CLINICAL STUDY PROTOCOL

Title:	A Phase 2a, Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Study to Determine the Safety, Tolerability, Pharmacokinetics, and Efficacy of ATI-1777 in Adult Patients with Moderate or Severe Atopic Dermatitis
Protocol number:	ATI-1777-AD-201
Study phase:	Phase 2a
Test product:	ATI-1777
IND number:	141,358
Sponsor:	Aclaris Therapeutics, Inc. 640 Lee Road Suite 200 Wayne, Pennsylvania 19087 USA Phone: [redacted]
Contract research organization:	PRA Health Sciences, Inc. 4130 Park Lake Avenue Suite 400 Raleigh, North Carolina 27612 USA Phone: [redacted]
Protocol version and date:	Version 4, 28-Jan-2021

This study will be performed in compliance with the principles of Good Clinical Practice.

PROTOCOL SIGNATURE PAGE – SPONSOR

This protocol has been reviewed and approved by the representative listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Aclaris Therapeutics, Inc. representative:

1/28/2021

Date

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by Aclaris Therapeutics, Inc. and, given approval/favorable opinion by the IRB, and I agree that it contains all necessary details for my staff and I to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by Aclaris Therapeutics, Inc. or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Aclaris Therapeutics, Inc. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by Aclaris Therapeutics, Inc. and inspection by the appropriate regulatory authorities.

I agree to make my patients' study records available to Aclaris Therapeutics, Inc. personnel, their representatives, and relevant regulatory authorities in order to verify data that I have entered into the electronic case report forms (eCRFs). I will retain the study-related essential documents until Aclaris Therapeutics, Inc. indicates that they are no longer needed. I am aware of my responsibilities as an investigator as provided by Aclaris Therapeutics, Inc.

I understand that Aclaris Therapeutics, Inc. may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing Aclaris Therapeutics, Inc.

Investigator:

Name	Title
Institution	
Signature	Date

SERIOUS ADVERSE EVENT CONTACT INFORMATION

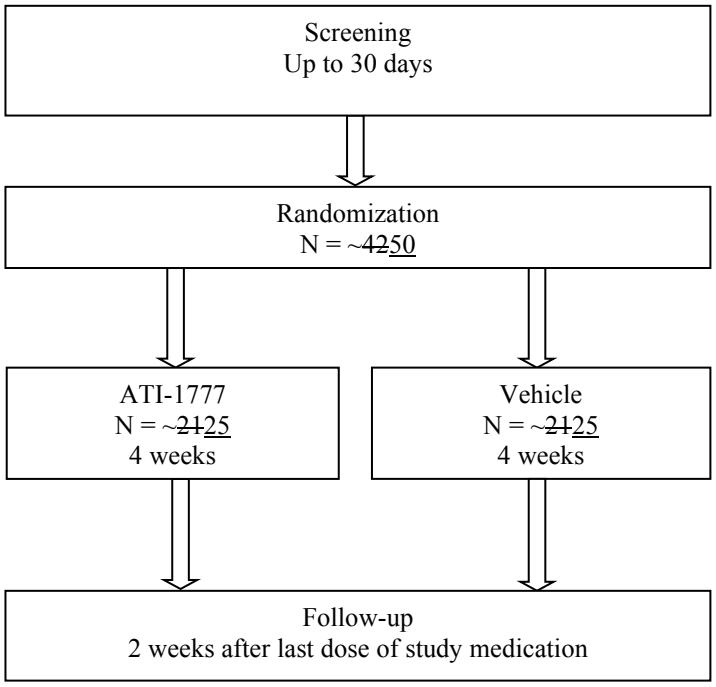
In the event of a serious adverse event (SAE), the investigator will send a safety report form within 24 hours of becoming aware of the SAE to:

ProPharma Group
FAX: [redacted]
Email: [redacted]

SUMMARY OF CHANGES

The changes introduced under Version 4 of the protocol (dated 28-Jan-2021) are being made to increase study enrollment to more accurately reflect the expected frequency of evaluable subjects and update the statistical methods to more accurately reflect the planned statistical analyses.

Text Affected	Changes
Protocol Summary – Planned number of patients Sentence 1	Revised: It is planned to enroll approximately ~~42~~50 patients.
Protocol Summary – Statistical method Determination of sample size Sentences 1 and 2	Revised: Data from 34 patients provides ~~90~~95.6% power to detect a statistically significant difference between the treatment groups in the primary endpoint (percent change from baseline in EASI scores). This power calculation is based upon a 1-sided treatment contrast within a 1-way ANOVA model and assumes group means of 65% and 20% for ATI-1777 and vehicle, respectively.
Protocol Summary – Statistical methods Efficacy Analyses	Revised: All efficacy summaries will be conducted on both the FAS and PP populations. All p-values for efficacy will be based on a 1-sided hypothesis test of the superiority of ATI-1777 to vehicle. The primary efficacy analysis will be the treatment comparison between ATI-1777 and vehicle for the percent change from baseline in EASI scores at Week 4. This treatment comparison will be made within the context of a Mixed Model Repeated Measures analysis where the EASI scores over time are treated as repeated measures within a given patient. Treatment group, time (study visit), and treatment by time interaction will enter the model as categorical factors, baseline EASI score and/or baseline severity of AD will be included as a continuous covariate, and patient ID will enter the model as a random effect. Treatment group model-based means and model-based differences in treatment groups will be provided along with corresponding ~~95~~90% confidence intervals and 1-sided p-values. Treatment comparisons between ATI-1777 and vehicle for each of the continuous efficacy endpoints that are conducted over time (Change in IGA, BSA, and PP-NRS) will be analyzed using a similar model as described for the primary endpoint. Treatment comparisons will be made for each post-

	baseline scheduled visit utilizing an appropriate analysis window scheme. Treatment group comparisons for categorical efficacy endpoints (IGA Response, EASI-50, -75, and -90) that are conducted over time will employ a logistic regression model fit at each scheduled visit separately, where appropriate. The logistic regression model will include treatment group as a factor and the baseline value and/or baseline severity of AD as a covariate. Model-based point estimates for the treatment proportions will be provided as well as model-based differences and corresponding ~~95~~90% confidence intervals and 1-sided p-values.
Study Schematic Figure 1 - Study Schematic	Revised: **Figure 1 Study Schematic** 
Section 4.1.2 – Treatment Period Sentence 1	Revised: A total of approximately ~~42~~50 patients who meet all the entry criteria will be randomized on Day 1 via an interactive voice/web response system (IXRS) to ATI-1777 or vehicle treatment in a 1:1 ratio.
Section 9.3 – Sample Size	Revised: A total of approximately ~~42~~50 patients will be enrolled in order to achieve 34 patients who complete the study. Data from 34 patients is estimated to provide ~~90~~95.6% power to detect a statistically significant difference between the

	treatment groups in the primary endpoint (percent change from baseline in EASI scores). This power calculation is based upon a 1-sided treatment contrast within a 1-way ANOVA model and assumes group means of 65% and 20% for ATI-1777 and vehicle, respectively. The group means were based upon slightly more conservative estimates than were observed in a Phase 2 study of topical ruxolitinib in AD (Kim et al 2020b). The variance for the percent change from baseline in EASI was assumed to be 38.3%. This variance assumption was based upon data observed in a pilot AD study for the topical compound ATI-502 (ATI-502-AD-201).
Section 9.4.5 – Treatment Period	Revised: All efficacy summaries will be conducted on both the FAS and PP populations. All p-values for efficacy will be based on a 1-sided hypothesis test of the superiority of ATI-1777 to vehicle. The primary efficacy analysis will be the treatment comparison between ATI-1777 and vehicle for the percent change from baseline in EASI scores at Week 4 based on the FAS. This treatment comparison will be made within the context of a Mixed Model Repeated Measures analysis where the EASI scores over time are treated as repeated measures within a given patient. Treatment group, time (study visit), and treatment by time interaction will enter the model as categorical factors, baseline EASI score and/or baseline severity of AD will be included as a continuous covariate and patient ID will enter the model as a random effect. Treatment group model-based means and model-based differences in treatment groups will be provided along with corresponding ~~95~~90% confidence intervals and 1-sided p-values. Treatment comparisons between ATI-1777 and vehicle for each of the continuous efficacy endpoints that are conducted over time (change in IGA, BSA, and PP-NRS) will be analyzed using a similar model as described for the primary endpoint. Treatment comparisons will be made for each post-baseline scheduled visit utilizing an appropriate analysis window scheme. Treatment group comparisons for categorical efficacy endpoints (IGA Response, EASI-50, EASI-75, and EASI-90) that are conducted over time will employ a logistic regression model fit at each scheduled visit separately, where appropriate. The logistic regression model will include treatment group as a factor and the baseline value and/or baseline severity of AD as a covariate. Model-based point estimates for the treatment proportions will be provided as

	well as model-based differences and corresponding ~~95~~90% confidence intervals and 1-sided p-values.
Section 9.4.9 – Handling of Missing Values Paragraph 2, Sentence 1	Revised: For the primary efficacy analysis and all continuous analyses based on the FAS population, missing data will be imputed using last observation carried forward (LOCF).

PROTOCOL SUMMARY

Protocol number: ATI-1777-AD-201

Protocol title: A Phase 2a, Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Study to Determine the Safety, Tolerability, Pharmacokinetics, and Efficacy of ATI-1777 in Adult Patients with Moderate or Severe Atopic Dermatitis

Sponsor: Aclaris Therapeutics, Inc.

Study phase: Phase 2a

Study sites: It is planned to recruit approximately 15 sites in the United States (US).

Objectives:

Primary:

The primary objective of this study is to assess the preliminary clinical efficacy of ATI-1777 topical solution in adult patients with moderate or severe atopic dermatitis (AD).

Secondary:

The secondary objective of this study is to assess the safety, tolerability, and pharmacokinetics (PK) of ATI-1777 topical solution twice daily for 4 weeks in adult patients with moderate or severe AD.

Study design:

This is a first-in-human, randomized, double-blind, parallel-group, vehicle-controlled study to evaluate the efficacy, safety, tolerability, and PK of ATI-1777 solution following twice-daily applications to target areas of patients with moderate or severe AD. All AD lesions in protocol allowed areas should be treated. All AD lesions in protocol allowed areas should be treated.

Patients will undergo screening evaluations to determine eligibility up to 30 days prior to randomization. Patients who meet all the entry criteria will be randomized on Day 1 to active or vehicle treatment. Patients will apply study drug (ATI-1777 topical solution 2.0% w/w or vehicle) twice daily for 4 weeks with weekly study visits and will return 2 weeks after the last dose of study medication for a Post-treatment Follow-up (PTFU) Visit. Adverse event (AE) collection, physical examinations, clinical disease assessments (Eczema Area and Severity Index [EASI], Investigator's Global Assessment [IGA], AD body surface area [BSA], Peak Pruritus Numerical Rating Scale [PP-NRS]), vital sign assessments, PK evaluations, and clinical laboratory evaluations will be performed as detailed in the Schedule of Events.

Study duration: Patients will undergo up to 30 days of screening, followed by 4 weeks of treatment and 2 weeks of PTFU.

The start of the study will be the date on which the first patient provides informed consent, and the end of the study will be the date of the last patient's last assessment.

Planned number of patients: It is planned to enroll approximately 50 patients. Patients will be randomized (1:1 to ATI-1777 Topical Solution 2.0% w/w or vehicle) to achieve approximately 34 evaluable patients having a non-missing Week 4 EASI assessment.

Target population: Patients aged between 18 and 65 years (inclusive) with moderate or severe AD

Inclusion Criteria:

Patients must meet the following criteria to be eligible for participation in the study:

1. Able to comprehend and willing to sign the IRB-approved informed consent form (ICF) prior to administration of study-related procedures.
2. Male patients or non-pregnant, non-nursing female patients 18 to 65 years old, inclusive, at the time of informed consent.

3. Pregnancy and Contraception:
   - Women of childbearing potential (WOCBP), must have a negative serum pregnancy test at the Screening Visit, a negative urine pregnancy test immediately prior to the first application of study medication on Day 1, and a negative urine pregnancy test at each study visit thereafter.
   - Sexually active heterosexual women must agree to use the following throughout the screening period and for 30 days after last study drug application. WOCBP who are not sexually active at Baseline and become sexually active during the study must agree to follow the birth control measures listed below.
     - Agree to use 2 forms of highly effective contraception, including 1 physical barrier (condom or diaphragm) plus another highly effective method, such as adequate hormonal method (e.g., contraceptive implants, injectables, oral contraceptives) or nonhormonal methods (e.g., intrauterine device) or male partner who is surgically sterile (vasectomy).
   - Male patients with partners of childbearing potential may be enrolled if they are:
     - Documented to be surgically sterile (vasectomy), or
     - Using 2 adequate forms of highly effective contraception, 1 of which should be a physical barrier until 90 days after the last administration of study medication.
4. Have a diagnosis of AD fulfilling the specified diagnostic criteria of Hanifin and Rajka (Hanifin and Rajka 1980).
5. Have at least a 6-month history of AD prior to the Screening Visit, and no significant AD flares for the 4 weeks prior to the Screening Visit.
6. Have at least 1 lesion that measures at least 3 cm^2 at the Screening Visit and on Day 1 prior to the first dose of study medication. This lesion must be representative of the patient's disease state, but not located on the hands, feet, or genitalia.
7. Have a stable diagnosis of moderate or severe (IGA score 3 or 4) AD at the Screening Visit.
8. Have AD affecting 3% to 20% BSA (not including head [neck, scalp, face], palms of hands, soles of feet, groin, and genitalia) at the Screening Visit.
9. Willing to refrain from washing area of treatment or swimming for 6 hours after each study medication application.
10. Willing to refrain from excessive sun exposure (e.g., sunbathing and/or tanning salon visits) and to minimize sun exposure (e.g., wear sun protective clothing, hat) as much as possible.
11. Willing to refrain from use of moisturizers, emollients, and sunscreen on AD study treatment areas for duration of protocol therapy.
12. Willing to refrain from participating in strenuous exercise that would cause profuse sweating for a period of 6 hours after each study medication application.
13. Willing to return to the clinic, follow all study instructions, attend all study visits, and complete study procedures.
14. In good general health and free of any known disease state or physical condition that, in the investigator's opinion, might impair evaluation of the patient or that might expose the patient to an unacceptable risk by study participation.
15. Willing and capable of taking appropriate coronavirus disease 2019 (COVID-19) risk mitigation precautions (e.g., wearing a mask in public, adhering to social distancing, etc.) as recommended or required by local, state, or federal guidelines during participation in the study.

Exclusion Criteria:

Patients with any of the following are excluded from the study:

1. Unstable course of AD (spontaneously improving or rapidly deteriorating) based on the patient history or as determined by the investigator during the Screening Period.
2. Refractory AD (i.e., AD that required frequent hospitalizations and/or frequent intravenous treatment for skin infections within the year before the Screening Visit).
3. AD of a severity (EASI >48) that the patient is not a candidate for a vehicle-controlled study.
4. Any signs or symptoms associated with AD therapy (e.g., history of anaphylaxis, hypersensitivity reactions, skin atrophy, striae, pigmentary changes) that, in the investigator's opinion, might impair evaluation of the AD or which exposes the patient to unacceptable risk by study participation.
5. Concomitant skin disease or clinically infected AD or presence of other skin disease in the area to be dosed that may interfere with study assessments.
6. Use of any of the following treatments within the indicated washout period prior to Day 1:
   - Phototherapy (ultraviolet A, ultraviolet B, or psoralen and ultraviolet A therapy) within 4 weeks prior to Day 1.
   - Systemic biologic immunosuppressant or immunomodulatory therapy (e.g., etanercept, alefacept, infliximab, dupilumab) within 12 weeks (or 5 half-lives of the product, whichever is longer) prior to Day 1.
   - Non-biologic immunosuppressants (e.g., methotrexate, retinoids, calcineurin inhibitors, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine) within 4 weeks prior to Day 1.
   - Janus kinase (JAK) inhibitors (systemic and topical) within 4 weeks prior to Day 1.
   - Systemic corticosteroids within 2 weeks prior to Day 1 (intranasal, inhaled, and topical ocular corticosteroids are allowed).
   - Cytostatic agents within 4 weeks prior to Day 1.
   - Crisaborole within 2 weeks prior to Day 1.
   - Systemic antibiotics within 30 days prior to Day 1.
   - Topical treatments for AD (corticosteroids, calcineurin inhibitors, topical H1 and H2 antihistamines, topical antimicrobials, and other medicated topical agents) within 2 weeks prior to Day 1.
   - Live attenuated vaccine treatment within 12 weeks prior to Day 1.
   - Other investigational product within 30 days or 5 half-lives (whichever is longer) prior to Day 1.
7. Previous failure to respond to prior therapy with JAK inhibitors (systemic or topical), as determined by the investigator.
8. Current use of an oral H1 antihistamine (e.g., diphenhydramine, terfenadine) UNLESS the patient is on a stable dose for at least 14 days prior to the Screening Visit.
9. Medical marijuana unless the patient is on a stable dose for at least 14 days prior to the Screening Visit.
10. Clinically significant laboratory abnormalities at the Screening Visit that, in the opinion of the investigator, could affect interpretation of study data or the safety of the patient's participation in the study.
11. Clinical laboratory values:
    - White blood cell count $<2\times10^9$/L
    - Absolute neutrophil count (ANC) <1800/μL
    - Platelet count <130,000/μL
    - Hemoglobin <8g/dL
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2× the upper limit of normal

- Lymphocyte count $<0.5\times10^9$/L

12. Investigator-assessed history of, or current physical findings of, severe, progressive, or uncontrolled immunologic, hepatic, gastrointestinal, pulmonary, cardiovascular, genitourinary (renal), hematological, neurologic or cerebral disorders, infectious disease or coagulation disorders that, as determined by the investigator, could affect the safety of the patient's participation in the study or would preclude participation in and completion of study assessments.
13. History of, current, or suspected systemic or cutaneous malignancy and/or lymphoproliferative disease within the last 5 years, other than patients with a history of adequately treated and well healed and completely cleared nonmelanoma skin cancers (i.e., basal or squamous cell carcinoma) or cervical carcinoma in situ treated successfully at least 1 year prior to the Screening Visit 1 with no evidence of disease.
14. Evidence of active, chronic, or latent infections at the time of enrollment or a systemic infection including but not limited to a history of treated infection (e.g., pneumonia, septicemia) within 3 months prior to Day 1.
15. Patient has a known active or history of incompletely treated or untreated active tuberculosis. Patients with a history of active tuberculosis must have documented adequate treatment verified by the investigator. Patients who demonstrate evidence of latent tuberculosis infection (positive QuantiFERON® Tuberculosis Gold Test) will only be allowed to participate in the study if there is documented evidence of a completed adequate treatment course for latent tuberculosis and if active tuberculosis is excluded per the investigator's judgment.
16. History of a serious local skin infection (e.g., cellulitis, abscess) within 5 years of the Screening Visit.
17. Positive serological test for human immunodeficiency virus (HIV) (antibody), hepatitis C virus (antibody), hepatitis B surface antigen, or hepatitis B core antigen antibody.
18. Known significant exposure (close contact [<6 feet] for ≥15 minutes) to an individual with a confirmed diagnosis of coronavirus disease 2019 (COVID-19) at any time during the Screening Period.
19. Herpes zoster or cytomegalovirus infection that resolved less than 2 months prior to the Screening Visit. Patients with a history of frequent outbreaks of herpes simplex virus (defined as 4 or more outbreaks a year).
20. Clinically significant electrocardiogram (ECG) findings such as, but not limited to, baseline mean QTcF >450 msec for males or >470 msec for females (use of the ECG algorithm is acceptable for this purpose).
21. Known allergy to any of the inactive ingredients in the study drug.
22. Female patients who are pregnant, nursing, or planning to become pregnant during the study.
23. Legal incapacity or limited legal capacity.
24. Major surgery within 3 months of the Screening Visit.
25. Any other condition that precludes adequate understanding, cooperation, and compliance with study procedures or any condition that could pose a risk to the patient's safety, as per the investigator's judgment.
26. Use of potent inhibitors of cytochrome P450 3A4 such as (but not limited to) clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal, and grapefruit.

Test product:

ATI-1777 topical solution 2.0% w/w applied to areas with AD.

Control Product:

Topical vehicle solution containing no ATI-1777.

Endpoints:

Primary

Percent change from baseline in EASI score at Week 4

Secondary

- Percent change from baseline in EASI score at each study visit
- Proportion of patients achieving an IGA score of 0 to 1 combined with an improvement of 2 or more points from baseline within 4 weeks of the start of treatment
- Proportions of patients who achieve 50%, 75%, and 90% improvement in EASI score (EASI-50, EASI-75, and EASI-90, respectively) within 4 weeks of the start of treatment
- Change from baseline in IGA score at each study visit
- Change from baseline in BSA at each study visit
- Change from baseline in PP-NRS score over time

Safety

- Incidence of treatment-emergent AEs (TEAEs) and SAEs
- Laboratory values
- Vital signs
- Physical examination results
- 12-lead ECG

Pharmacokinetics

A sparse sampling approach will be employed because it is not anticipated that clinically relevant plasma concentrations will be observed. A total of 8 PK samples will be collected from each patient.

One sample will be collected before study medication application, and 1 sample will be collected approximately 2 hours after application on each of Days 1, 8, and 15.

Samples for Day 28 will be collected from 3 subgroups of patients within each of the specified time windows as follows:

- Subgroup 1: One sample predose and one sample at 0.5 to 2.5 hours post application
- Subgroup 2: One sample at 2.5 to 5 hours post application and one sample at least 2 hours later
- Subgroup 3: One sample at 5 to 8 hours post application and one sample at least 2 hours later (prior to the subsequent application)

Statistical methods: Details of all statistical summaries will be provided in the study-specific statistical analysis plan (SAP).

Determination of sample size:

Data from 34 patients provides 95.6% power to detect a statistically significant difference between the treatment groups in the primary endpoint (percent change from baseline in EASI scores). This power calculation is based upon a 1-sided treatment contrast within a 1-way ANOVA model and assumes group means of 65% and 20% for ATI-1777 and vehicle, respectively. The group means were based upon slightly more conservative estimates than were observed in a Phase 2 study of topical ruxolitinib in AD. The variance for the percent change from baseline in EASI was assumed to be 38.3%. This variance assumption was based upon data observed in a pilot AD study for the topical compound ATI-502 (ATI-502-AD-201).

Analysis populations:

- Full Analysis Set (FAS): All patients who have been randomized and administered at least one dose of study medication. The efficacy analyses will be conducted on the FAS population as randomized; the safety analyses and summaries will be conducted on the FAS as treated.

- Per-Protocol (PP) Population: All patients who have non-missing Week 4 EASI scores recorded. The PP population will be analyzed as treated.
- PK Population: All patients who receive at least 1 dose of study medication and provide at least 1 plasma concentration value.

Analysis methods:

All data will be presented by treatment group. Descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables. Baseline is defined as the last non-missing measurement before or on the date of first administration of study medication.

Efficacy Analyses:

All efficacy summaries will be conducted on both the FAS and PP populations. All p-values for efficacy will be based on a 1-sided hypothesis test of the superiority of ATI-1777 to vehicle.

The primary efficacy analysis will be the treatment comparison between ATI-1777 and vehicle for the percent change from baseline in EASI scores at Week 4. This treatment comparison will be made within the context of a Mixed Model Repeated Measures analysis where the EASI scores over time are treated as repeated measures within a given patient. Treatment group, time (study visit), and treatment by time interaction will enter the model as categorical factors, baseline EASI score and/or baseline severity of AD will be included as a continuous covariate, and patient ID will enter the model as a random effect. Treatment group model-based means and model-based differences in treatment groups will be provided along with corresponding 90% confidence intervals and 1-sided p-values.

Treatment comparisons between ATI-1777 and vehicle for each of the continuous efficacy endpoints that are conducted over time (Change in IGA, BSA, and PP-NRS) will be analyzed using a similar model as described for the primary endpoint. Treatment comparisons will be made for each post-baseline scheduled visit utilizing an appropriate analysis window scheme.

Treatment group comparisons for categorical efficacy endpoints (IGA Response, EASI-50, -75, and -90) that are conducted over time will employ a logistic regression model fit at each scheduled visit separately, where appropriate. The logistic regression model will include treatment group as a factor and the baseline value and/or baseline severity of AD as a covariate. Model-based point estimates for the treatment proportions will be provided as well as model-based differences and corresponding 90% confidence intervals and 1-sided p-values.

Safety Analyses:

The FAS will be used for the analysis of safety data (AEs, clinical laboratory values, vital signs, physical examination results, and ECGs). AEs will be coded with the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as AEs with onset dates on or after the date of first administration of study medication and before the end of the study, or that exist prior to the first dose and worsen with dosing. TEAEs will be presented by system organ class and preferred term in frequency tables. Patients with multiple AEs will be counted only once within each preferred term and system organ class. Key patient information for patients with an AE with an outcome of death, patients with SAEs, and patients with an AE leading to discontinuation of study medication will be listed.

Laboratory data (hematology, serum chemistry, coagulation, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively. Laboratory data outside study-specific reference ranges will be listed. Vital signs and ECG parameters will be presented descriptively.

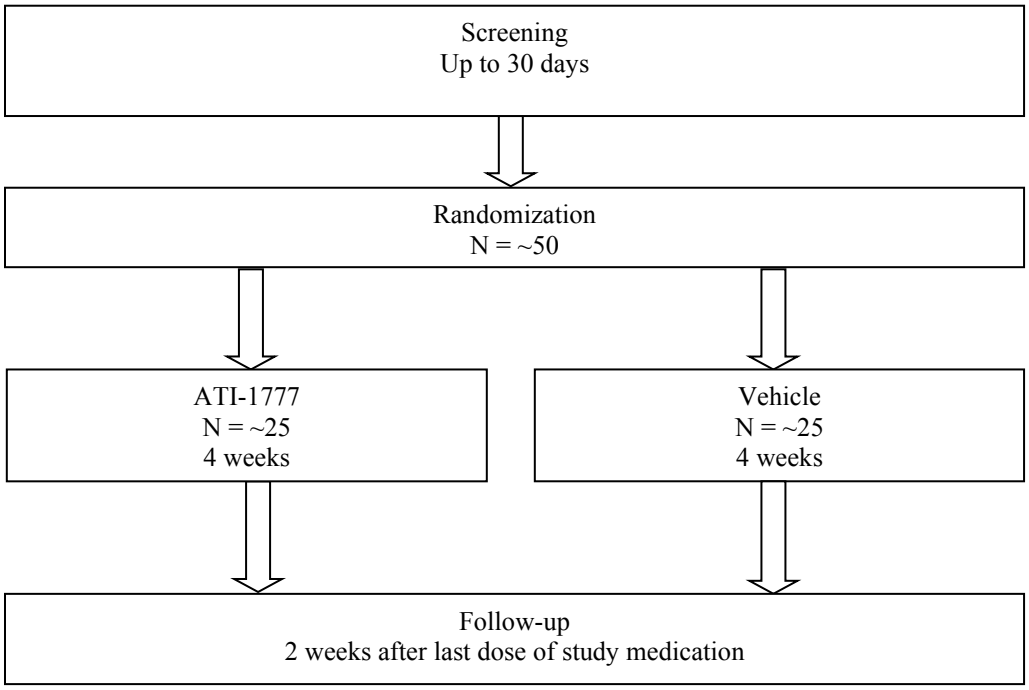
Plasma Drug Concentrations

Plasma concentrations of ATI-1777 will be summarized by nominal time point and day.

Protocol version and date: Version 4, 28-Jan-2021

STUDY SCHEMATIC

Figure 1 Study Schematic



SCHEDULE OF EVENTS

Table 1 Schedule of Events

Study Period	Screening	Treatment Period				PTFU
Study Day	**-30 to -1**	**Day 1**	**Day 8 ±3 days**	**Day 15 ±3 days**	**Day 28/ET ±2 days**	**Day 42 ±3 days**
Informed Consent[1]	X					
Inclusion/Exclusion criteria	X	X				
Demographics	X					
Medical history, including AD history	X	X				
Full physical examination[2]	X					
Brief physical examination[2]		X			X	
SARS-Cov-2 nasopharyngeal test		X				
ECG[3]	X			X	X	
Vital signs[4]	X	X	X	X	X	X
Serum pregnancy test[5]	X					
Urine pregnancy test		X	X	X	X	
Clinical chemistry, hematology, urinalysis[6]	X	X	X	X	X	
Virology (Hepatitis B and C, HIV)	X					
QuantiFERON® Tuberculosis Gold Test	X					
Randomization		X				
PK sample[7]		X	X	X	X	
Fitzpatrick skin type assessment	X					
EASI[8]	X	X	X	X	X	
IGA[8]	X	X	X	X	X	
BSA[8]	X	X	X	X	X	
PP-NRS[8]		X	X	X	X	
Photography	X	X	X	X	X	
Dispense study drug and patient diary		X	X	X		
Study drug instruction, first administration, and observation		X				
Study drug administration (by patient)[9]		X	X	X	X	
Collection of study drug, patient diary review, including medication compliance			X	X	X	
AE assessment[10]	X	X	X	X	X	X
Prior and concomitant medication review	X	X	X	X	X	X

AD = atopic dermatitis; AE = adverse event; BSA = body surface area; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; ET = Early Termination; HIV = human immunodeficiency virus; ICF = informed consent form; IGA = Investigator's Global Assessment; PK = pharmacokinetic; PP-NRS = Peak Pruritus Numerical Rating Scale; PTFU = Post-treatment Follow-up; SAE = serious adverse event; SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of child bearing potential

1. A written, signed ICF must be obtained from each patient prior to performing any study-related procedure.
2. A full examination will be performed at the Screening Visit. A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, and extremities. A brief examination will be performed at the Day 1 and Day28/ET Visits and any unscheduled visits and will include symptom-focused assessments.
3. Triplicate 12-lead ECGs will be obtained as outlined in Section 6.3.4.
4. Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate. Height will be measured and recorded at the Screening Visit, and weight will be measured and recorded at each study visit.
5. Serum pregnancy test at the Screening Visit, urine pregnancy test at all other specified time points; for WOCBP only.
6. On dosing day(s), sampling for the analysis of clinical laboratory parameters will be performed before the administration of study medication.
7. PK samples will be drawn as outlined in Section 6.4.
8. IGA and BSA assessed at the Screening Visit to ensure inclusion criteria are met. EASI, IGA, BSA, and PP-NRS assessed prior to study medication application on Day 1 to establish baseline and at study visits and end of the study (or ET) to document severity and extent of AD following study medication. The patient will complete the PP-NRS in their diary each morning before applying study medication during the Treatment Period.
9. Study medication will be applied at the site on study visit days, except Day 28 for PK subgroups 2 and 3. On Day 28, study medication will be applied at home to accommodate the timing of PK sample collection for PK subgroups 2 and 3.
10. Nonserious AEs will be collected after the patient's first application of study drug and continue until the patient's last visit. SAEs will be collected from the time the patient signs the ICF until the patient's last visit.

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LIST OF ABBREVIATIONS

AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BSA	body surface area
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CSR	clinical study report
eCRF	electronic case report form
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HDL-C	high-density lipoprotein cholesterol
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
IL	interleukin

INR	international normalized ratio
IRB	institutional review board
IXRS	interactive voice/web response system
JAK	Janus kinase
HIV	human immunodeficiency virus
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
PK	pharmacokinetic(s)
PTFU	Post-treatment Follow-up
PP	per-protocol
PP-NRS	Peak Pruritus Numerical Rating Scale
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
STAT	signal transducer and activator of transcription
TC	total cholesterol
TG	triglycerides
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential

1 INTRODUCTION AND RATIONALE

1.1 Background

1.1.1 Atopic Dermatitis

AD is a chronic, relapsing pruritic inflammatory skin disease involving inflammation and skin barrier defects in relation to environmental stimuli (Hanifin et al 2001; Rajka and Langeland 2020; Tanei et al 2020). It is currently estimated that 10% to 30% of children and 0.3% to 14% of adults in developed countries are affected by the disorder (Kim et al 2020a; Montillo et al 2019; Napolitano et al 2020). AD has been typically categorized into infantile (age <2 years), childhood (age 2 to 12 years), and adolescent/adult (>12 years, but not over middle age) types according to patient age and characteristics of typical skin lesions; most recently, a newly defined subgroup of elderly patients (≥60 years) was added into the classification system (Tanei et al 2020). The highest prevalence of AD (i.e., 95% of the cases) is in children aged under 5 years , but overall, 60% of the AD cases are reported in children aged under one year (Souta et al 2019). No matter what age, the disorder results in significant morbidity and adversely affects quality of life. Intense itching characteristic of the disease often leads to skin trauma and significant sleep disturbances (Kapur et al 2018).

1.1.2 Current Treatments

Current pharmacological approaches for treatment of AD aim to reduce inflammation, eradicate infections induced by bacteria or other parasites, reduce pruritic symptoms, and prevent eczema propagation (Souta et al 2019). Behavioral management to reduce exposure with antigen sources from pollens, mite dust, traffic or tobacco smoke, volatile organic compounds, and animal fur is recommended. Frequent bathing to remove surface allergens and use of moisturizers is also an integral part of managing AD and can reduce disease severity.

Food and Drug Administration (FDA)-approved treatments for AD include corticosteroids (topical and systemic), calcineurin inhibitors (topical), a phosphodiesterase-4 (PDE-4) inhibitor (topical), and dupilumab (systemic), a humanized monoclonal antibody that blocks signaling of interleukin (IL)-4/IL-13.

Corticosteroids are available for treatment of AD by various routes of administration. Topical corticosteroids are the most commonly used medications and are first-line in pharmacologic treatment of AD for those individuals who have failed to respond to good skin care and regular use of emollients alone. Systemic steroids for treatment of AD are not recommended by the American Academy of Dermatology. Although corticosteroid use may result in rapid disease improvement, skin lesions commonly recur with worse severity on discontinuation. In addition, corticosteroids carry the risk of hypothalamic pituitary- adrenal axis suppression, with the potential for glucocorticosteroid insufficiency.

Two non-steroid topical treatment options include calcineurin inhibitors and a PDE-4 inhibitor. The FDA-approved calcineurin inhibitors include tacrolimus 0.1% ointment, tacrolimus 0.03% ointment, and pimecrolimus 1% cream. These treatments are considered second-line agents for the management of AD flares. They are intended for short-term use and non-continuous chronic treatment of mild to moderate AD in non-immunocompromised adults and children 2 years of age and older who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. The PDE-4 inhibitor, crisaborole 2% ointment, is approved for mild to moderate AD.

Dupilumab, a fully humanized monoclonal antibody against the shared alpha subunit of IL-4 and IL-13 receptors, is considered first-line systemic treatment for moderate or severe AD in adults. Phototherapy may also be an option for patients who are candidates for systemic therapy. However, phototherapy may require frequent in-office visits (e.g., several times a week). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts.

Additional to the FDA-approved treatments specific for AD, systemic immunosuppressants (e.g., azathioprine, ciclosporin, methotrexate, and mycophenolate mofetil), antihistamines, and antimicrobials are used in common practice.

Although there are FDA-approved products for the treatment of AD, there is a role for additional efficacious drug products with acceptable safety profiles.

1.1.3 Janus Kinase Inhibitors for Treatment of Atopic Dermatitis

Lesional skin from patients with AD contains elevated levels of proinflammatory cytokines and cellular infiltrates of CD4+ T cells that propagate disease pathophysiology (Howell et al 2019; Rodriques and Torres 2020). The cytokine microenvironment in AD appears complex, with patients presenting with different cytokine signatures at different stages of the disease (Solimani et al 2019). The Janus kinase (JAK) family of signal transducers presents itself as an advantageous treatment target since a variety of cytokines exert their biological effects through the JAK–signal transducer and activator of transcription (STAT) pathway. The JAK family comprises 4 cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and TYK2; there are 7 STAT proteins: STAT 1, 2, 3, 4, 5a, 5b, and 6. The JAK-STAT signaling molecules interact downstream of numerous cytokines involved in the autoimmune and inflammatory responses. AD is driven particularly by cytokines such as IL-4, IL-13, IL-15, and interferon gamma. All of these cytokines are largely regulated by JAK1 and JAK3. As such, inhibitors of these 2 JAK kinases, in particular, could be valuable in controlling the associated inflammation found in AD. JAK inhibitors also have the potential to restore skin barrier function through effect on filaggrin expression (Amano et al 2015).

The efficacy of orally administered JAK inhibitors, such as baricitinib (JAK1/2; Guttman-Yassky et al 2019), upadacitinib (JAK1; Guttman-Yassky et al 2020) and abrocitinib (JAK1; Gooderham et al 2019), and topical administration of tofacitinib

(JAK1/3; Bissonnette et al 2016) in Phase 2 clinical trials in AD provides proof of concept for this approach. Although clinical studies have confirmed the potential for both oral and topical treatment of AD with JAK inhibitors (Alves de Medeiros et al 2016; Bissonnette et al 2016; Eyerich and Novak 2013; Levy et al 2015), none are currently approved by the FDA. However, further adding to proof of concept, topical delgocitinib (Corectim®), a pan-JAK inhibitor, was recently approved in Japan for treatment of adult patients with AD (Dhillon 2020).

1.1.4 ATI-1777

ATI-1777 is a potent inhibitor of both JAK1 and JAK3 enzymes and has shown pharmacological activity in a porcine model of dermal inflammation following topical administration. This new chemical entity competes with adenosine triphosphate at its binding site within the kinase domain, therefore, inhibiting phosphorylation of and the activation of JAKs, recruitment of STATs, and downstream effects on gene expression. Topical delivery of JAK inhibitors, limiting systemic circulation, may be the best option for treatment of AD since oral administration of JAK inhibitors (e.g., tofacitinib and ruxolitinib) can result in significant side effect liabilities. ATI-1777 was designed to act locally in the skin and to be metabolically labile, thereby resulting in short-lived circulating drug levels – an approach aimed to provide efficacy and minimize the risks of systemic toxicity. Approval of topical JAK inhibitors with selective profiles will add to the nonsteroidal options for treatment of AD. Aclaris Therapeutics, Inc. is developing ATI-1777 topical solution as a treatment for AD. ATI-1777 is a potent, selective, reversible adenosine triphosphate–competitive inhibitor of JAK 1/3.

1.1.5 Nonclinical Studies

The nonclinical development program for ATI-1777 included dermal penetration, pharmacokinetic (PK), and toxicity studies following topical application, i.e., the intended route of administration. The intravenous PK of ATI-1777 was characterized by a mono-exponential pattern of elimination with a mean elimination half-life of <1 hour. Consistent with its rapid clearance and short half-lives in vivo, metabolism of ATI-1777 in vitro was rapid in liver microsomes from various nonclinical species and human (half-life for loss of parent compound was ≤30 minutes) and was rapid to moderate in hepatocytes from these same species (half-life for loss of parent compound ranged from 13.5 to 54.6 minutes). Oral bioavailability of ATI-1777 was low. Oral dose escalation studies confirmed increased systemic exposure with increasing dose, and generally higher exposure in female than male rats. Importantly, systemic exposure to ATI-1777 was negligible following topical application to the dermis of minipigs such that plasma levels in humans are expected to be similarly negligible and also significantly lower than the concentration needed to inhibit JAK 1/3 in human whole blood (~45 ng/mL). Details on the systemic (intravenous and oral) PK and absorption, distribution, and metabolism profile of ATI-1777 can be found in the Investigator's Brochure (IB).

Seven-day and 28-day repeat-dose oral toxicity studies in rats demonstrated that ATI-1777 was well tolerated at levels up to 600 mg/kg/day and 300 mg/kg/day,

respectively. The oral no-observed-adverse-effect levels (NOAELs) were considered to be equal to or greater than the maximum doses administered in each study.

Following once daily topical administration of ATI-1777 for 28 or 29 days at doses up to 160 mg/day in male and female minipigs, no ATI-1777-related effects were noted. Thus, the NOAEL was considered to be 160 mg/day. This dose level corresponded to mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values of 3.77 ng/mL and 23.5 ng•h/mL, respectively, in males and 1.99 ng/mL and 10.7 ng•h/mL, respectively, in females on Day 28 of the dosing phase and dermal ATI-1777 concentrations of 9150 to 75200 ng/g in abraded skin biopsies and 13,100 to 99,800 ng/g in non-abraded skin biopsies at the completion of dosing.

ATI-1777 did not demonstrate phototoxicity or ocular toxicity, nor was it a contact allergen.

ATI-1777 was not genotoxic based on the in vitro bacterial reverse mutagenicity (Ames) and in vivo micronuclei formation assays. Carcinogenesis and reproductive toxicology studies have yet to be conducted.

For further details regarding the nonclinical safety evaluation of ATI-1777, refer to the IB.

1.2 Study Rationale

ATI-1777 is aimed to act locally in the skin and to be metabolically labile, with short-lived circulating drug levels that should provide efficacy and minimize the risks of systemic toxicity.

This first-in-human study is being conducted as a preliminary assessment of the efficacy and the safety and tolerability of ATI-1777 in adult patients with moderate or severe AD and to examine the potential for ATI-1777 systemic exposure. The study seeks to demonstrate that efficacy can be achieved, using a tolerated topical concentration of ATI-1777 without systemic levels that exceed the 50% inhibitory concentration (IC_{50}) for inhibition of JAK 1/3 in human whole blood (i.e., ~45 ng/mL).

The study is being conducted in the target population because of the potential for differences in absorption of ATI-1777 through the skin of patients with AD compared with that of healthy volunteers.

The 2% w/w concentration was chosen based on repeat-dose toxicity and toxicokinetic studies in minipigs, which showed a topical NOAEL of ≥160 mg/day.

1.3 Benefit/Risk Assessment

This is a first-in human study and there is no previous clinical experience with ATI-1777. More detailed information about the anticipated benefits and risks can be found in the IB.

1.3.1 Potential Benefits

It is anticipated that treatment with ATI-1777 will result in a clinically significant improvement in AD. Topical administration of tofacitinib (JAK1/3; Bissonnette et al 2016) and ruxolitinib (JAK 1/2; Kim et al 2020a) in Phase 2 and most recently encouraging Phase 3 efficacy and safety data following topical administration of ruxolitinib (Incyte Press Release 2020) in clinical trials in patients with AD provides proof of concept for this approach.

1.3.2 Potential Risks

Potential risks are derived from information provided in the product labels for JAK inhibitors approved in oral dose forms for indications other than AD. Tofacitinib, upadacitinib, and baricitinib are approved for the treatment of rheumatoid arthritis; tofacitinib is also approved for the treatment of psoriatic arthritis and ulcerative colitis; and ruxolitinib is approved for the treatment of myelofibrosis and polycythemia vera. ATI-1777 is designed to be metabolically labile with limited systemic exposure to minimize these systemic toxicities. There were no ATI-1777-related dermal or systemic effects observed following repeated daily dermal applications to minipigs for to 28 days, where little or no quantifiable systemic exposure was observed. Effects observed after repeated oral administration of ATI-1777 to rats, which achieved substantial and dose-related systemic exposure to ATI-1777, were considered to represent a spectrum of clinical effects known to be associated with oral JAK inhibitors.

1.3.2.1 Infections

Serious infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported with orally administered JAK1 and JAK3 inhibitors. Patients with evidence of active, chronic, or latent infections or history of serious local skin infections or tuberculosis at the Screening Visit will be excluded from this study. Infections will be monitored during the study and will be reported as AEs.

1.3.2.2 Viral Reactivation

Viral reactivation and herpes zoster have been observed in clinical studies with tofacitinib and upadacitinib. Patients who screen positive for HIV (antibody), hepatitis B or C, patients with herpes zoster or cytomegalovirus infections that resolved less than 2 months prior to the Screening Visit, and patients with a history of frequent outbreaks (defined as 4 or more outbreaks a year) of herpes simplex virus will be excluded from this study. Viral infections and activations will be monitored during the study and will be reported as AEs.

1.3.2.3 Malignancies

Malignancies were observed in clinical studies with baricitinib, tofacitinib, upadacitinib, and ruxolitinib. Patients with a history of, or current or suspected systemic or cutaneous malignancy and/or lymphoproliferative disease within the 5 years prior to the study will

be excluded from the study. Malignancies will be monitored during the study and will be reported as AEs.

1.3.2.4 Thrombosis

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with baricitinib and upadacitinib. Patients with symptoms of thrombosis will be monitored during the study and thromboses will be reported as AEs.

1.3.2.5 Cytopenias

Cytopenias (lymphopenia, neutropenia, anemia, and thrombocytopenia) have been reported after chronic oral dosing with commercially available JAK1/JAK2 and pan-JAK inhibitors such as ruxolitinib, upadacitinib, and tofacitinib. Treatment with ATI-1777 should be avoided in patients with cytopenias. Patients with laboratory values indicative of cytopenias will be excluded from the study. Cytopenias will be monitored during the study and reported as AEs.

1.3.2.6 Liver Enzyme Elevations

Liver enzyme elevations were observed in patients receiving oral JAK1/JAK3 inhibitors. Patients with elevated liver enzymes AST or ALT ≥2 × the upper limit of normal [ULN]) at the Screening Visit will be excluded from study participation. Routine monitoring of liver parameters will be conducted throughout the study.

1.3.2.7 Lipid Parameters

Treatment with JAK1/JAK3 inhibitors has been associated with increases in lipid parameters including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Lipid parameters will be evaluated throughout the study.

1.3.3 Benefits and Risks Conclusion

Considering the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with ATI-1777 are justified by the anticipated benefits that may be afforded to patients with AD.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the preliminary clinical efficacy of ATI-1777 topical solution in adult patients with moderate or severe AD.

2.2 Secondary Objectives

The secondary objectives of this study are to assess the safety, tolerability, and PK of ATI-1777 topical solution twice daily for 4 weeks in adult patients with moderate or severe AD.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is percent change from baseline in EASI score at Week 4.

3.2 Secondary Endpoints

The secondary endpoints are:

- Percent change from baseline in EASI score at each study visit
- Proportion of patients achieving an IGA score of 0 to 1 combined with an improvement of 2 or more points from baseline within 4 weeks of the start of treatment
- Proportions of patients who achieve 50%, 75%, and 90% improvement in EASI score (EASI-50, EASI-75, and EASI-90, respectively) within 4 weeks of the start of treatment
- Change from baseline in IGA score at each study visit
- Change from baseline in AD BSA at each study visit
- Change from baseline in PP-NRS score over time

3.3 Pharmacokinetic Endpoints

The PK endpoint is ATI-1777 concentration in plasma samples obtained using a sparse sampling approach.

3.4 Safety Endpoints

The safety endpoints are:

- Incidence of TEAEs and SAEs, including incidence of adverse events of special interest (AESIs) (e.g., application site reactions)
- Laboratory values
- Vital signs
- Physical examination results
- 12-lead ECG results

4 STUDY PLAN

4.1 Overall Study Design and Plan

This is a first-in-human, randomized, double-blind, parallel-group, multicenter, vehicle-controlled study to evaluate the efficacy, safety, tolerability, and PK of ATI-1777 solution following twice-daily applications to target areas of male and female patients, aged 18 to 65 years, inclusive, with moderate or severe AD. All AD lesions in protocol allowed areas should be treated. The study will be conducted at approximately 15 sites in the (US).

The study will consist of a Screening Period of up to 30 days, a 4-week Treatment Period, and a 2-week follow-up period. The maximum total duration of the study for patients remaining in the study until their final follow-up assessment will be 73 days.

A study schematic is provided in Figure 1 and a Schedule of Events is provided in Table 1.

4.1.1 Screening Period

The investigator will obtain a signed ICF from the patient before any study procedures are performed. For further details regarding the informed consent process, see Section 10.3. Patients will undergo screening evaluations within 30 days of Day 1 to determine study eligibility (see Section 5). All the results of the screening evaluations should be available at the time that patient eligibility is reconfirmed prior to dosing.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Certain procedures conducted as part of the participant's routine clinical management and obtained before signing of informed consent may be utilized for screening purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Events (Table 1).

At the end of the Screening Period, participants meeting all inclusion and no exclusion criteria will enter the Treatment Period.

4.1.2 Treatment Period

A total of approximately 50 patients who meet all the entry criteria will be randomized on Day 1 via an interactive voice/web response system (IXRS) to ATI-1777 or vehicle treatment in a 1:1 ratio. Patients will be stratified at randomization by severity of AD (moderate versus severe). The study is randomized and double-blinded with regard to ATI-1777 and vehicle in order to prevent bias in treatment allocation and in the assessment of treatment effect. The investigator, site personnel, the sponsor, and their representatives involved in monitoring and conducting the study, and the patients will be blinded to the study medication administered. See Section 7.3 for further details on the

method of assigning patients to the treatment groups, and Section 7.2 for details on access to the treatment codes in the event of emergency unblinding.

During the Treatment Period, patients will apply study drug (ATI-1777 topical solution 2.0% w/w or vehicle) twice daily for 28 days to target areas affected by AD. Patients will be trained by site personnel on how to appropriately apply the study medication. See Section 7.4 for further details on the dose and administration of ATI-1777 and vehicle.

On Day 1 of the study, patients will apply drug in the clinic. The application site will be assessed for serious or severe local AEs prior to discharge from the clinic. Subjects will be informed to contact the site if a severe or serious event occurs. Subjects will be asked to pay particular attention to any events in the first 24 hours after drug administration.

During treatment, patients will attend weekly study visits. At the study visits, AE collection, physical examinations, clinical disease assessments (EASI, IGA, BSA, and PP-NRS), vital sign assessments, PK evaluations, and clinical laboratory evaluations will be performed as detailed in the Schedule of Events (Table 1). Patients will complete a daily diary recording their dose administration and PP-NRS itch score during the study.

For all study participants, blood samples will be collected for PK analysis according to the sparse sampling approach described in Section 6.4.

Participants who discontinue study medication earlier than Day 28 will have an Early Termination (ET) Visit at the time of study medication discontinuation and will return for a PTFU Visit, 2 weeks (±3 days) after the Day 28/ET Visit (see Table 1).

4.1.3 Follow-up Period

Participants will return 2 weeks (± 3 days) after the Day 28/ET Visit for a PTFU Visit (see Table 1).

4.1.4 Sentinel Dosing

A sentinel dosing strategy will be employed. A minimum of 4 and a maximum of 8 patients will be initially enrolled in the study. Study enrollment will then be paused until the initial 4 to 8 patients have completed their Day 8 Visit and safety data from these patients has been reviewed by the sponsor and the ProPharma safety physician to determine whether the study should continue or be stopped. If the safety data from the first 4 to 8 patients indicate that it is safe to continue the study, enrollment will be resumed.

The first 4 to 8 patients will continue in the study according to the Schedule of Events in Table 1 while the review of their safety data is ongoing and will continue in the study after enrollment resumes.

4.2 Unscheduled Visits

If a patient experiences an AE at any time during the study, they may attend an unscheduled visit in consultation with the investigator for evaluation and possible treatment of the event. Assessments may be collected at the discretion of the investigator. In the event of a concern with an AE/SAE, an unscheduled visit can be conducted and the following assessments may be performed as needed: vital signs, ECG, physical examination, laboratory assessments, PK samples, EASI, IGA, BSA, PP-NRS, and photography. If it is determined during an unscheduled visit that a patient will discontinue the study, all assessments for Day 28/ET (see Table 1) should be completed.

4.3 Discussion of Study Design

The efficacy parameters being evaluated (EASI, BSA, IGA, and PP-NRS) are widely used and well-recognized indicators of the disease state of AD. A randomized, double-blind, vehicle-controlled design is being employed to mitigate bias in the collection and analysis of efficacy data.

Although this is a first-in-human study, the study is being conducted in the target population because of the potential for differences in absorption of ATI-1777 through the skin of patients with AD compared with that of healthy volunteers.

Plasma samples will be collected to preliminarily assess PK using a sparse sampling approach. As ATI-1777 is a topical medication and the molecule is metabolically labile, it is expected to have only minimal or no systemic exposure.

The 2% w/w concentration was chosen based on nonclinical toxicity and PK studies in repeat-dose rat and minipig models, which showed a NOAEL of 300 mg/kg/day.

4.4 Stopping Rules

4.4.1 Individual Patient Stopping Rules

A patient will stop treatment with investigational agent if one or combination of the following occurs during the study:

- An infection which meets the criteria as a study medication-related SAE
- A deep venous thrombosis and/or pulmonary embolism
- Lymphoma
- Hy's law (see Section 6.3.2.1)

Treatment with study medication should be temporarily interrupted in the event of severe AEs considered related to study medication, or in the event of one or more of the abnormal laboratory values in Table 5.

4.4.2 Study Stopping Rules

The sponsor and ProPharma safety physician will meet regularly (every 4 weeks) and assess the ongoing safety of the study. Attention will be paid to the number of severe AEs and SAEs, with particular focus paid to the number of patients who meet individual patient stopping rules. PK data will be used in the assessment: events associated with high plasma levels will be considered of high significance.

If the study is stopped, a restart will not occur without agreement of the IRB and the sponsor's medical monitor.

4.5 End of Study

A patient is considered to have completed the study if he/she has completed all study visits.

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

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 must meet the following criteria to be eligible for participation in the study:

1. Able to comprehend and willing to sign the IRB-approved ICF prior to administration of study-related procedures.
2. Male patients or non-pregnant, non-nursing female patients 18 to 65 years old, inclusive, at the time of informed consent.
3. Pregnancy and Contraception:
   - WOCBP (see Section 6.3.3), must have a negative serum pregnancy test at the Screening Visit, a negative urine pregnancy test immediately prior to the first application of study medication on Day 1, and a negative urine pregnancy test at each study visit thereafter.
   - Sexually active heterosexual women must agree to use the following throughout the screening period and for 30 days after last study drug application. WOCBP who are not sexually active at Baseline and become sexually active during the study must agree to follow the birth control measures listed below.
     - Agree to use 2 forms of highly effective contraception, including 1 physical barrier (condom or diaphragm) plus another highly effective method, such as adequate hormonal method (e.g., contraceptive implants, injectables, oral contraceptives) or nonhormonal methods (e.g., intrauterine device) or male partner who is surgically sterile (vasectomy).
   - Male patients with partners of childbearing potential may be enrolled if they are:
     - Documented to be surgically sterile (vasectomy), or
     - Using 2 adequate forms of highly effective contraception, 1 of which should be a physical barrier until 90 days after the last administration of study medication.
4. Have a diagnosis of AD fulfilling the specified diagnostic criteria of Hanifin and Rajka (Hanifin and Rajka 1980).
5. Have at least a 6-month history of AD prior to the Screening Visit, and no significant AD flares for the 4 weeks prior to the Screening Visit.
6. Have at least 1 lesion that measures at least 3 cm^2 at the Screening Visit and on Day 1 prior to the first dose of study medication. This lesion must be representative of the patient's disease state, but not located on the hands, feet, or genitalia.
7. Have a stable diagnosis of moderate or severe (IGA score 3 or 4) AD at the Screening Visit.
8. Have AD affecting 3% to 20% BSA (not including head [neck, scalp, face], palms of hands, soles of feet, groin, and genitalia) at the Screening Visit.

9. Willing to refrain from washing area of treatment or swimming for 6 hours after each study medication application.
10. Willing to refrain from excessive sun exposure (e.g., sunbathing and/or tanning salon visits) and to minimize sun exposure (e.g., wear sun protective clothing, hat) as much as possible.
11. Willing to refrain from use of moisturizers, emollients, and sunscreen on AD study treatment areas for duration of protocol therapy.
12. Willing to refrain from participating in strenuous exercise that would cause profuse sweating for a period of 6 hours after each study medication application.
13. Willing to return to the clinic, follow all study instructions, attend all study visits, and complete study procedures.
14. In good general health and free of any known disease state or physical condition that, in the investigator's opinion, might impair evaluation of the patient or that might expose the patient to an unacceptable risk by study participation.
15. Willing and capable of taking appropriate coronavirus disease 2019 (COVID-19) risk mitigation precautions (e.g., wearing a mask in public, adhering to social distancing, etc.) as recommended or required by local, state, or federal guidelines during participation in the study.

5.2 Exclusion Criteria

Patients with any of the following are excluded from the study:

1. Unstable course of AD (spontaneously improving or rapidly deteriorating) based on the patient history or as determined by the investigator during the Screening Period.
2. Refractory AD (i.e., AD that required frequent hospitalizations and/or frequent intravenous treatment for skin infections within the year before the Screening Visit).
3. AD of a severity (EASI >48) that the patient is not a candidate for a vehicle-controlled study.
4. Any signs or symptoms associated with AD therapy (e.g., history of anaphylaxis, hypersensitivity reactions, skin atrophy, striae, pigmentary changes) that, in the investigator's opinion, might impair evaluation of the AD or that exposes the patient to unacceptable risk by study participation.
5. Concomitant skin disease or clinically infected AD or presence of other skin disease in the area to be dosed that may interfere with study assessments.
6. Use of any of the following treatments within the indicated washout period prior to Day 1:
    - Phototherapy (ultraviolet A, ultraviolet B, or psoralen and ultraviolet A therapy) within 4 weeks prior to Day 1.
    - Systemic biologic immunosuppressant or immunomodulatory therapy (e.g., etanercept, alefacept, infliximab, dupilumab) within 12 weeks (or 5 half-lives of the product, whichever is longer) prior to Day 1.

- Non-biologic immunosuppressants (e.g., methotrexate, retinoids, calcineurin inhibitors, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine) within 4 weeks prior to Day 1.
- JAK inhibitors (systemic and topical) within 4 weeks prior to Day1.
- Systemic corticosteroids within 2 weeks prior to Day 1 (intranasal, inhaled, and topical ocular corticosteroids are allowed).
- Cytostatic agents within 4 weeks prior to Day 1.
- Crisaborole within 2 weeks prior to Day 1.
- Systemic antibiotics within 30 days prior to Day 1.
- Topical treatments for AD (corticosteroids, calcineurin inhibitors, topical H1 and H2 antihistamines, topical antimicrobials, and other medicated topical agents) within 2 weeks prior to Day 1.
- Live attenuated vaccine treatment within 12 weeks prior to Day 1.
- Other investigational product within 30 days or 5 half-lives (whichever is longer) prior to Day 1.

7. Previous failure to respond to prior therapy with JAK inhibitors (systemic or topical), as determined by the investigator.
8. Current use of an oral H1 antihistamine (e.g., diphenhydramine, terfenadine) UNLESS the patient is on a stable dose for at least 14 days prior to the Screening Visit.
9. Medical marijuana unless the patient is on a stable dose for at least 14 days prior to the Screening Visit.
10. Clinically significant laboratory abnormalities at the Screening Visit that, in the opinion of the investigator, could affect interpretation of study data or the safety of the patient's participation in the study.
11. Clinical laboratory values:
    - White blood cell (WBC) count $<2\times10^9$/L
    - ANC <1800/μL
    - Platelet count <130,000/μL
    - Hemoglobin <8g/dL
    - AST or ALT >2×ULN
    - Lymphocyte count $<0.5\times10^9$/L
12. Investigator-assessed history of, or current physical findings of, severe, progressive or uncontrolled immunologic, hepatic, gastrointestinal, pulmonary, cardiovascular, genitourinary (renal), hematological, neurologic or cerebral disorders, infectious disease or coagulation disorders that, as determined by the investigator, could affect the safety of the patient's participation in the study or would preclude participation in and completion of study assessments.
13. History of, current, or suspected systemic or cutaneous malignancy and/or lymphoproliferative disease within the last 5 years, other than patients with a history of adequately treated and well healed and completely cleared nonmelanoma skin

cancers (i.e., basal or squamous cell carcinoma) or cervical carcinoma in situ treated successfully at least 1 year prior to the Screening Visit 1 with no evidence of disease.

14. Evidence of active, chronic, or latent infections at the time of enrollment or a systemic infection including but not limited to a history of treated infection (e.g., pneumonia, septicemia) within 3 months prior to Day1.
15. Patient has a known active or history of incompletely treated or untreated active tuberculosis. Patients with a history of active tuberculosis must have documented adequate treatment verified by the investigator. Patients who demonstrate evidence of latent tuberculosis infection (positive QuantiFERON® Tuberculosis Gold Test) will only be allowed to participate in the study if there is documented evidence of a completed adequate treatment course for latent tuberculosis and if active tuberculosis is excluded per the investigator's judgment.
16. History of a serious local skin infection (e.g., cellulitis, abscess) within 5 years of the Screening Visit.
17. Positive serological test for HIV (antibody), hepatitis C virus (antibody), hepatitis B surface antigen, or hepatitis B core antigen antibody.
18. Known significant exposure (close contact [<6 feet] for ≥15 minutes) to an individual with a confirmed diagnosis of COVID-19 at any time during the Screening Period.
19. Herpes zoster or cytomegalovirus infection that resolved less than 2 months prior to the Screening Visit. Patients with a history of frequent outbreaks of herpes simplex virus (defined as 4 or more outbreaks a year).
20. Clinically significant ECG findings such as, but not limited to, baseline mean QTcF >450 msec for males or >470 msec for females (use of the ECG algorithm is acceptable for this purpose).
21. Known allergy to any of the inactive ingredients in the study drug.
22. Female patients who are pregnant, nursing, or planning to become pregnant during the study.
23. Legal incapacity or limited legal capacity.
24. Major surgery within 3 months of the Screening Visit.
25. Any other condition that precludes adequate understanding, cooperation, and compliance with study procedures or any condition that could pose a risk to the patient's safety, as per the investigator's judgment.
26. Use of potent inhibitors of cytochrome P450 3A4 such as (but not limited to) clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal, and grapefruit.

5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but who do not meet 1 or more criterion required for participation and are not subsequently

entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.3.1 Retesting During Screening

Laboratory parameters and/or assessments that are included in the screening procedures (Table 1) may be repeated during the Screening Period in consultation with the sponsor's medical monitor. Retesting will be allowed when the significance of a laboratory result is unclear and the retest will help interpretation and decision making for entry to the study. Retesting will not be undertaken when the laboratory results clearly indicate clinically significant disease that could impact study interpretation or the safety of a study subject during participation.

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

5.3.2 Rescreening

This study will permit 1 rescreening of a participant who has failed 1 or more inclusion or exclusion criteria. Consultation with the medical monitor may be needed to identify whether rescreening is clinically relevant. If rescreened, the participant must sign a new ICF and the same Patient Number will be assigned.

For participants who are rescreened, consult with the medical monitor to confirm which parameters and/or assessments that were collected as part of the original Screening Period procedures may be utilized.

5.4 Premature Discontinuation

5.4.1 Premature Discontinuation of Study Medication

Patients should be permanently discontinued from study medication in the event of any of the following:

- The patient experiences significant worsening of AD such that additional therapy for the treatment of AD is required
- Confirmed, active infection with the SARS-CoV-2 virus
- Infection requiring parenteral antimicrobial therapy or hospitalization
- Symptomatic herpes zoster
- Malignancy – except for nonmelanoma skin cancer not in or near the treatment area
- Anaphylactic or severe allergic reaction
- WBC count: $<1 \times 10^9$/L or second occurrence of $<2 \times 10^9$/L – in each case, value should be confirmed by retesting before treatment discontinuation

- ANC: $<0.5 \times 10^9$/L or second occurrence of $<1 \times 10^9$/L – in each case, value should be confirmed by retesting before treatment discontinuation
- Lymphocyte count: $<0.3 \times 10^9$/L or second occurrence of $<0.5 \times 10^9$/L – in each case, value should be confirmed by retesting before treatment discontinuation
- Platelet count: $<50 \times 10^9$/L or second occurrence of $<75 \times 10^9$/L – in each case, value should be confirmed by retesting before treatment discontinuation
- Hemoglobin: <6.5 g/dL or second occurrence of <8 g/dL – in each case, value should be confirmed by retesting before treatment discontinuation
- AST or ALT:
  - 5×ULN persisting for 2 weeks of study medication interruption or second event of >5×ULN
  - >3×ULN and (total bilirubin >2×ULN or international normalized ratio [INR] of >1.5)
  - 3×ULN with total bilirubin >2×ULN or symptoms of hepatocellular injury [fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)].
- Any patient who develops any of the following ECG findings during the active treatment phase will be instructed to stop study medication and will be withdrawn from the study:
  - Clinically significant rhythm disturbance other than sinus rhythm or ectopic supraventricular rhythm (ectopic atrial rhythm).
  - Clinically significant conduction disturbance including PR >240 msec, pre-excitation (delta wave and PR <120 msec), second degree or higher atrioventricular block.
  - New finding of QRS >120 ms (if not present at the Screening Visit. For example, patients with Right Bundle Branch Block at screening would not need to be withdrawn from the study if their subsequent ECGs remained unchanged).
  - Evidence of QT-interval prolongation, defined as an increase in the QTcF interval >60 ms from Visit 1.
  - Acute signs of ischemia or infarction.
  - Any ECG abnormality that may, in the opinion of the investigator, represent a new medical issue of concern.

In addition, patients should discontinue study medication if any of the following occurs:

1. The patient withdraws his/her consent to participate in the study.
2. The patient develops an illness that would interfere with his/her continued participation in the study.
3. The patient is noncompliant with study procedures or medication, in the opinion of the investigator.
4. The patient is confirmed to be pregnant.
5. The sponsor or regulatory agency requests withdrawal of the patient.

If a patient is prematurely discontinued from study medication, the patient may remain in the study. The patient should complete the assessments outlined for each study visit; see Table 1. The patient should also attend the PTFU Visit.

Every effort will be made to ensure that patients who prematurely discontinue study medication complete the study.

Patients who discontinue study medication prematurely will not be replaced.

Patients are permitted to temporarily discontinue and restart study medication.

5.4.2 Premature Discontinuation from the Study

Participation in the study is strictly voluntary. A patient has the right to withdraw from the study at any time for any reason, without any reprisal.

At the time of premature study discontinuation, the investigator should make every effort to ensure the patient completes the assessments indicated at the Day 28/ET Visit and completes the PTFU Visit approximately 14 days after the ET Visit; see Table 1. The only exception to this requirement is when consent is withdrawn for all study procedures or the participant loses the ability to consent freely (e.g., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a patient withdraws consent to participate in the study, the study monitor/sponsor will be informed immediately. If there is a medical reason for withdrawal, the patient should remain under the supervision of the investigator until satisfactory health has returned.

If the patient withdraws consent for disclosure of further information, the sponsor may retain and continue to use any collected data 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.

Although a patient is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights.

Patients who prematurely discontinue from the study cannot subsequently rejoin the study.

For details on the discontinuation of study sites or the study as a whole, see Section 15.

5.4.3 Lost to Follow-up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.
- 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, 2 telephone calls and 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 source record.

6 DESCRIPTION OF STUDY ASSESSMENTS

Refer to Table 1 for the schedule of assessments.

6.1 Demographics and Other Screening Assessments

Safety assessments that are also part of the screening assessments are described in Section 6.3.

6.1.1 Medical History

Medical history, including any ongoing illnesses, will be recorded in the eCRF, with the start date and stop date (if applicable) of the illness/condition. Medical history will be collected at the Screening Visit and updated, if necessary, on Day 1 prior to the first administration of study medication.

6.1.2 Demographics

Demographic data, including year of birth/age, sex, race, and ethnicity will be recorded in the eCRF.

6.1.3 Tuberculosis Test

An interferon gamma release assay/QuantiFERON Tuberculosis Gold Test for active/latent tuberculosis will be performed at the Screening Visit. The test will be provided by the central laboratory.

Patients who demonstrate evidence of latent tuberculosis infection (positive QuantiFERON Tuberculosis Gold Test) will only be allowed to participate in the study if there is documented evidence of a completed adequate treatment course for latent tuberculosis and if active tuberculosis is excluded per the investigator's judgment.

In case of indeterminate results, the test may be repeated once.

6.1.4 SARS-CoV-2 Testing and Monitoring

At Day 1, all patients entering the treatment phase of the study must have a nasopharyngeal (preferred) or oropharyngeal swab collected prior to the first dose of study medication to test for the presence of the SARS-CoV-2 virus. The sample will be sent to the study's central lab for analysis by reverse transcription polymerase chain reaction with results reported as either 'Detected' or 'Not detected' for SARS-CoV-2 viral particles. If central laboratory testing cannot be performed at the time of Day 1 (i.e., lab supplies are not yet available) and the study site is able to perform equivalent testing locally, they may choose to do so, as long as the test results are available in the patient's research chart for sponsor review. Patients should not initiate study medication

treatment in the absence of central laboratory or locally equivalent testing being performed.

Patients will be allowed to dose with study medication in the interval between sample collection at Day 1 and result reporting as long as there is no clinical suspicion of COVID-19 infection or recent significant exposure (close contact [<6 feet] for ≥15 minutes) of the patient to an individual with a confirmed, active infection.

If the patient's results are positive for SARS-CoV-2 following sample collection at Day 1, the patient will be notified immediately upon receipt of the results and treatment with study medication will be permanently discontinued. The patient will be advised to begin self-isolation and self-monitoring procedures according to any applicable local, state, and/or federal health recommendations. Referral to an appropriate health care provider for management of the patient's COVID-19 diagnosis should also be made. The patient should be seen for the PTFU Visit (see Table 1) only at such time that the investigator assesses the risk for incidental transmission from viral shedding to be minimized. The patient's COVID-19 diagnosis will be reported as medical history unless the patient's clinical course progresses such that criterion for SAE reporting is met (see Section 8.3), in which case, all applicable safety reporting procedures will be followed by the site.

Sites will also have the option to perform an unscheduled test for the SARS-CoV-2 virus at any time during the treatment phase of the study should a patient's clinical presentation necessitate it in the investigator's opinion. The same notification and referral procedures, as outlined in the preceding paragraphs, should be followed by the site. However, it is expected that any COVID-19 diagnosis made from a sample collected after the initiation of study be reported as an AE per the requirements of Section 8 of this protocol.

6.1.5 Fitzpatrick Skin Type Assessment

Patients' skin type will be classified according to Fitzpatrick skin type at the Screening Visit as follows:

- Type I: Pale white skin, blue/green eyes, blond/red hair. Always sunburns, does not tan.
- Type II: Fair skin, blue eyes. Burns easily, tans poorly.
- Type III: Darker white skin. Tans after initial burn.
- Type IV: Light brown skin. Burns minimally, tans easily.
- Type V: Brown skin. Rarely burns, tans darkly easily.
- Type VI: Dark brown or black skin. Never burns, always tans darkly.

6.1.6 Lesion Photography

Photographs of representative lesions will be taken at each study visit. Sites will be required to submit the patient's baseline photographs to Canfield Scientific's database.

Canfield Scientific will supply all investigational sites with study-specific camera equipment to photograph each patient's identified target AD treatment areas (up to 2 target locations). Sites will be supplied with color stickers to identify each target area. Details regarding the use of the equipment and how to upload the photographs to the Canfield database will be supplied to the sites in the Photography Manual.

6.2 Efficacy Assessments

6.2.1 Eczema Area and Severity Index

The EASI (Hanifin et al 2001; Rullo et al 2008) assesses the extent and severity of AD. This study will employ a modified EASI that excludes evaluation of the head (neck, scalp, face), palms of hands, soles of feet, groin, and genitalia. The modified EASI will evaluate AD in each of 3 body regions (trunk [excluding groin and genitalia], upper extremities [excluding palms of hands], and lower extremities [excluding soles of feet]). The EASI scoring system uses a defined process to grade the severity of the signs of AD and the extent affected. If possible, the same individual should conduct the extent and severity evaluations at each visit.

6.2.1.1 Extent

Each respective body region will be given a score between 0 and 6 based on the percentage involvement in that region according to Table 2. Precise measurements are not required.

Table 2 Extent of Atopic Dermatitis in Each Body Region

% Involvement	0%	1% to 9%	10-29%	30-49%	50-69%	70-89%	90-100%
Region Score	0	1	2	3	4	5	6

6.2.1.2 Severity

For each respective body region, the severity of each of 4 signs (erythema, edema/papulation, excoriation, lichenification) will be graded by the investigator or qualified designee on a 0- to 3-point scale ([0] none, [1] mild, [2] moderate, [3] severe) in AD-affected areas. Half scores are allowed. The average severity across AD-affected areas in each body region will be used as the score for that region.

6.2.1.3 Score Calculation

The investigator or qualified designee will enter the extent and severity values into the eCRF. The final EASI score will then be calculated by an electronic data capture system as described in Table 3.

Table 3 EASI Score Calculation

Body Region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area Score	Multiplier	Score
Trunk	(+	+	+	)	×	× 0.3	
Upper extremity	(+	+	+	)	×	× 0.2	
Lower extremity	(+	+	+	)	×	× 0.4	
						Final EASI score is the sum of the 3 region scores:	_____

EASI = Eczema Area and Severity Index

6.2.2 Investigator's Global Assessment

The IGA is the investigator's assessment of the overall appearance of the lesions at a particular point in time. At every study visit, the investigator will assess the IGA using the scale in Table 4 and report the one score that best describes the overall appearance of the lesions. It is not necessary that all characteristics under Morphological Description be present. 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".

The investigator or qualified designee will enter the score into the eCRF. Whenever possible, the same individual should conduct the evaluation at each visit.

Table 4 IGA Scoring

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.

IGA = Investigator's Global Assessment

6.2.3 Body Surface Area

The total percentage of the patient's AD-affected BSA will be estimated by the investigator or designee using the handprint method, which estimates that the area of a patient's full handprint (fingers and thumbs together) constitutes 1% of their total BSA.

The BSA should be calculated for the EASI score using Regional Percentage Estimates as described in the study training video.

Whenever possible, the same evaluator should perform the estimation at each study visit. If new areas of AD develop while the patient is on the study, these new areas will not be assessed.

6.2.4 Peak Pruritus Numerical Rating Scale

The PP-NRS (Yosipovitch et al 2019) is a single patient-reported item designed to measure peak pruritus, or 'worst' itch, over the previous 24 hours based on the following question: 'On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable," how would you rate your itch at the worst moment during the previous 24 hours?'.

Prior to study medication application on Day 1, the study coordinator should show the PP-NRS scale to the patient, explain the scale and ask the patient to indicate which integer best describes the worst pruritus the subject experienced for their AD over the previous 24 hours.

The patient will complete this assessment and record in their diary each morning before applying study medication during the Treatment Period.

The patient will report the diary rating to site staff at each visit, who will enter it into the patient's source documents and eCRF.

6.3 Safety Assessments

6.3.1 Adverse Events

AEs will be followed, recorded, and reported in line with the procedures described in Section 8.

6.3.2 Clinical Laboratory Evaluations

All laboratory samples will be processed and shipped to the central laboratory, as described in the Laboratory Manual. The central laboratory will analyze the samples or send them to reference laboratory(ies) for analysis, as indicated in the manual. Refer to the central Laboratory Manual for the maximum total volume of blood to be collected per patient throughout the study.

Non-fasting blood and urine samples will be collected at the times indicated in Table 1. On dosing day(s) sampling for the analysis of clinical laboratory parameters will be performed before the administration of study medication.

The following parameters will be assessed:

Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, RBC morphology, platelets, total WBC count, differential WBC count, lymphocyte count, and ANC

Biochemistry: albumin, alkaline phosphatase, ALT, amylase, AST, blood urea nitrogen, bicarbonate, calcium, chloride, creatine phosphokinase (CPK), creatinine, phosphorus, gamma glutamyltransferase (GGT), glucose, lactate dehydrogenase (LDH), lipase, LDL-C, HDL-C, potassium, sodium, total and direct bilirubin, TC, and triglycerides (TG)

Urinalysis: pH, specific gravity, creatinine, glucose, bilirubin, blood, and protein

Screening serology tests will be performed to assess HIV (antibody), hepatitis C (antibody), hepatitis B surface antigen, or hepatitis B core antigen antibody. For hepatitis B, the following tests will be done at the Screening Visit and patients with a positive result for either hepatitis B surface antigen and or hepatitis B core antigen antibody will be excluded from the study.

Serum (β-human chorionic gonadotrophin) pregnancy testing will be performed at the Screening Visit, and urine pregnancy tests will be performed at the other study visits in the Treatment Period.

Refer to the Laboratory Manual for details regarding the collection, processing, and shipping of the blood and urine samples.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Whenever possible, the underlying cause for clinically relevant laboratory value should be recorded as an AE, rather than the laboratory value itself. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during the patient's participation in the study or within 2 weeks after the last dose of study medication 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 such values do not return to normal/baseline within a period of time judged reasonable by the investigator, then the etiology should be identified, and the sponsor notified.

6.3.2.1 Potential Drug-induced Liver Injury

Hy's Law cases have the following 3 components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of ≥3-fold elevations above the ULN of ALT or AST than the placebo
2. Among study patients showing such aminotransferase elevations, often with aminotransferases much greater than 3×ULN, one or more also shows elevation of serum total bilirubin to >2×ULN or INR >1.5, without initial findings of cholestasis (elevated ALP)
3. No other reason can be found to explain the combination of increased aminotransferase and total bilirubin, such as viral hepatitis A, B, or C; evidence for biliary obstruction; acute alcoholic hepatitis (recent drinking and AST >2×ALT are supportive); recent history of severe hypotension or congestive heart failure; other underlying viral disease; pre-existing or acute liver disease; or another drug (including non-prescription products such as herbal supplements) capable of causing the observed injury

During the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential drug-induced liver injury criteria at any point during the study.

In the event that a patient shows laboratory results of:

- AST or ALT: >5×ULN persisting for 2 weeks after study medication interruption or second occurrence of >5×ULN
- ≥ 3×ULN and (total bilirubin ≥2×ULN or INR >1.5)
- ≥ 3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

Please refer to Appendix 4 for further information.

6.3.3 Pregnancy

WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (e.g., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no menses without an alternative medical cause. WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Day 1 prior to randomization.

Serum (β-human chorionic gonadotrophin) or urine pregnancy tests will be performed for WOCBP at the Screening Visit. Urine pregnancy tests will be performed at each study visit.

Serum pregnancy test results must be negative and must be available before Day 1. A pregnancy test must be performed at each study visit, and the result must be negative for the patient to continue to be eligible. If the test result is positive, the patient must be excluded from the study (if at the Screening Visit) or discontinued from the study (if at subsequent study visits). The serum pregnancy tests will be analyzed by the central laboratory; urine pregnancy tests will be analyzed locally.

Male patients will be required to inform the investigator if their partner becomes pregnant during the study.

The investigator should inform the sponsor within 24 hours of learning of the pregnancy or partner pregnancy by completing and submitting a pregnancy report form to the ProPharma Group, as shown in SERIOUS ADVERSE EVENT CONTACT INFORMATION.

If a patient becomes pregnant, she will not receive any further study medication. 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. Any pregnant patient or pregnant partner of a male patient and the fetus will be closely followed up throughout the duration of the pregnancy to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality). The investigator will ask the patient to provide informed consent to record information on the health of the baby. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be required for no longer than 6 to 8 weeks beyond 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.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

6.3.4 12-lead Electrocardiogram

Triplicate 12-lead ECGs will be obtained as outlined in Table 1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

The ECG tracing should include the date and time of the assessment and the signature of the person who made the interpretation; the tracing will be archived at the study site.

6.3.5 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

6.3.6 Physical Examination

Physical examinations will be performed by a Doctor of Medicine (MD) or equivalent, or someone who is authorized to perform the examinations by training and has been delegated this task by the investigator.

A full examination will be performed at the Screening Visit. A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, and extremities.

An abbreviated examination will be performed at the Day 1 and Day28/ET Visits and will include symptom-focused assessments. An abbreviated examination does not preclude examination of any of the other body systems as clinically indicated. Every effort should be made to ensure the same evaluator will complete the examination for each participant at all visits throughout the study. Documentation of who performed the examination is to be recorded in the patient source documentation.

Height will be measured and recorded at the Screening Visit, and weight will be measured and recorded at each study visit. The patient should be dressed in light clothing, without shoes.

6.4 Pharmacokinetics

The PK of ATI-1777 will be preliminarily evaluated by measurement of ATI-1777 concentrations in plasma samples obtained using a sparse sampling schedule. A sparse sampling approach is being employed because it is not anticipated that clinically relevant plasma concentrations will be observed.

Actual time of PK sample collection, the time of last application of study medication, and the volume of study medication applied in the last study medication application must be collected in the eCRF.

A total of 8 PK samples will be collected from each patient.

One sample will be collected before study medication application and 1 sample will be collected approximately 2 hours after application on each of Days 1, 8, and 15.

Samples for Day 28 will be collected from 3 subgroups of patients within each of the specified time windows as follows:

- Subgroup 1: One sample predose and one sample at 0.5 to 2.5 hours post application

- Subgroup 2: One sample at 2.5 to 5 hours post application and one sample at least 2 hours later
- Subgroup 3: One sample at 5 to 8 hours post application and one sample at least 2 hours later (prior to the subsequent application)

The IXRS system will be used to randomly assign patients to subgroups.

The plasma samples will be analyzed for ATI-1777 using a validated assay. Samples will be used to evaluate the PK of ATI-1777. Each plasma sample will be divided into 2 aliquots (1 each for PK and a backup).

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the Laboratory Manual.

7 TREATMENTS

7.1 Investigational Product(s)

7.1.1 Description of Study Medications

Test Product	
Name:	ATI-1777
Dose(s):	Up to 8 mL 2% w/w topical solution applied to affected skin areas
Mode of administration:	Topical application to AD-affected skin areas
Manufacturer:	*Drug Substance:* GVK Biosciences Pvt. Ltd Hyderabad, India *Drug Product:* Tergus Pharma Durham, North Carolina, USA

Vehicle	
Substance:	Topical vehicle solution identical in appearance to ATI-1777
Dose(s):	Up to 8 mL topical solution applied to affected skin areas
Mode of administration:	Topical application to AD-affected skin areas
Manufacturer:	Tergus Pharma Durham, North Carolina, USA

7.1.2 Preparation, Handling, and Storage

The investigator (or designee) is responsible for the safe and proper storage of study medication at the site. ATI-1777 topical solution and vehicle topical solution will be stored under controlled conditions according to the storage requirements described on the label(s). ATI-1777 topical solution and vehicle topical solution should be stored at room temperature 15°C – 25°C (59°F – 77°F), with excursions permitted up to 30°C (86°F). The investigator (or designee) will instruct the patients to store the study medication in accordance to the instructions on the label.

7.1.3 Packaging, Labeling, and Shipment

ATI-1777 topical solution and vehicle topical solution will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

Fifty mL of ATI-1777 topical solution or vehicle topical solution will be provided in 60-mL amber glass bottles with 1-mL droppers metered to 0.25 mL.

ATI-1777 topical solution and vehicle topical solution will be shipped and stored under controlled conditions according to the storage requirements.

Refer to the Pharmacy Manual for full details for packaging, labeling, and shipment of the study medication.

7.2 Blinding

The study is double-blinded; therefore, the sponsor, investigators, study personnel, and the study patients will remain blinded to treatment allocation.

ATI-1777 and vehicle will be coded and labeled in a manner that protects blinding. The IXRS will permit rapid identification of the product (in case of medical emergencies), that does not permit detectable breaking of the blind.

Breaking of the blind is only allowed in the case of an emergency, when knowledge of the study medication is essential for the clinical management of the patient. The investigator must make every effort to contact the sponsor's medical monitor prior to breaking the blind and must contact the sponsor within 1 business day after the event, without revealing to the sponsor (or designee) the results of the code break, except to the ProPharma Group safety team. Patients whose treatment assignments are unblinded will not receive any further study medication.

Emergency unblinding will be organized through the IXRS. The investigator must record the date of unblinding and the reason. All breaks of the blind must be adequately documented in the patient's source documentation.

If an SAE is reported, the designated global patient safety representative may unblind the treatment assignment for the individual patient through IXRS in order to meet regulatory reporting requirements.

7.3 Method of Assigning Treatment

Each patient will be assigned a unique Patient Number, which will be obtained from the IXRS following the patient providing informed consent. The investigator will keep a record (the screening log) of patients who enter screening.

Randomization will be performed via a centralized IXRS. On Day 1, eligible patients will be assigned to ATI-1777 or vehicle in a 1:1 ratio. Patients will be allocated to treatment according to the randomization code.

If a patient withdraws from study participation, his/her unique identification number(s) cannot be re-used for another patient.

Patients will be stratified at randomization by severity of AD (moderate versus severe).

7.4 Dose and Administration

Patients will be instructed to apply a thin film of study medication, twice daily, once in the morning and approximately 8 to 12 hours later, to the identified target AD areas. Study medication should be applied using the metered dropper to drop study medication onto the skin and gently rubbing in over the target area. No more than a total of 8 mL of study medication should be applied to all combined target areas at a given administration session. Study medication should be applied to clean dry skin. The patient must wash her/his hands thoroughly before and after each study medication administration.

Investigational site staff will dispense study medication to the patient on Day 1. Subsequent study medication dispensing will be determined by the site based on the amount used between visits. Study medication bottles will be weighed by the site staff at the time of dispensing and when the bottles are returned. Patients are to return used and unused study medication bottles at each study visit so that the bottles can be weighed. Sites can re-dispense partially used bottles of study medication.

Patients will be trained by site staff on the appropriate application of study medication before the first application on Day 1, and the first application will be supervised by site staff. Patients may be retrained after Day 1 if site staff determines that it is necessary. Throughout the study, patients will record the amount applied in a patient diary.

Additional details on the application of study medication are in Appendix 2 and the Pharmacy Manual.

7.4.1 Identification of Target Treatment Areas

On Day 1, the investigator will identify a target treatment area(s) that meets all inclusion criteria (e.g., a diagnosis of AD based on the criteria of Hanifin and Rajka (Hanifin and Rajka 1980; Appendix 3), BSA between 3% and 20%, inclusive, and an IGA score of 3 or 4). The target treatment area cannot include the head (neck, scalp, face), palms of hands, soles of feet, groin, or genitalia. The investigator will record the identified target treatment area(s) on the body map in the patient's source documents and give to the patient to take home for reference. Up to 2 target treatment areas will be photographed at each specified protocol time point (see Table 1). Sites will use colored stickers to mark the treatment areas prior to the photographs being taken.

Patients will continue treatment of all target areas identified on Day 1, even if the lesion(s) have cleared. If new areas of AD develop while the patient is on study, study medication may be applied to these areas. New areas should be treated at the first sign of disease and continue until the Day 28 visit. New areas of treatment will be recorded in the source notes at the time the patient begins treating them with study medication.

7.4.2 Dose Modification

Study medication dosing for individual patients will be allowed to be paused and restarted if it is deemed to be in the best interest of the patient's safety due to AE. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the patient. All treatment interruptions and the reason for the interruption should be recorded in the eCRF.

Treatment with ATI-1777 should be temporarily interrupted in the event of severe AEs considered related to ATI-1777, or in the event of one or more of the abnormal laboratory values in Table 5.

Table 5 Study Medication Interruption Criteria

Laboratory Test	Hold Study Medication if:	Resume Study Medication if:
WBC count	$<2\times10^9$/L	$\geq2.5\times10^9$/L
ANC	$<1\times10^9$/L	$\geq1.5\times10^9$/L
Lymphocyte count	$<0.5\times10^9$/L	$\geq0.75\times10^9$/L
Platelet count	$<75\times10^9$/L	$\geq100\times10^9$/L
Hemoglobin	8 g/dL or a decrease >2g/dL	≥10 g/dL
AST or ALT	>3×ULN	<2×ULN or within 20% of baseline values
Serum creatinine	>2×ULN	<1.5×ULN or within 10% of baseline value

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal range; WBC = white blood cell

If a patient has one or more of the abnormal laboratory values noted in Table 5, the investigator or designee upon receipt and review of the central laboratory report should instruct the patient to hold study medication applications. The investigator or designee should ask the patient about symptoms, concomitant illnesses and medications and repeat the test(s) as soon as possible. The medical monitor must be notified of dose interruptions due to AEs or laboratory abnormalities noted in Table 5.

If the retest confirms the abnormal laboratory value, then the study medication should continue to be held followed by repeat testing once a week or sooner at the discretion of the investigator. The patient should be followed until the laboratory abnormality(s) returns to normal or to baseline values.

7.4.3 Intervention After the End of the Study

There is no intervention planned for patients after the end of the study.

7.5 Precautions and/or Lifestyle Considerations

Prior to the application of the study medication, the identified AD treatment area(s) should be washed and cleaned using the patient's routine cleansing products. The area should be dried completely prior to the application of the study medication. Patients must not wash the treatment area, go swimming, or perform physical exercise that may cause profuse sweating for a period of 6 hours after applying the study medication. While on study, patients should continue to use their routine cleansing and cosmetic products.

Patients may not use a non-therapeutic, bland emollient, moisturizers, or sunscreens on areas being treated with study medication for the duration of the study. Moisturizers, emollients, and sunscreens may be used on areas not being treated with study medication. Patients must take special precautions to try and limit sun exposure to all identified treatment areas by wearing protective clothing and applying sunscreen to areas not being treated with study medication.

7.6 Prior and Concomitant Medications

All medications (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken from 3 months before the Screening Visit until the end of the follow-up period will be recorded in the appropriate section of the eCRF. The following details must be recorded in the eCRF:

- Medication name, ideally the generic name
- Reason for use
- Start and end date of administration
- The dose and frequency of administration

The medical monitor should be contacted if there are any questions regarding prior or concomitant medication or procedures.

7.6.1 Prior Medications

Prior medications are defined as medications taken prior to the first dose of study medication and discontinued before the first dose of study medication. Prior medication information will be collected at the Screening Visit and updated, if necessary, on Day1 prior to the first administration of study medication.

See Section 15 for details of medication that is permitted or prohibited according to the inclusion and exclusion criteria.

7.6.2 Concomitant Medication

Concomitant medications are defined as any medication taken after the first dose of study medication until the Day 42/PTFU Visit.

Concomitant medications (e.g., prescription, over-the-counter, or herbal) should be administered during the study only if they are prescribed for treatment of specific clinical events.

Use of any of the following treatments is prohibited during the study:

- Phototherapy (ultraviolet A, ultraviolet B, or psoralen and ultraviolet A therapy).
- Systemic biologic immunosuppressant or immunomodulatory therapy (e.g., etanercept, alefacept, infliximab, dupilumab).
- Non-biologic immunosuppressants (e.g., methotrexate, retinoids, calcineurin inhibitors, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine).
- JAK inhibitors (systemic and topical).
- Systemic or topical corticosteroids (intranasal, inhaled, and topical ocular corticosteroids are allowed if used to treat other medical conditions).
- Cytostatic agents.
- Crisaborole.
- Systemic antibiotics.
- Topical treatments for AD (corticosteroids, calcineurin inhibitors, topical H1 and H2 antihistamines, topical antimicrobials, and other medicated topical agents).
- Live attenuated vaccine treatment.
- Other investigational products.
- Use of potent inhibitors of cytochrome P450 3A4 such as (but not limited to) clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal, and grapefruit.

7.7 Overdose

It is not anticipated that ATI-1777 will be systemically absorbed, and dosing will vary between patients. Treatment of suspected overdose with ATI-1777 should consist of clinically appropriate supportive measures.

7.8 Compliance

Site staff will train patients in the correct application of the study medication to each patient and will check that each patient is following the instructions properly. Any deviation from the correct use of the study medication will be recorded in the eCRF. Study staff will counsel the patients, as required to make sure patients are compliant with study medication applications.

The volume of each study medication applied in each application will be recorded in a patient diary, which will be reviewed at each study visit. The investigator or designee will be responsible for monitoring patient compliance through diary review, questioning the patient, documenting missed doses, if any, weighing the bottle before dispensing and after return, and performing a visual inspection of the quantity in the study medication bottles (used and unused). A record of the study medication dispensed to and returned by each patient will be maintained and reconciled with study medication and compliance

records at the site. The study medication start and stop dates, including dates for study medication delays and/or dose reductions, will also be recorded in the eCRF.

7.9 Accountability

The study medication must not be used for any purpose other than that defined in this protocol. All supplies of study medication will be accounted for in accordance with GCP.

The pharmacist or (designee) should maintain accurate records of all study medication supplies received during the study. These records should include the dates and amounts of study medication that were received at the site, dispensed, and destroyed or returned to the sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study medication and study patients. If errors or damage in the study medication shipments occur, the investigator should contact the sponsor (or its designee) immediately. Copies of the study medication accountability records will be provided by each investigator for inclusion in the trial master file. The study monitor will periodically check the supplies of study medication held by the investigator or pharmacist to verify accountability of the study medication used.

Investigators will maintain records that document adequately that the patients were provided the medication specified by the protocol and reconcile all study medication received from the sponsor (or designee).

After the end of the study, all unused study medication and all medication containers should be destroyed at the study center or returned to the sponsor (or designee) for destruction. In either instance, complete documentation will be returned to the sponsor. The study medication resupply will be managed by the IXRS.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

TEAEs are defined as AEs with an onset date on or after the first administration of study medication and before the date of last administration of study medication + 14 days.

8.1.2 Serious Adverse Events

An SAE is any event that meets any of the following criteria:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization. The event will be considered an SAE when, based upon appropriate medical and scientific judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Definition of Terms

Life-threatening: an AE is life-threatening if the patient was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that, if it had occurred in a more severe form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery, or for procedures planned prior to the patient providing informed consent, or routine clinical procedures that are not the result of an

AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

In general, hospitalization signifies that the patient has been detained (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. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

8.1.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction is defined as any AE for which there is a reasonable possibility that the study medication caused the AE (where 'reasonable possibility' means there is evidence to suggest a causal relationship between the study medication and the AE), the AE is not listed in the IB or is not listed at the specificity or severity that has been observed, and the AE meets at least one of the criteria for seriousness (see Section 8.1.2).

8.1.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to study medication interruption, modification, or discontinuation must be recorded as an AE or SAE, as applicable. In addition, laboratory or other abnormal assessments (e.g., in ECGs, X-rays, or vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 8.1.1 and 8.1.2. Whenever possible, the underlying cause for clinically relevant laboratory value (e.g., anemia) should be recorded as an AE, rather than the laboratory value itself (e.g., decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities, see Section 6.3.2.

8.1.5 Adverse Events of Special Interest

The AESIs for this study are TEAEs of:

- Application site AEs
- Serious infections

- Malignancies
- Thrombosis
- Cytopenias
- Liver enzyme elevation AEs (e.g., ALT, AST, bilirubin, GGT, LDH)
- Increased lipid parameter AEs (e.g., TC, LDL-C, HDL-C, TG)

An AESI should be reported by the investigative site using the relevant page of the eCRF. The documentation and processing of AESIs is further detailed in the investigator site file.

8.2 Assessment of Adverse Events

8.2.1 Severity

Severity grading for every AE is to be performed by the investigator based on his/her best medical judgment as follows:

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate: minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
- Severe: medically significant; disabling; or limiting self-care activities of daily living

The terms serious and severe are not synonymous. The general term "severe" is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a "severe" headache). This is NOT the same as serious, which is usually associated with events that pose a threat to a patient's life or ability to function (see Section 8.1.2). A severe AE (classified as "severe" or "life-threatening") does not necessarily need to be considered serious. For example, a WBC count of 1000/mm^3 to less than 2000/mm^3 is considered severe but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.2.2 Causality

Investigators are required to systematically assess the causal relationship between the AEs and SAEs and the exposure to the study medication using the following definitions:

Related:

- The AE follows a reasonable temporal sequence to study medication administration, and it cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications).

- The AE follows a reasonable temporal sequence to study medication administration, and it is a known reaction to the drug under study or a related chemical group or is predicted by known pharmacology.

Not Related:

- The AE does not follow a reasonable sequence from study medication administration, or it can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

8.3 Documenting and Reporting Adverse Events

Reporting of SAEs will begin when the patient has provided informed consent. Nonserious events that occur between receipt of informed consent and the first study medication application will be added to the patient's medical history. Reporting of nonserious AEs will begin with the first application of study medication. Nonserious events that occur between receipt of informed consent and the first study medication application will be added to the patient's medical history. Reporting of all AEs will continue through the PTFU Visit or 14 days after last administration of study medication, whichever is later.

Occurrence of AEs may be volunteered spontaneously by the patient; discovered as a result of general, nonleading verbal questioning by the study staff; or determined by physical examination or other safety assessments. All AEs will be monitored and recorded in the eCRF throughout the entire study.

For all AEs, the investigator must pursue and obtain adequate information (a description of the event, severity, time of occurrence [including whether the AE onset was before, during, or after the study medication application], duration, and any action, e.g., treatment/follow-up tests). The outcome of the event should be provided along with the investigator's assessment of the relationship to the study medication. The investigator must also assess whether the event meets the criteria for classification as an SAE.

It is the investigator's responsibility to review all documentation (e.g., hospital notes, laboratory reports, and diagnostic reports) related to an AE. Wherever possible, the investigator's diagnosis, not the individual signs and symptoms, will be documented as the AE.

Investigators are not obligated to actively seek AEs or SAEs after the patient's conclusion of study participation. However, if the investigator learns of any SAE, including 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 medication or study participation, the investigator must promptly notify the sponsor.

8.4 Reporting of Serious Adverse Events

For SAEs with an onset inside the reporting period (i.e., onset after provision of informed consent and up to the PTFU Visit or 14 days after the last application of study medication administration (for SAEs), whichever is later) and SAEs considered related to study medication that occur after this reporting period (e.g., during poststudy follow-up), the investigator must immediately (no later than 24 hours after becoming aware of the event) inform the ProPharma Group of the SAE utilizing the safety report form (see SERIOUS ADVERSE EVENT CONTACT INFORMATION).

The investigator is obliged to respond to any request for follow-up information (e.g., additional information, event outcome, final evaluation, or other records where needed) or to any question the sponsor (or designee) may have concerning the SAE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the sponsor (or designee) and, as applicable, to allow the sponsor to meet strict regulatory timelines associated with expedited reporting obligations for events of this nature.

8.5 Adverse Event and Serious Adverse Event Follow-up

During the study (and after the End-of-Study Visit), all AEs and SAEs should be followed proactively by the investigator until the event resolves or the condition stabilizes to a level acceptable to the investigator, until the event is otherwise explained, or until the patient is lost to follow-up. At the time the patient's study participation ends, all ongoing AEs and SAEs should be evaluated for resolution. New or updated information will be recorded in the originally completed eCRF and the investigator will submit any updated SAE information to the sponsor within 24 hours of receipt of the information.

8.6 Safety Reporting Oversight

In accordance with ICH GCP and 21 CFR312.32, the sponsor (or designee) will inform investigators of "findings that could affect adversely the safety of patients, impact the conduct of the trial, or alter the IRB's approval/favorable opinion to continue the trial."

The sponsor has a legal responsibility to notify the FDA about the safety of a study medication under clinical investigation. The sponsor will comply with US regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators. To support compliance with these requirements, the investigator must provide requested information in a timely manner.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will file

it along with the IB and will notify the IRB, if appropriate, according to local requirements.

9 STATISTICS

9.1 General Procedures

All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations. Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) by the sponsor or its representatives.

Details of all statistical summaries will be provided in the study-specific SAP. The SAP will be approved prior to any lock of the study database and unblinding of the study data. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol.

Patients will be stratified at randomization according to their baseline disease severity (moderate versus severe).

All data will be presented by treatment group. Descriptive statistics (number of observations, mean, standard deviation [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

Baseline is defined as the last non-missing measurement before or on the date of first administration of study medication.

9.2 Analysis Populations

FAS: All patients who have been administered at least one dose of study medication. The FAS will be used for both the efficacy and safety analyses. The efficacy analyses will be conducted on the FAS population as randomized, and the safety analyses and summaries will be conducted on the FAS as treated.

PP Population: All patients who have non-missing Week 4 EASI scores recorded. The PP population will be analyzed as treated. Important protocol deviations that could affect the primary endpoint will be defined and agreed upon before unblinding.

PK Population: All patients who receive at least 1 dose of study medication and provide at least 1 plasma concentration value.

9.3 Sample Size

A total of approximately 50 patients will be enrolled in order to achieve 34 patients who complete the study. Data from 34 patients is estimated to provide 95.6% power to detect a statistically significant difference between the treatment groups in the primary endpoint (percent change from baseline in EASI scores). This power calculation is based upon a 1-sided treatment contrast within a 1-way ANOVA model and assumes group means of 65% and 20% for ATI-1777 and vehicle, respectively. The group means were

based upon slightly more conservative estimates than were observed in a Phase 2 study of topical ruxolitinib in AD (Kim et al 2020b). The variance for the percent change from baseline in EASI was assumed to be 38.3%. This variance assumption was based upon data observed in a pilot AD study for the topical compound ATI-502 (ATI-502-AD-201).

9.4 Statistical Methods

9.4.1 Primary Endpoint

The primary endpoint is the percent change from baseline in EASI score at Week 4.

9.4.2 Secondary Endpoints

The secondary endpoints are:

- Percent change from baseline in EASI score at each study visit
- Proportion of patients achieving an IGA score of 0 to 1 combined with an improvement of 2 or more points from baseline within 4 weeks of the start of treatment
- Proportions of patients who achieve EASI-50, EASI-75, and EASI-90 within 4 weeks of the start of treatment
- Change from baseline in IGA score at each study visit
- Change from baseline in BSA at each study visit
- Change from baseline in PP-NRS score over time

9.4.3 Pharmacokinetic Endpoint

The PK endpoint is the concentration of ATI-1777 in plasma samples obtained using a sparse sampling approach.

9.4.4 Safety Endpoints

The safety endpoints are:

- Incidence of TEAEs and SAEs
- Laboratory values
- Vital signs
- Physical examination results
- 12-lead ECG results

9.4.5 Analysis of Efficacy

All efficacy summaries will be conducted on both the FAS and PP populations. All p-values for efficacy will be based on a 1-sided hypothesis test of the superiority of ATI-1777 to vehicle.

The primary efficacy analysis will be the treatment comparison between ATI-1777 and vehicle for the percent change from baseline in EASI scores at Week 4 based on the FAS. This treatment comparison will be made within the context of a Mixed Model Repeated Measures analysis where the EASI scores over time are treated as repeated measures within a given patient. Treatment group, time (study visit), and treatment by time interaction will enter the model as categorical factors, baseline EASI score and/or baseline severity of AD will be included as a continuous covariate and patient ID will enter the model as a random effect. Treatment group model-based means and model-based differences in treatment groups will be provided along with corresponding 90% confidence intervals and 1-sided p-values.

Treatment comparisons between ATI-1777 and vehicle for each of the continuous efficacy endpoints that are conducted over time (change in IGA, BSA, and PP-NRS) will be analyzed using a similar model as described for the primary endpoint. Treatment comparisons will be made for each post-baseline scheduled visit utilizing an appropriate analysis window scheme.

Treatment group comparisons for categorical efficacy endpoints (IGA Response, EASI-50, EASI-75, and EASI-90) that are conducted over time will employ a logistic regression model fit at each scheduled visit separately, where appropriate. The logistic regression model will include treatment group as a factor and the baseline value and/or baseline severity of AD as a covariate. Model-based point estimates for the treatment proportions will be provided as well as model-based differences and corresponding 90% confidence intervals and 1-sided p-values.

9.4.6 Analysis of Safety

The FAS will be used for the analysis of safety data (AEs, clinical laboratory, vital signs, physical examination results, and ECGs).

AEs will be coded with MedDRA. TEAEs are defined as AEs with onset dates on or after the date of first administration of study medication through the end of the study, or that exist prior to the first dose and worsen with dosing. TEAEs will be presented by system organ class and preferred term in frequency tables. Patients with multiple AEs will be counted only once within each preferred term and system organ class. Key patient information for patients with an AE with an outcome of death, patients with SAEs, and patients with an AE leading to discontinuation of study medication will be listed.

Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively. Laboratory data outside study-specific reference ranges will be listed.

Vital signs and ECG parameters will be presented descriptively.

9.4.7 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, ethnicity, and race) and baseline characteristics (including height, weight, and disease characteristics) will be presented descriptively.

9.4.8 Pharmacokinetic Endpoints

Individual and mean plasma concentrations at each sampling time point for ATI-1777 will be listed and summarized in a tabular form including means, geometric means, ranges, standard deviations, and coefficients of variation. Mean concentrations will be plotted versus nominal time on linear and semilogarithmic scales.

9.4.9 Handling of Missing Values

Patients who discontinue study medication will be asked to come to each visit for the scheduled assessments up to the end of the study.

For the primary efficacy analysis and all continuous analyses based on the FAS population, missing data will be imputed using last observation carried forward (LOCF). Missing data will not be imputed for continuous efficacy analyses that are based on the PP population. For responder-type categorical endpoints (such as EASI-50, EASI-75, and EASI-90), missing data will be treated as a non-response. Specific details regarding the imputation of missing data and intercurrent events will be described further in the SAP.

Patients who prematurely discontinue the study will be evaluated based on the data collected at each visit attended. Data collected during the ET Visit will be used as an end-of-study assessment for these patients. If the ET Visit was performed >1 day after the last dose was administered, then the previous visit will be used as the end-of-study assessment.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in accordance with the Note for Guidance on GCP ICH Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US FDA Code of Federal Regulations (CFR; Title 21 Parts 50, 56, 312), the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

10.2 Institutional Review Board/Independent Ethics Committee

Before initiating a study, the investigator/institution must have written and dated approval/favorable opinion from the IRBs for the study protocol/amendment(s), written ICF, any ICF updates, patient recruitment procedures (e.g., advertisements), and any written information to be provided to patients and a statement from the IRBs that these comply with GCP requirements (if applicable). A current copy of the IB should be included as part of the written application to the IRB.

The IRB approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings, including adverse drug reactions that are both serious and unexpected, as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to the requirements of all applicable regulations
- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study patients

10.3 Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator should have the IRB's written approval/favorable opinion of the written ICF and any other written information to be provided to patients.

- The investigator or his/her representative will explain the purpose and nature of the study as well as possible adverse effects to the patient or his/her legally acceptable representative and answer all questions regarding the study.

- Patients must be informed that their participation is voluntary, and consent can be withdrawn at any point.
- Patients or their legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of US FDA CFR Title 21 Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, and the IRB or study site.
- Prior to a patient's participation in the study, the written ICF should be signed and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion.
- 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 original copy of the signed ICF will be retained at the study site.
- A copy of the ICF and any other written information must be provided to the patient or the patient's legally acceptable representative.
- If the ICF is revised, the revised ICF must have received the IRB's approval/favorable opinion in advance of its use. Patients must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The patient or the patient's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented.

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

If a patient is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The witness should sign and personally date the ICF after:

- The written ICF and any other written information to be provided to patients is read and explained to the patient or the patient's legally acceptable representative
- The patient or the patient's legally acceptable representative has orally consented to the patient's participation in the study
- The patient or the patient's legally acceptable representative has signed and personally dated the ICF, if they are capable of doing so

By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the patient or the patient's legally acceptable representative, and that informed consent was freely given by the patient or the patient's legally acceptable representative.

10.4 Financing and Insurance

10.4.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

10.4.2 Insurance, Indemnity, and Compensation

Aclaris Therapeutics, Inc. will maintain an appropriate clinical study insurance policy.

10.4.3 Financial Disclosure

Investigators and subinvestigators 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.

11 RECORDS MANAGEMENT

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

An eCRF will be used to store and transmit patient information. The eCRF must be reviewed and electronically signed and dated by the investigator. The investigator is responsible for verifying that the data entries are accurate and correct by signing the eCRF.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (e.g., investigators and the study coordinator). The eCRF must be completed as soon as possible after any patient evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

During each study visit, a physician participating in the study will maintain progress notes in the patient's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the patient, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the investigator's assessment as to whether or not the reported AE is related to study medication
- Changes (including dosages) in concomitant medications/therapies (including medical foods) or procedures
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the patient via telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the investigator (or designee). If the reason for the change is not apparent, a brief

explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

The PRA data management department will write a data management plan, which will be finalized prior to performing any data validation.

11.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and computer printouts, screening logs, completed scales, quality of life questionnaires, and recorded data from automated instruments.

The investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

All source documents from this study are to be maintained by the investigator and made available for inspection by authorized personnel. The investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB review, and regulatory inspections. The sponsor should verify that each patient has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB review, and regulatory inspection.

11.2 Case Report Form Completion and Data Management

An eCRF will be used to store and transmit patient information. The file structure and format for the eCRF will be provided by the sponsor or its representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (e.g., investigators and the study coordinator). The eCRF must be completed as soon as possible after any patient evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

11.3 Study Files and Record Retention

All data derived from the study will remain the property of the sponsor. The sponsor assumes accountability for actions delegated to other individuals, e.g., the CRO.

Records must be retained in accordance with the current ICH guidelines on GCP. All essential study documents, including records of patients, source documents, eCRFs, and the study medication inventory, must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of ATI-1777. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. The sponsor is responsible for informing the investigator when these documents need no longer be retained.

The investigator is not to dispose of any records relevant to this study without written permission from the sponsor and is to provide the sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is patient to inspection by the sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

12 AUDITING AND MONITORING

Sponsor-assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as assessing patient enrollment, compliance with protocol procedures, completeness and accuracy of data entered into the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The investigator must agree to sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the investigator will assist with the sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the Study Monitoring Plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. Government regulatory authorities may also inspect the investigator during or after the study. The investigator (or designee) should contact the sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

12.1 Risk and Quality Tolerance Limits

The sponsor will review risk control measures outlined in the study-specific monitoring plan periodically to ascertain whether the implemented clinical quality management activities remain effective and relevant. The clinical quality management approach and any important deviations from the predefined quality tolerance limits and remedial actions adopted will be described in the clinical study report (CSR).

12.2 Protocol Adherence and Deviations

The investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the investigator, site personnel, or the patient.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. For example, important protocol deviations may include enrolling patients in violation of key eligibility criteria designed to ensure a specific patient population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The investigator should not implement any deviation from the protocol without agreement from the sponsor and prior review and approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard to a study patient, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or telephone number.

In the event of an important protocol deviation, the investigator will discuss the deviation with the sponsor’s medical monitor and will come to an agreement as to whether the patient should be withdrawn from the study due to the important protocol deviation.

13 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by the sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB, and the investigator must await approval before implementing the changes. The sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

The current version of the ICF will require similar modification if the IRB, investigator, and/or sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the patient and/or impact the patient's involvement as a study patient. In such cases, the ICF will be renewed for enrolled patients before their continued participation in the study.

14 STUDY REPORT AND PUBLICATIONS

This study will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites, as necessary.

The sponsor is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. The sponsor should ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of CSR (ICH E3).

The publication policy of the sponsor is discussed in the investigator's clinical research agreement.

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.

15 STUDY START AND TERMINATION

The study start date is the date on which the first patient provides informed consent.

The end of the study is defined as the last patient's last assessment.

This study may be terminated prematurely in whole or in part due to a change in the benefit/risk profile for ATI-1777 such that continuation of the study would not be justified on medical or ethical grounds. This determination may be made by the study investigators in conjunction with the sponsor, or by the IRB or the US FDA. The sponsor may also elect to terminate the study if enrollment is sufficiently slow to prevent the completion of the study in an acceptable timeframe, or if ATI-1777 development is discontinued. Both the sponsor and the investigator reserve the right to terminate the study or the participation in the study at an investigator's site at any time. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

If the study is prematurely terminated or suspended for any reason, the sponsor/investigator/site personnel should promptly inform the study patients and should assure appropriate therapy and follow-up for the patients. Where required by the applicable regulatory requirements, the IRB should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the site personnel. The investigator/site personnel should promptly inform the sponsor and the IRB. The investigator/site personnel should also provide the sponsor and the IRB a detailed written explanation of the termination or suspension.

16 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the sponsor. However, authorized regulatory officials, IRB personnel, and the sponsor and its authorized representatives are allowed full access to the records.

All study patients must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The patients must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Identification of patients and eCRFs shall be by unique patient identification numbers (such as randomization number) only. All personal identifiers according to applicable regulations (e.g., name, telephone number) must be redacted permanently by the site personnel and replaced with the patient's unique identification number in all records and data before transfer to the sponsor (or designee).

All personal details will be treated as confidential by the investigator and staff at PRA.

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18 APPENDICES

APPENDIX 1 – STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	Aclaris Therapeutics, Inc. 640 Lee Road Suite 200 Wayne, Pennsylvania 19087 USA Phone: [redacted]
Sponsor's medical expert:	[redacted] Aclaris Therapeutics, Inc. 640 Lee Road Suite 200 Wayne, Pennsylvania 19087 USA Phone: [redacted]
Sponsor's project manager:	[redacted] Aclaris Therapeutics, Inc. 640 Lee Road Suite 200 Wayne, Pennsylvania 19087 USA Phone: [redacted]
Contract research organization's project manager:	[redacted] PRA Health Sciences, Inc. 4130 Park Lake Avenue Suite 400 Raleigh, North Carolina 27612 USA Phone: [redacted]
Medical monitor:	[redacted] Aclaris Therapeutics, Inc. 640 Lee Road Suite 200 Wayne, Pennsylvania 19087 USA Phone: [redacted]
Pharmacovigilance:	ProPharma Group 2635 University Avenue West, Suite 195 St Paul, MN 55114 USA FAX: [redacted] Email: [redacted]

CRO:	PRA Health Sciences, Inc. 4130 Park Lake Avenue Suite 400 Raleigh, North Carolina 27612 USA Phone: [redacted]
Central laboratory:	ACM Global Laboratories 160 Elmgrove Park Rochester, New York 14624 USA Phone: [redacted]
ATI-1777 manufacturer:	*Drug Substance:* GVK Biosciences Pvt. Ltd Plot No. 28 A IDA Nacharam Hyderabad – 500076, India *Drug Product:* Tergus Pharma 2810 Meridian Parkway Suite 120 Durham, NC 27713 USA
ATI-1777 distributor:	Xerimis, Inc. 102 Executive Drive Moorestown, NJ 08057 USA

A log of the name and title of the investigators who are responsible for conducting the study, and the address and telephone numbers of the study sites will be maintained.

The names and addresses of any other laboratories involved in the study (further to those stated above) will be provided in the Laboratory Manual.

APPENDIX 2 - PATIENT INSTRUCTIONS

Preparation and General Instructions:

1. Reminder to:
   a) Refrain from bathing, swimming and/or participating in strenuous exercise that would cause profuse sweating for 6 hours after application of study medication.
   b) Refrain from applying moisturizers, emollients, and sunscreen to AD treatment areas for the duration of protocol therapy. Moisturizers, emollients, and sunscreens may be applied to non-AD treatment areas.
   c) Refrain from excessive sun exposure (e.g., sunbathing and/or tanning salon visits) and minimize sun exposure (e.g., wear sun protective clothing, hat) as much as possible.
2. Gather a clean washcloth and towel, the study medication bottle, and dropper.
3. Skin should be clean and dry before applying study medication.
4. Wash your hands with soap and water before and after using this study medication.
5. Record your 'worst' itch over the previous 24 hours on your diary in the morning before applying study medication.
6. Apply a thin layer of study medication to the identified AD target skin area as instructed by the study doctor or the study staff. Keep applying study medication to the area throughout the study, even if the skin begins to clear. If new areas of AD appear, study medication may be applied to these areas.
7. Avoid study medication contact with the eye.
8. You will apply study medication twice a day, approximately 8 to 12 hours apart.
9. Document on your diary whether you completed the morning and/or evening dose and total amount of drug (mL) applied at each application timepoint.
10. Remember to bring your study medication bottles both used and unused to each study visit along with your diary.

Study Medication Application:

1. Draw up exactly 1 mL of study medication into the dropper. The medication level should be at the 1-mL line.
2. During study medication application, avoid any study medication running into your eyes.
3. Squeeze a few drops of study medication onto the center of the identified target AD area and gently rub the study medication into your skin. Keep applying a few drops and rubbing into your skin until **the entire area** is covered with a thin film of study medication.
4. Draw up additional medication 1 mL at a time to cover the entire AD area. No more than a total of 8 mL should be used to treat all affected areas. Less than 8 mL may be used if a lower amount is sufficient to cover all affected skin areas.
5. Place the dropper back on the bottle and make sure it is closed tightly.
6. Document the total amount of mL used at each application timepoint on your diary.
7. It is important to continue to apply study medication to the target AD areas throughout the study, even if the skin begins to clear.

8. Wash your hands after using this product to prevent any residue being left on your hands.
9. If you missed a dose or doses, record the missed dose or doses in your diary and tell the study staff at your next visit.

Missed Doses: If you miss a dose of this study medicine, apply it as soon as possible. However, if it is almost time for your next dose, skip the missed dose, and go back to your regular dosing schedule.

Storage: Store the medicine in the original glass bottle in the carton provided at room temperature, away from heat, moisture, and direct light. Keep from freezing. Keep out of the reach of children.

APPENDIX 3 - HANIFIN AND RAJKA DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS (HANIFIN AND RAJKA 1980)

Major criteria: Must have 3 or more of the following:

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

Minor criteria: Should have 3 or more of:

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

APPENDIX 4 - POSSIBLE HY'S LAW LIVER CHEMISTRY ACTION AND FOLLOW-UP ASSESSMENTS

Suggested Actions and Follow-up Assessments[1]	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study medication. • Report the event to the sponsor or designee **within 24 hours.** • Complete an SAE data collection tool if the event also met the criteria for an SAE.[2] • Perform liver chemistry follow-up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING** below). • **Do not restart/rechallenge** participant with study treatment unless allowed per the protocol and sponsor approval **is granted**. • If restart/rechallenge is either **not allowed per the protocol or not granted**, permanently discontinue study treatment. The participant may continue in the study for any protocol-specified follow-up assessments. **MONITORING:** **If ALT ≥3×ULN AND bilirubin ≥2×ULN or INR >1.5:** • Repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT ≥3×ULN AND bilirubin <2×ULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	• Viral hepatitis serology[3] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for ATI-1777 drug concentration[4] • Serum CPK and lactate dehydrogenase • Fractionate bilirubin, if total bilirubin ≥2×ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF **If ALT ≥3×ULN AND bilirubin ≥2×ULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James et al 2019]).

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; eCRF = electronic case report form; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment if ALT ≥3×ULN **and** bilirubin ≥2×ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥3×ULN **and** bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.
3. Hepatitis A immunoglobulin M antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C ribonucleic acid; cytomegalovirus immunoglobulin M antibody; Epstein-Barr viral capsid antigen immunoglobulin M antibody (or, if unavailable, heterophile antibody or monospot testing); and hepatitis E immunoglobulin M antibody.
4. Drug concentration sample may not be required for participants known to be receiving placebo or non-comparator treatments. Record the date/time of the blood sample draw and the date/time of the last dose of study treatment prior to the blood sample draw in the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated, do not obtain a blood sample. Instructions for sample handling and shipping are in the reference manual.