Safety population will be based on the intervention actually received and will be used for the summaries of all safety assessments.
Pharmacokinetic	All patients who received any amount of active study intervention (PRN473) and have at least one PK sample taken will be included in the PK population. The PK population will be used for the summaries of all PK data.
ITT	All randomized patients who did actually receive at least 1 complete dose of study intervention with at least 1 post-study intervention administration measurement, with available efficacy.
Efficacy	All randomized patients who did actually receive at least 80% of prescribed study intervention in the Blinded Period and/or at least 80% of prescribed study intervention in the Open-Label Period and with at least 1 post-study intervention administration efficacy measurement in the corresponding period, Patients will be analyzed according to the intervention they actually received.
Biomarker	All patients with no important deviations impacting Biomarker measurements, for whom the Biomarker data are considered sufficient and interpretable.

9.4 STATISTICAL ANALYSES

The Statistical Analysis Plan (SAP) will be issued prior to database lock and will include a more technical and detailed description of the statistical analyses and the tables and graphs described in this section.

This section is a summary of the planned statistical analyses of the key endpoints.

9.4.1 General considerations

In general, descriptive statistics (ie, arithmetic mean, standard deviation [SD], median, minimum, and maximum) will be calculated for continuous valued measurements, for each treatment where appropriate. Changes and percent changes from baseline to each applicable scheduled post-baseline timepoint will similarly be summarized by treatment where appropriate. Frequency summaries (ie, count and percentage of observations at each category level) will be applied for categorical data for each scheduled timepoint by treatment where appropriate.

9.4.2 Endpoints

Endpoints are listed in Table 3.

9.4.3 Analysis of efficacy data

Efficacy analyses will be based on the Efficacy population. A patient will be considered evaluable per endpoint and study period, if they receive at least 80% of prescribed study intervention in that period and have a post-baseline assessment of the corresponding endpoint for that period (ie, after Day 1 or after Day 15).

Where appropriate, supplemental analyses will be presented excluding observations after administration of rescue medication. Imputation would then be performed for missing observations including those due to withdrawal due to lack of efficacy, as will be specified in the SAP.

Efficacy analyses will be an early explorative assessment and performed without the aim of formal inferential statistics. No adjustment will be made for multiple analyses.

Treatment differences or ratios will be assessed for PRN473 Gel, 5% versus placebo, mainly at Day 15. Data will be presented by treatment for the Blinded Period where assessed per lesion, and overall otherwise, as well as for the Open-Label Period.

9.4.3.1 Lesion Total Sign Score (TSS)

Main comparison for TSS will be the comparison between PRN473 Gel, 5% and placebo for change from Baseline to Day 15.

Change in TSS will be analyzed with a linear mixed effects model with fixed terms for treatment and with baseline TSS as a covariate

Change in TSS = baseline TSS + treatment + error

and with an unstructured matrix of treatment variances and covariance for patient, using SAS Proc Mixed®. In case of convergence problems, other variance-covariance structures will be explored. Baseline TSS will be defined as the mean TSS from the two treated lesions at baseline.

The 95% Confidence Interval (CI) for the treatments effect will be obtained for the difference between treatment means within the linear mixed effects model framework. Additionally, 80% CIs will be derived and presented.

Descriptive statistics and graphical displays will be provided for all timepoints.

Additional explorative analyses may be performed.

9.4.3.2 Further efficacy endpoints during the blinded period

Further efficacy endpoints during the blinded period will be summarized per treatment and timepoint:

- Change from Baseline in daily lesional PP-NRS score up to Day 15
- Change from Baseline in lesional validated IGA score at Days 8 and 15
- Lesional validated IGA response (proportion of patients with a validated IGA score of 0 or 1 and ≥2-grade improvement from Baseline) at Days 8 and 15

Further explorative analyses may be performed.

9.4.3.3 Eczema Area and Skin Severity Index (EASI)

The following endpoints will be derived and analysed:

- Change from Baseline in EASI at Days 29 and 43
- Change from Day 15 in EASI to Days 29 and 43
- Proportion of patients with EASI 50, EASI 75, and EASI 90 from Day 15 to Days 29 and 43

Changes in EASI from Day 15 to Day 29 and to Day 43 will be analyzed descriptively. Estimations with 95% and 80% CIs may be derived. Descriptive statistics and graphical displays will be provided per timepoint.

Frequency tables will be provided for EASI 50, EASI 75, and EASI 90.

Further explorative analyses may be performed.

9.4.3.4 Validated Investigator Global Assessment-Atopic Dermatitis (vIGA-AD)

The proportion of patients achieving at least 2 grade reduction in vIGA-AD to clear (vIGA-AD 0) or almost clear (vIGA-AD 1) from Day 15 to Days 29 and 43 will be summarized.

Further explorative analyses may be performed.

9.4.3.5 Further efficacy endpoints during the open-label period

Further efficacy endpoints during the open label period will be summarized per timepoint:

- Change from Baseline in TSS for the 2 target lesions at Days 29 and 43.
- Change in PP-NRS from Day 15 to Days 29 and 43
- Proportion of patients achieving at least 3-point reduction from Day 15 in PP-NRS at Days 29 and 43
- Proportion of patients achieving at least a 4-point reduction from Day 15 in PP-NRS at Days 29 and 43
- Change from Day 15 in weekly mean of PP-NRS at Days 29 and 43
- Change from Day 15 in SCORAD at Days 29 and 43
- Change from Day 15 in percentage of treatable BSA at Days 29 and 43
- Change from Baseline in POEM at Days 15, 29, and 43
- Change from Baseline in DLQI at Days 15, 29, and 43

9.4.4 Analysis of safety data

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, figures) and, if needed, on statistical analysis (appropriate estimations, confidence intervals). No statistical significance tests will be performed on safety data.

Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor, according to predefined criteria/thresholds based on literature reviews and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG parameters.

All the safety analyses will be performed based on the safety population. Where appropriate, supplemental analyses will be presented excluding observations after administration of rescue medication.

For all safety data variables, the following observation periods are defined and used for classification of AEs, determination of on-treatment PCSA values, and the last on-treatment value for laboratory and vital sign parameters:

- The pre-treatment period is defined as the time between informed consent signature and the first study intervention administration.
- The treatment-emergent period is defined as the time from the first study intervention administration through the End of Study visit.
- The post treatment period is defined as the time starting after the treatment-emergent period.

9.4.4.1 Assignment to treatment and study phase

Safety data will be assigned to study phase as following:

- Blinded Period, if the TEAE onset was between the first administration (Day 1) of any study intervention in the Blinded Period and the first administration of study intervention (PRN473 Gel, 5%) in the Open-Label Period (scheduled Day 15).
- Open-Label Period, if the TEAE onset was after the first administration of study intervention (PRN473 Gel, 5%) in the Open-Label Period (scheduled Day 15).

Adverse events which are possibly related to study intervention and have onset date after the first dose of PRN473 will be considered possibly related to PRN473, unless they are documented as possibly related to the study intervention formulation of the placebo-treated lesion and not possibly related to the study intervention formulation of the PRN473 Gel, 5%-treated lesion.

Table 8 - Safety analysis

Safety Measures	Statistical Analysis Methods
Adverse events • AEs • TEAEs • SAEs • AEs leading to study intervention or study discontinuation • AEs leading to death • PCSAs	Treatment-emergent adverse event incidence tables will be presented by System Organ Class, high-level group term, high-level term, and Preferred Term for each study period and overall, showing the number (n) and percentage (%) of patients experiencing a TEAE. Multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator for computation of percentages will be the corresponding safety population. In addition, TEAEs will be described according to maximum intensity and relation to the study intervention. Adverse events that occur outside the treatment emergent period will be listed separately. Proportion of patients with at least 1 TEAE, treatment-emergent SAE, TEAE leading to death, and TEAE leading to definitive treatment discontinuation will be tabulated by study period and overall. The incidence of PCSAs occurring during the TE period will be summarized overall and by baseline status.

Abbreviations: AE = adverse event; PCSA = potentially clinically significant abnormality; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

9.4.4.2 Analyses of adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version in use by the Sponsor at the time of database lock). Clinical judgment should be used to determine the severity of AEs.

Adverse events will be classified into predefined standard categories according to chronological criteria:

- Pre-treatment AEs: AEs that occurred, worsened, or became serious during the pre-treatment period.
- Treatment-emergent AEs: AEs that occurred, worsened, or became serious during the TE period.
- Post-treatment AEs: AEs that occurred, worsened, or became serious during the post-treatment period.

If the onset date (or time) of an AE (occurrence, worsening, or becoming serious) is incomplete or missing, the AE will be considered as a TEAE unless a partial date (or time) shows it as a pre- or post-treatment event.

All AEs reported in the study will be listed, sorted by patient, onset date, and time.

Main summary will be per study period (Blinded Period, Open-Label Period) and overall.

If selected TEAEs from the Blinded Period can be clearly assigned to one of the study intervention treated lesions, they may be presented additionally assigned to the treatment of the corresponding lesion.

Any TEAEs which may occur between the first administration of placebo and the first administration of PRN473 Gel, 5% will be presented separately.

9.4.4.3 Local cutaneous tolerability

Signs of local cutaneous intolerability as incidence and severity of application-site burning/stinging, itching, and erythema will be summarized for the Blinded Period by treatment (PRN473 Gel, 5% or placebo) and overall for the open-label phase.

9.4.4.4 Extent of study treatment exposure and compliance

A summary table presenting the exposure of treatment (ie, the number of days or weeks of administration) will be provided by treatment group for the Safety population.

9.4.4.5 Laboratory data

Descriptive statistics of all laboratory data variables (values and changes from Baseline) will be calculated for each scheduled visit (Baseline and post-Baseline timepoints). Frequencies for PCSAs will be presented.

9.4.4.6 Vital signs

Descriptive statistics of all vital signs variables (values and changes from Baseline) will be calculated for each scheduled visit (Baseline and post-Baseline timepoints). Frequencies for PCSAs will be presented.

9.4.4.7 Electrocardiogram

Descriptive statistics (including number, mean, median, standard deviation, minimum, and maximum) of all ECG variables (values and changes from Baseline), will be calculated for each visit (Baseline and post-Baseline timepoints). Frequencies for PCSAs will be presented.

9.4.5 Analysis of pharmacokinetic data

Due to the negligible amount of systemic absorption observed following topical administration of PRN473 Gel to healthy subjects, the PK sampling scheme is designed to be semi-sparse. For that reason, plasma PRN473 concentrations, but not plasma PRN473 PK parameters, will be reported.

9.4.5.1 Pharmacokinetic parameters

Not applicable.

9.4.5.2 Analysis of pharmacokinetic concentrations

For PK concentrations, the arithmetic mean, SD, median, minimum, maximum, percent coefficient of variation (CV%), geometric mean, geometric coefficient of variation (geometric CV%), and the number of observations below the limit of quantification (BLQ) values will be presented by timepoint. For the purpose of calculating summary statistics, plasma concentrations (and applicable metabolites) that are BLQ will be set to 0 if taken before first study intervention , and to missing elsewhere. Additional analyses will be performed as deemed necessary upon review of the data.

Graphical displays of concentrations over time may also be presented.

9.4.6 Other analyses

9.4.6.1 Biomarkers

Changes from baseline in biomarkers using blood samples, skin tape stripping and skin biopsy will be analyzed between treatments within patients. Statistical analyses of biomarkers will be exploratory in nature and will be detailed in a Biomarker SAP.

9.4.6.2 Further exploratory endpoint(s)

Details on the analysis of further endpoints will be provided in the SAP.

9.5 INTERIM ANALYSIS

An interim analysis for internal decision making may be implemented with approximately 25 or more of the planned participants who have completed the Blinded Period (Day 14). Available data of the Open Label Period may be included in the analysis as appropriate. The outcome is meant for internal decision making and may lead to early termination of the study in case of unfavorable signals or continuation without any changes.

The Sponsor team that will analyze the data will include: a Medical Monitor, a biostatistician, a programmer, and a safety designee. Only the biostatistician and the programmer will have the access to unblinded individual data at the time of the analysis, which will not be provided to other Sponsor team members reviewing the data. Details of the analysis will be specified in a dedicated analysis plan, and results will be provided in a restricted way following a dissemination plan, issued before any treatment code release for the analysis established upfront before the unblinding. The blinding will be preserved notably toward the Investigator, other site staff involved in the conduct of the trial, and participants.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient 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.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the signed ICF must be provided to the patient.

Patients who are rescreened are required to sign a new ICF.

10.1.4 Data protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient, who will be required to give consent for data to be used as described in the informed consent.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of eCRFs will be provided.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) may be used to identify systematic issues that can impact patient safety and/or reliability of study results. Data quality parameters will be monitored during the study and important deviations tracked, and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marking applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6 Source documents

Source documentation provides evidence for the existence of the patient and substantiate the integrity of the data collected. Source documentation is kept at the Investigator's site.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documentation must be consistent with the source documentation or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Monitoring Plan.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documentation; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.7 Study and site start and closure

10.1.7.1 Trial Stopping Rules

The trial will be terminated if major safety concerns related to PRN473 or placebo emerge. Trial safety stopping criteria are:

- More than one PRN473-related death
- Three or more life-threatening (Common Terminology Criteria for Adverse Events [CTCAE], Grade 4) PRN473-related treatment-emergent adverse events (TEAEs)
- Sponsor chooses to terminate the study

10.1.7.2 Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator.
- Total number of patients included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigator, the IECs/IRBs, the regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patients and should assure appropriate therapy and/or follow-up.

10.1.8 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CONTRACEPTIVE AND BARRIER GUIDANCE

10.2.1 Definition

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

Women in the following categories are considered WONCBP:

1. Any female with permanent infertility due to one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.
2. Postmenopausal female

A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.

- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

10.2.2 Contraception guidance

- If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a to medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male patient can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] - oral - intravaginal - transdermal - injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] - oral - injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient)*

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.2.3 Collection of pregnancy information

Male patients with partners who become pregnant

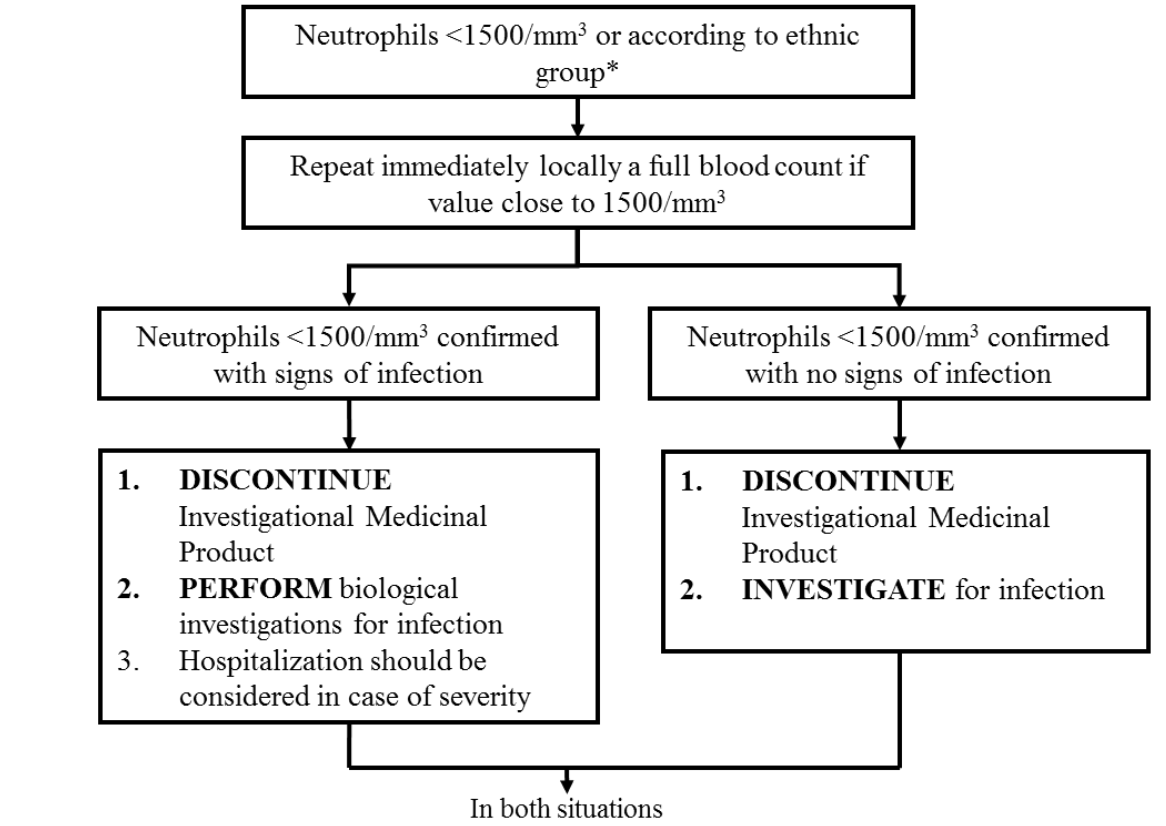
- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive the IMP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female patients who become pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.3 APPENDIX 3: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW UP ASSESSMENTS AND STUDY INTERVENTION RECHALLENGE GUIDELINES

NEUTROPENIA

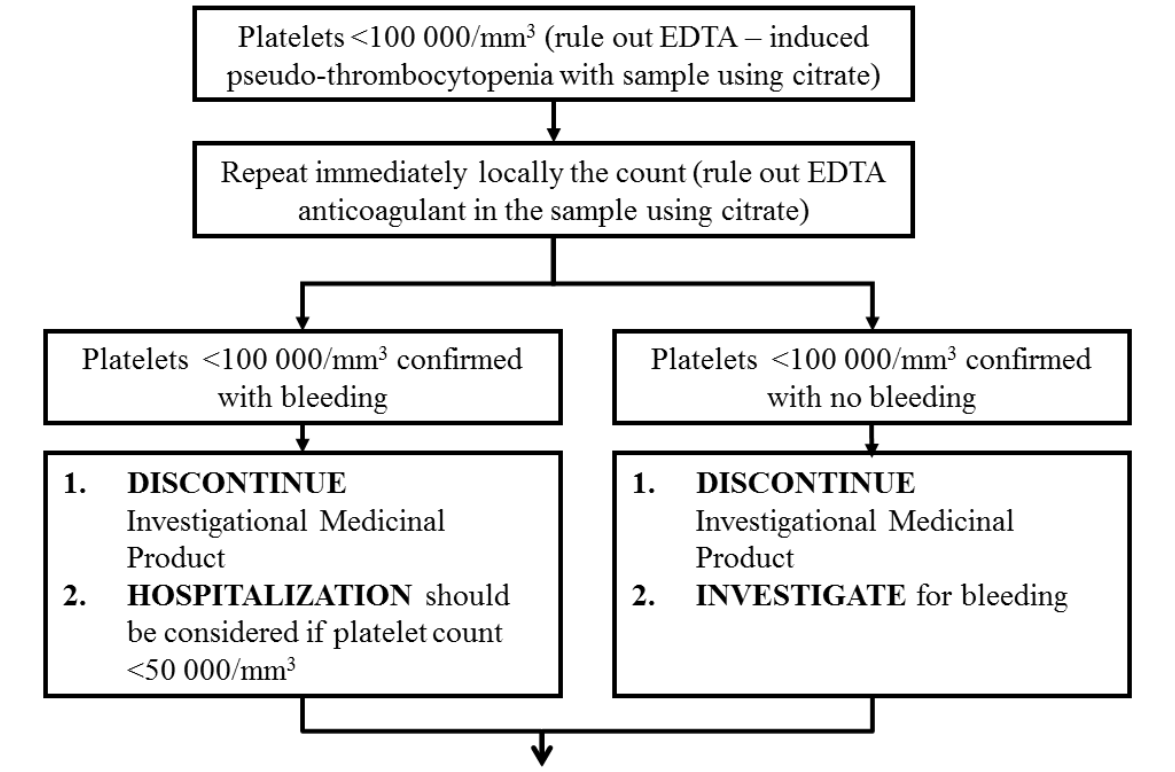


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm³

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 8.3.1.3 is met.

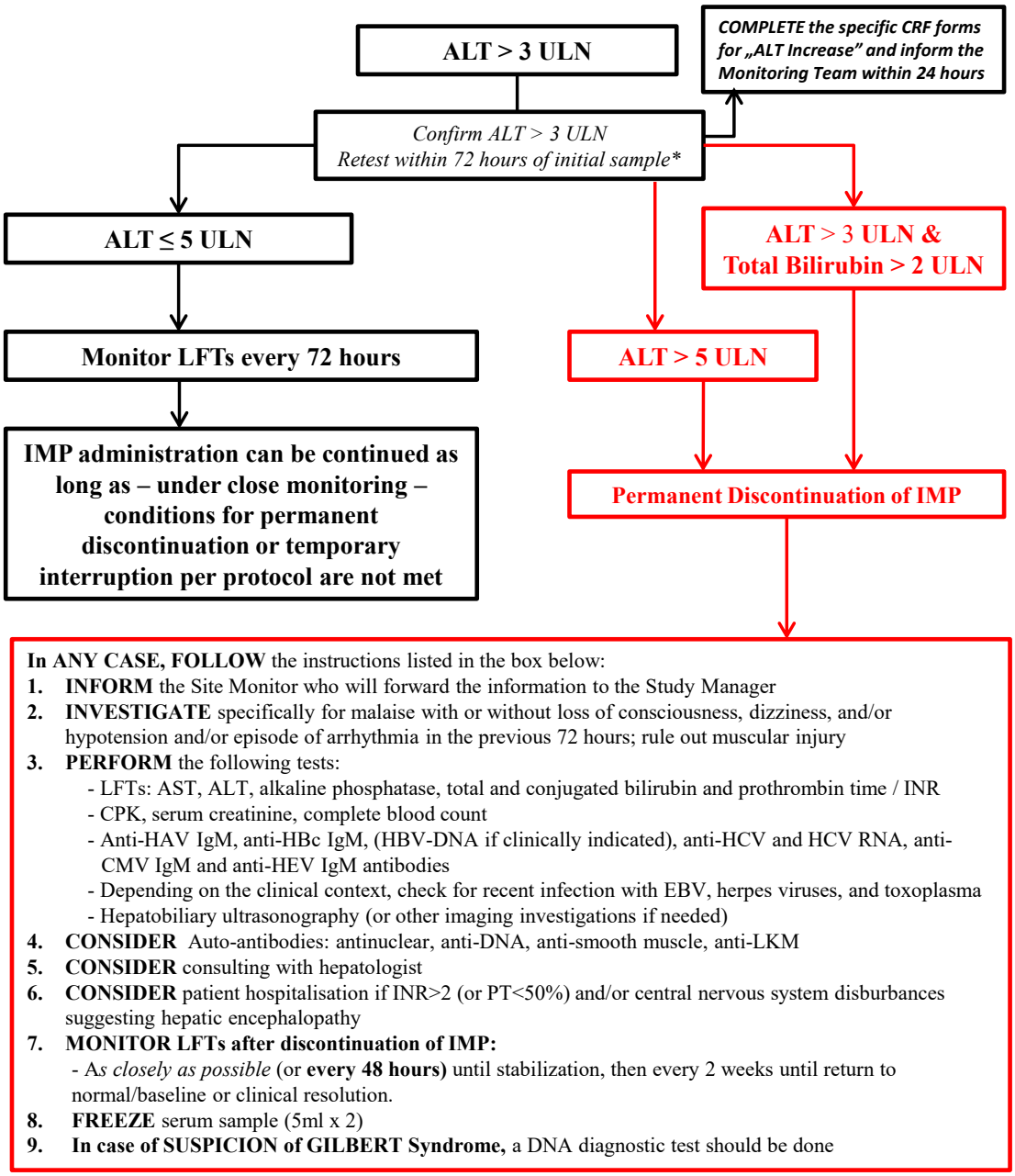
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about alcohol habits, any drug intake including quinine (drinks), heparin administration, aspirin, immunotherapy, etc.
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Locally:
     - Bleeding time and coagulation tests (INR or PT, aPTT, D-Dimers)
     - Infectious serologies to be performed according to clinical symptoms / medical history
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
7. **DECISION** for bone marrow aspiration to be taken in specialized unit
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 8.3.1.3 is met.

INCREASE IN ALT



In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - A*s closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 8.3 for guidance on safety reporting.

Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

10.4 APPENDIX 4: ADDITIONAL APPENDICES

10.4.1 Grading of application site tolerability symptoms

Grade	Burning/Stinging	Pruritus	Erythema
0 (none)	No stinging/burning	No pruritus	No detectable erythema; skin of normal color
1 (mild)	Slight warm, tingling sensation; not really bothersome	Occasional, slight itching/scratching	Slight pinkness present
2 (moderate)	Definite warm, tingling sensation that is somewhat bothersome	Constant or intermittent itching/scratching that is not disturbing sleep	Definite redness, easily recognized
3 (severe)	Hot, tingling/stinging sensation that has caused definite discomfort	Bothersome itching/scratching that is disturbing sleep	Intense redness

Adapted from: Zane 2016.

10.4.2 Validated investigator global assessment-atopic dermatitis (vIGA-AD)

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

10.4.3 Lesion Total Sign Score (TSS)

Scale	Erythema	Induration/Papulation	Excoriation	Lichenification
0 (none)	None	None	None	None
1	Mild	Mild	Mild	Mild
2	Moderate	Moderate	Moderate	Moderate
3	Severe	Severe	Severe	Severe

10.4.4 Hanifin and rajka criteria

The patient must have 3 of the major criteria and 3 of the minor criteria to be eligible for the study.

Major Criteria
1. Pruritus
2. Typical morphology and distribution Flexural lichenification in adults Facial and extensor eruptions in infants and children
3. Chronic or chronically relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Criteria	
1. Xerosis	12. Keratoconus
2. Ichthyosis/palmar hyperlinearity, keratosis pilaris	13. Anterior subcapsular cataracts
3. Immediate (type 1) skin-test reactivity	14. Orbital darkening
4. Raised serum IgE	15. Facial pallor, facial erythema
5. Early age of onset	16. Pityriasis alba
6. Tendency toward cutaneous infections (especially *Staphylococcus aureus* and herpes simplex), impaired cell-mediated immunity	17. Anterior neck folds
	18. Itch when sweating
	19. Intolerance to wool and lipid solvents
7. Tendency toward non-specific hand or foot dermatitis	20. Perifollicular accentuation
	21. Food intolerance
8. Nipple eczema	22. Course influenced by environmental or emotional factors
9. Cheilitis	
10. Recurrent conjunctivitis	23. White dermographism, delayed blanch
11. Dennie-Morgan infraorbital fold	

Source: Hanifin 1980.

10.5 APPENDIX 5: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment (amended protocol 02) is located directly before the Table of Contents.

Amendment 01 (15 June 2021)

This amended protocol 01 (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended to incorporate feedback from health authorities as well as other clarifications deemed necessary by the Sponsor.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated protocol version and date.	Administrative.
Protocol amendment summary of changes table	Inserted table to include the document history related to the initial Clinical Study Protocol and the Amended Clinical Study Protocol. Inserted for the current Amended Clinical Study Protocol text related to the overall rationale and protocol amendment summary of changes table.	New section per Sanofi protocol template and process.
Section 1.1 synopsis; Section 4.1 overall design; Section 4.3 justification of dose; Section 5.1 inclusion criteria #7; Section 6.2 Preparation/handling/storage/accountability	Updated the investigational skin lesion from "10*10 cm" to "100cm^2"	To provide flexibility for the lesional area.
Section 1.1 synopsis; Section 1.2 schema; Section 4.1 overall design; Section 5.1 inclusion criteria #5,#6; Section 6.7.3 rescue medicine	Added "genital" in the excluded treatable areas for PRN473 Gel administration.	To respond the FDA's comment of considering exclusion of mucosal sites such as the genitalia.
Section 1.1 synopsis; Section 1.2 schema; Section 4.1 overall design	Added the following text to clarify the administration of study intervention during Open Label period "…and should continue to treat the assigned areas throughout the Open Label Period."	For clarity.
Section 1.1 synopsis, Section 4.1 overall design	Updated the text from" To evaluate the PK (plasma concentrations) and biomarkers of PRN473, blood samples will be collected throughout the study" to "…will be collected at	For clarity.

Section # and Name	Description of Change	Brief Rationale
	study visits accordingly to the SoA (Section 1.3)."	
Section 1.1 synopsis; Section 5.1 inclusion criteria	Replaced the eligibility regarding patient's vIGA-AD score at "screening" instead of "baseline "in inclusion #5	To correct a typo.
	Introduced a new inclusion criterion as "inclusion #8" for male contraception/abstinence requirements. And renumbered the following inclusion criteria.	To introduce the male contraception/abstinence requirements in patient eligibility
	Updated the inclusion #9 with Sanofi common text language on female contraception/abstinence and pregnancy testing requirements following decision tree.	To align with Sanofi common text and safety guidance.
Section 1.1 synopsis; Section 5.2 exclusion criteria	Updated the exclusion #17 of any malignancy history to "History of any malignancy except skin basal cell or squamous cell carcinomas in situ that have been removed and completely resolved at least 5 years ago"	To respond the FDA's comment.
	Introduced a new exclusion criterion for laboratory abnormalities as exclusion #18	To align with Sanofi common text and safety guidance.
	Introduced a new exclusion criterion for QT intervals as exclusion #19	To align with Sanofi common text and safety guidance. To respond the FDA's comment to add subject stopping criteria based on ECG abnormalities.
	Introduced the diagnostic assessments for HIV HBV and HCV as exclusion #20, #21, and #22 respectively.	To align with Sanofi common text and safety guidance. To respond the FDA's comment to obtain HIV test prior to study enrollment.

Section # and Name	Description of Change	Brief Rationale
	Added the exclusion #23 on medical condition of tuberculosis as "Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest X-rays (posterior anterior and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration ≥ 5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) TB test such as QuantiFERON®-TB Gold Plus test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold Plus test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold Plus test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression"	To align with Sanofi common text and safety guidance. To respond the FDA's comment to obtain Mantoux TST test prior to study enrollment.
	Introduced the history of serious infection or currently active infection (including COVID-19) as exclusion #24	To align with Sanofi common text and safety guidance.
	Introduced the receipt of COVID-19 vaccine as exclusion #25	To align with COVID-19 vaccine safety profile.
Section 1.3 SoA	Updated the assessment item from "Evaluation of BSA involvement" to "Evaluation of treatable BSA"	For clarity.
	Added FSH test and footnote f to clarify it is for post-menopausal women of non-childbearing potential only. Renumbered the footnote thereafter.	To align with Table 6.
	Added Urinalysis test.	To align with inclusion #10 and Table 6
	Removed the footnote b from PP-NRS assessment	To correct an error and be consistent within protocol.
	Day 15 has been included in footnote q of biomarker collection.	To correct an omission
	Revised the footnote i with "The vIGA-AD will be conducted on all treated lesions at screening and Day 15, 29 and 43 during Open Label period.	To clarify the vIGA-AD is for all treated lesions and the scheduled study visit.

Section # and Name	Description of Change	Brief Rationale
	Added “predose at Day 15” at the end of footnote j .	To correct an omission.
	Newly added footnote k “The lesional vIGA-AD will be administered predose separately on each of the 2 target lesions only during Blinded Period and predose at Day 15” and crossed link to Lesional vIGA assessment. Renumber the footnote thereafter.	To clarify the lesional vIGA-AD is only for 2 target lesions and the scheduled study visit.
Section 1.3 SoA, Section 8.9 lesion photography	Added “to document biopsy location and” for the purpose of photograph in footnote j and section 8.9.	For clarity.
Section 1.3 SoA, Table 6	Introduced the diagnostic assessments for Serology (HIV, hepatitis B and C) and TB test in screening visit.	To align with Sanofi common text and safety guidance. To respond the FDA’s comment to obtain HIV test prior to study enrollment.
Section 4.1 overall design	Added the text clarifying study duration.	For clarity and align with synopsis.
Section 4.3 justification for dose	Added the following text “Patients will measure the dose by the fingertip unit method and the expected dose variability when the compound is topically self-applied by this method may be up to two-fold excess of compound which is reasonably below the safety margin.”	To introduce the guidance for patient self-administration of study intervention in open-label period.
Section 4.4 end of study definition	Updated the definition for patient completed the study to “A patient is considered to have completed the study if he/she has completed all phases of the study including the Day 43 and Day 56 safety follow up phone call.”	For clarity.
Section 6.7.1 COVID-19 vaccination	Introduced a new section for the guidance and requirements of use COVID-19 vaccination.	To clarify the guidance of COVID-19 vaccination during study in the context of its approval.
Section 6.7.2 prohibited medications, Table 5	Added any live vaccines in excluded medications and treatments list.	To align with vaccine safety profile.
Section 6.7.4 rescue medicine	Updated the text to “Rescue topical medications use will be at the discretion of the Investigator after discussion with the Medical Monitor if the patient is flaring above 14% treatable BSA (excluding scalp, palms, soles and genitalia) during the last two weeks of the Open Label Period. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease	To respond the FDA’s comment to provide a plan for patients who flare and have >14% treatable BSA during the open label period.

Section # and Name	Description of Change	Brief Rationale
	severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this, if necessary. Patients who receive rescue treatment will be asked to continue with study treatment and procedures."	
Section 7.1 discontinuation of the study intervention	Section has been updated to include subject stopping criteria based on liver chemistry and ECG abnormalities. In addition, introduced a new sub-section 7.1.4 for hematology stopping criteria.	To align with Sanofi common text and safety guidance.
Section 8.2.3 electrocardiograms	Added the following text "Refer to Section 7.1.3 for QTc withdrawal criteria and any additional QTc readings that may be necessary."	For clarity. To respond the FDA's comment to add subject stopping criteria based on ECG abnormalities.
Section 8.2.4.1 clinical laboratory tests Table 6	Corrected the clinical chemistry assessment from "Urate/Urea" to "Blood urea nitrogen (BUN)"	For clarity.
	Added "Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 Liver Chemistry Stopping Criteria and Appendix 5 Liver and other safety: suggested actions and follow-up assessments. All events which may indicate severe liver injury (possible Hy's Law) must be reported to Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis)." as footnote a and renumbered the following footnotes.	To align with Sanofi common text and safety guidance. To respond the FDA's comment to add subject stopping criteria based on liver chemistry.
Section 8.2.5 Pregnancy testing; Section 8.3.6 Pregnancy	Whole section been updated.	To align with Sanofi common text and safety guidance.
Section 8.3.5 Regulatory reporting requirements for SAEs	Included the regulatory requirement of reporting SUSAR as one of the listed bullet points.	To align with Sanofi common text and safety guidance.
Section 8.3.7 Expedited reporting requirements	Added the time window for expedited reporting of AE.	To align with Sanofi common text and safety guidance.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.3 analysis of efficacy data	Included the following text "Where appropriate, supplemental analyses will be presented excluding observations after administration of rescue medication. Imputation would then be performed for missing observations including those due to withdrawal due to lack of efficacy, as will be specified in the SAP."	To include efficacy data after the use of rescue medication.
Section 9.4.4 analysis of safety data	Included the following text "Where appropriate, supplemental analyses will be presented excluding observations after administration of rescue medication."	To include safety data after the use of rescue medication.
Section 10 supporting documentation and operational considerations	Added a new subsection 10.1.7.1 for trial stopping rules in Appendix 1	To align with Sanofi common text and safety guidance.
	Included the contraceptive and barrier guidance, laboratory decision trees for neutropenia and thrombocytopenia as Appendix 2.	To align with Sanofi common text and safety guidance.
	Included neutropenia and thrombocytopenia decision trees in Appendix 3	To align with Sanofi common text and safety guidance.
	Grouped the original appendices 1 to 4 as the subsection of Appendix 4 of additional appendices.	For clarity.
	Protocol amendment history added as Appendix 5 per Sanofi template.	Administrative update.
Throughout document	Replaced "study drug" with "study intervention".	To align with Sanofi protocol template terminology recommendation.
Throughout document	Other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections)	Minor, therefore, have not been summarized

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