Statistical Analysis Plan (SAP)

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 Version No./Date:	V2.0/10SEPT2020
CRF Version No./Date:	V1.1/27OCT2020
SAP Version No./Date:	V1.0/06NOV2020

1. Approvals

Sponsor	
Sponsor Name:	Aclaris Therapeutics
Representative/ Title:	[redacted]
Signature /Date:	
PRA	
Biostatistician / Title:	[redacted]
Signature /Date:	

(NOTE: Electronic Signatures should only be used if allparties have the ability to eSign.)

2. Change History

Version/Date	Change Log
1.0	Created as new

3. Table of Contents

4. Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Aclaris Therapeutics, Inc. (Aclaris) Protocol ATI-1777-AD-201.

5. Scope

The SAP outlines the following:

- Study Objectives
- Study Design
- Endpoints
- Applicable Study Definitions
- Statistical Methods

6. Introduction

This SAP should be read in conjunction with the study protocol V2.0, 10SEP2020 and electronic case report form (eCRF) V1.1 27OCT 2020. Any further changes to the protocol or eCRF may necessitate updates to the SAP. Changes following approval of the first version SAP will be tracked in the SAP Change History.

Final approval of the SAP by the Aclaris and PRA statisticians will occur prior to database lock and unblinding study treatment.

6.1. Changes from Protocol

The sample size computation was changed from one based upon a two-sided hypothesis test to one based upon a one-sided hypothesis test in order to match the planned primary analysis. The missing continuous efficacy endpoints will be imputed using last observation carry forward (LOCF) for all the continuous efficacy endpoints instead only for the primary efficacy endpoint (Protocol Section 9.4.9). Baseline severity of atopic dermatitis (AD) (moderate versus severe) was added as a covariate in the models assessing the efficacy parameters.

7. Study Objectives

7.1. Primary Objectives

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.

7.2. Secondary Objectives

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.

8. Study Design

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 patients with moderate or severe AD. 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 inclusion/exclusion 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, ECG assessments, and clinical laboratory evaluations will be performed as detailed in the Schedule of Events in Table 1.

All AD lesions in protocol allowed areas should be treated. The study will be conducted at approximately 15 sites in the United States (US).

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

It is planned to enroll approximately 42 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.

8.1. 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.

8.2. 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 serious adverse event (SAE)
- A deep venous thrombosis (DVT) and/or pulmonary embolism (PE)
- Lymphoma
- Hy's law (Appendix 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 Appendix 2.

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 institutional review board (IRB) and the sponsor's medical monitor.

The study overview is specified in Figure 1.

The schedule of study events is specified in Table 1.

Figure 1 Study Schematic

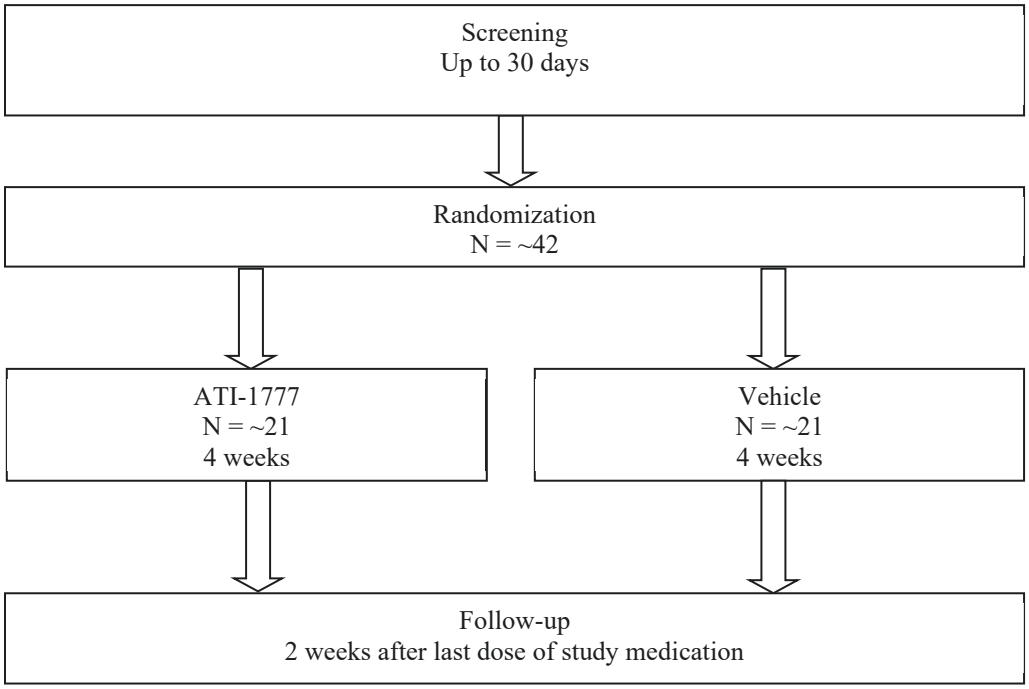

Table 1 Schedule of Events

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	
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 **Error! Reference source not found.**.
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 **Error! Reference source not found.**.
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.

8.3. Sample Size Considerations

A total of approximately 42 patients will be enrolled and randomized in order to achieve 34 patients who complete the study. 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 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).

8.4. Randomization

At Visit 2, in the morning of Day 1, eligible patients will be randomly assigned in a 1:1 ratio via an interactive voice/web response system (IXRS) to ATI-1777 or vehicle treatment.

Enrolled patients will be allocated a unique patient number in a sequential order by trial site. Following randomization, Aclaris will provide all study medication in a packed and labelled kit, and the IXRS will identify the kit number to be dispensed to the patient at each relevant visit according to the treatment assigned in the randomization schedule.

9. Study Endpoints, Variables and Covariates

9.1. Endpoints

The table below lists the endpoints vs objectives for the study.

Objectives	**Endpoints**
Primary	Primary endpoint
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.	Percent change from baseline in EASI score at Week 4.
Secondary	Secondary efficacy endpoints
	• 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 at each study visit
Pharmacokinetic	Pharmacokinetic endpoints
The secondary objective of this study is to assess the safety, tolerability, and pharmacokinetics (PK) of ATI-1777 topical solution twice daily for 4	The PK endpoint is ATI-1777 concentration in plasma samples obtained using a sparse sampling approach.

weeks in adult patients with moderate or severe AD.	
Safety	Safety endpoints
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.	• Incidence of treatment-emergent adverse event (TEAE)s and SAEs, including incidence of adverse event of special interest (AESI) (e.g., application site reactions) • Laboratory values • Vital signs • Physical examination results • 12-lead ECG results

9.2. Population Sets

The following analysis sets are defined in accordance with the International Council for Harmonization (ICH)-E9 guidance.

9.2.1. 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.

9.2.2. Per-Protocol (PP) Set

The Per-Protocol (PP) set is defined as a subset of the FAS who have non-missing Week 4 EASI scores recorded with no major protocol deviations deemed to compromise the assessment of efficacy. Major protocol deviations will be identified as a subset of the Important protocol deviations and fully defined prior to unblinding of the trial. The PP analysis will only be conducted on efficacy endpoints and patients analyzed according to their actual treatment.

9.2.3. Pharmacokinetic (PK) Analysis Set

All patients who have received at least 1 dose of active study medication and provided at least 1 plasma concentration value will be included in the PK Analysis Set.

9.3. Predetermined Covariates and Prognostic Factors

The following factors will be adjusted as covariates:

- Baseline severity of AD (moderate vs severe)
- Continuous baseline severity EASI score/BSA score/IGA score
- Baseline BSA (3 to 10 vs greater than 10 to 20) to be used for PK spaghetti plots

10. Conventions and Derivations

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

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.

10.1.1. Study day and Visit Window

For each patient there will be a baseline period, a four-week treatment period and a two-week post treatment follow up period.

Study day is defined relative to the date of the first dose of study drug. For assessments that occur after this visit date, study day is calculated as (assessment date – first dose date + 1). For assessments that occur prior to first dose date, study day will be calculated as (assessment date – first dose date). There is no study Day 0. When there are multiple observations within a visit window, the value closest to the target day will be analyzed.

The visit window (Table 2) and PK draw window (Table 3) appear in the table below.

Table 2 will be used to define the analysis window for safety assessments (vital signs, ECGs, lab assessment) and for efficacy assessment of EASI, IGA, BAS, PP-NRS). Plasma concentrations will be summarized according to nominal time (no analysis visit windows) and may be plotted according to actual time relative to the time of first dose, as appropriate.

Table 2 Visit Window and Target day

Visit	Target Study Day	Analysis Visit	Visit Window
Visit 1		Screening	< Time of First Dose
Visit 2	1	Day 1	Time of First Dose < Study Day ≤ Day 3
Visit 3	8	Day 8	Day 4< Study Day ≤ Day 11
Visit 4	15	Day 15	Day 12 < Study Day ≤ Day 21
Visit 5	28/ET	Day 28/ET	Day 22 < Study Day ≤ Day 34
Visit 6	42	Day 42	Day 35 < Study Day ≤ Day 45

Table 3 PK Draw Timing

Visit	Target Day	Nominal Time
Visit 2	Day 1	• At Predose and 2 hours postdose
Visit 3	Day 8	• At Predose and 2 hours postdose
Visit 4	Day 15	• At Predose and 2 hours postdose
Visit 5	Day 28/ET	• 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)

10.1.2. Baseline

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

10.1.3. Change from baseline

Change from baseline (CFB) will be calculated as (post-baseline – baseline). CFB will be calculated for patients with both a baseline and post-baseline value as applicable.

Percent CFB will be calculated as (CFB/baseline)*100, where applicable.

If a baseline value has not been recorded for a parameter, then CFB will not be calculated for that parameter.

11. Interim Analyses

No interim analysis will be conducted.

12. Statistical Methods

All analyses will use SAS version 9.4 or higher.

Categorical variables will be summarized using counts and percentages based on the specified population total. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous data will be summarized using non-missing observations (n, mean, standard deviation (SD), median, Quartile 1, Quartile 3, minimum, and maximum). The median, minimum, and maximum values will be displayed to the same level of the precision as the raw value. Mean, median, Q1 and Q3 will be rounded to 1 decimal place greater than the precision of the original value. The SD will be rounded to 2 decimal places greater than the precision of the original value. Confidence intervals, least square mean (LSM) and standard error (SE) will be provided as appropriate. Confidence intervals, LSM will present the same precision as the mean value whereas SEs will present the same precision as SD.

P-values will be rounded to 3 decimal places. P-values less than 0.001 will be presented as "<0.001" and p-values greater than 0.999 will be presented as ">0.999."

Statistical hypothesis testing will be one-sided and carried out at the 5% level of significance. Testing will be performed on the primary endpoint and secondary endpoints as appropriate. No adjustments for multiplicity will be made.

If there is strong collinearity between the baseline EASI score/BSA score/IGA score and the baseline severity of AD (moderate versus severe), the continuous baseline score will be included the efficacy analysis.

All the listings will be displayed by treatment arm, patient identifier and date of assessment. Age, gender, and race will be presented on each listing.

12.1. Patient Disposition

12.1.1. Disposition

The number of patients screened, randomized, randomized and treated, randomized and not treated, and the number of patients in the analysis sets will be summarized for all screened patients.

The number and percentage of patients will also be summarized for the following patient disposition categories:

1. Completed study drug treatment PP
2. Discontinued study drug early and the reason for discontinuation
3. Completed the study including PTFU
4. Discontinued from the study early and the reason for discontinuation

The table will be presented by treatment arm using the FAS.

All patient's disposition data will be listed.

12.1.2. Important Protocol Deviations

As a guideline, important protocol deviations (IPDs) are:

- Non-compliance with study drug
- Pregnancy
- Other deviations that violate inclusion or exclusion criteria
- Outside Study Windows

Important protocol deviations will be listed.

12.2. Demographic and Baseline Characteristics

12.2.1. Demographics

Baseline data will be summarized for continuous and categorical variables as applicable.

The following demographic and baseline characteristics will be summarized for the FAS by treatment arm and overall:

- Sex (female, male)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Age (years), as continuous variable and Age groups (≥ 18 years to <30 years, ≥ 31 years to <40 years, ≥ 41 years to <50 years, ≥ 51 years to <65 years,).
- Height at baseline (cm)
- Weight at baseline (kg)
- Body mass index at baseline (kg/m^2) defined as Weight (kg)/$[Height (m)]^2$
- Child-bearing potential
- Fitzpatrick skin type
- Baseline AD severity (moderate vs severe)

Demographic and baseline characteristics will also be listed. No statistical testing will be performed on the aforementioned demographic data.

12.2.2. Medical History

Medical history will be summarized by treatment arm and overall for all patients in the FAS. Medical history data will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 220 and summarized by system organ class (SOC) and preferred term (PT). No inferential testing will be performed in this section. Medical history data will be presented in a data listing.

12.3. Treatments

12.3.1. Prior, Concomitant and Prohibited Medications

Medications that stop prior to the first dose of study drug will be classified as prior medication. Medications that start on or after the first dose of study drug until the Day 42/PTFU visit will be classified as concomitant. If a medication starts before the first dose of study drug and stops on or after the first dose of study drug, then the medication will be classified as both prior and concomitant.

Medications will be categorized by medication group and subgroup according to World Health Organization Drug Dictionary Enhanced (WHODRUG 2017JUL DDE B2).

For any medications/nondrug therapies taken from 3 months before the screening visit until the end of the PTFU, inclusively, the medication name, the start and stop date, dose, unit, frequency, route of administration, and indication will be recorded.

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)
- Janus kinase (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

In order to flag prohibited medications taken in the study, each medication taken will be compared against the list of the prohibited medications the clinical medical officer provided after reviewing the concomitant medication database. Prior, Concomitant and Prohibited medications will be summarized based on the number and percentage of patients using each medication along with the number and percentage of patients using at least one medication within each medication group and subgroup.

Missing or partial medication start/stop date will be imputed as described in Appendix 4. A conservative approach will be used when flagging medications. The medication will be classified as concomitant when a decision is unable to be made even with imputed start/stop medication date.

Prior, Concomitant and Prohibited medications will be summarized for the FAS by treatment arm and overall. Medication data will also be presented in a data listing.

12.3.2. Extent of Study Drug Exposure

The duration of exposure to study drug, number of days dosed is taken and compliance with study drug dosing will be summarized by treatment arm using the FAS. Study drug accountability including the weight of the dispensed and returned bottles will be listed. Study drug not returned will be assumed to have been taken.

Study drug compliance (percentage) will be derived using values from the Patient Diary as shown below:

[# of days patient reported taking study drug / # of days patient was in the study] * 100%

The descriptive statistics of the continuous study drug compliance will be summarized by treatment group and overall. Days with missing patient diary data will not be included in the calculation above. Percentage of patients meeting Study Drug Compliance will be presented in the following categories: < 80%, ≥ 80% to < 90%, ≥ 90% to <100%, ≥ 100% to <110%, ≥ 110% to <120%, and ≥ 120%.

Major non-compliance is defined as compliance < 80% or compliance > 120%.

12.4. Efficacy Analyses

All efficacy analyses will be performed on both the FAS and PP analysis set. Efficacy data will also be presented in data listing.

12.4.1. Multiplicity

No adjustments or analysis to detect multiplicity will be performed.

12.4.2. Imputation Methods

For the continuous efficacy analysis 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.

12.4.3. Primary Estimand

Given the primary objective described in Section 7, we seek an estimand that will measure the effect of ATI-1777 administration on the signs and symptoms of AD as measured by the percent change from baseline in EASI scores in

adult patients with moderate to severe AD as compared to placebo in the absence of other interventions or interruptions. This estimand will not be directly measurable if, in the judgment of the investigator, interventions are required for the sake of the patient safety and/or comfort. This estimand will also not be directly measurable if missing data result from a patient withdrawing consent or losing interest in study participation (loss to follow-up). This section outlines the measures and methods that will be used adjust the primary endpoint to account for these types of intercurrent events to obtain as close an estimand to the desired objective as possible.

12.4.3.1. The Population

The patients of primary interest in this study are adult patients with moderate or severe AD. This population of patients is largely reflected by the inclusion/exclusion criteria in the protocol. Generally, the targeted population for this estimand is agnostic to the degree of compliance to treatment administration and adherence to protocol specified procedures; in the spirit of the Intention-To-Treat principle. However, the targeted population is required to have been treated with at least one dose of study medication (see FAS analysis population description in Section 9.2.1).
There is no stratum of patients based on the potential for an intercurrent event that is needed to define the targeted population for this study. It is anticipated that the group of severe AD patients in this study will be more difficult to treat. The randomization strategy for this study incorporates stratification by AD severity to help balance in the treatment groups within the AD severity. This stratification group will also be accounted for in the population-level summary methods used to compute the estimand.

12.4.3.2. Primary Endpoint

The primary endpoint is the percent change from baseline in EASI score at Week 4 on FAS. Missing data will be imputed using LOCF.

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 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.

Each respective body region will be given a score between 0 and 6 based on the percentage involvement in that region according to Table 4. Precise measurements are not required.

Table 4 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

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.

The final EASI score will then be calculated by an electronic data capture system as described in Table 5.

Table 5 EASI Score Calculation

Body Region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area Score	Multiplier	Score
Trunk	(X +	X +	Z +	AA)?	×	× 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

12.4.3.3. Imputation for Intercurrent Events

An intercurrent event is one that occurs after the first dose of study medication and either precludes the observation of the primary variable/endpoint or affects its interpretation. The following is a list of intercurrent events that could occur during this study:

- Death
- Withdrawal from study
- Withdrawal of study medication due to an AE
- Rescue with a non-protocol specified treatment for AD

Missing data and data following these intercurrent events will be imputed using the LOCF methodology.

12.4.3.4. Primary Analysis

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. Change from baseline is calculated as described in section 10.1.3. This treatment comparison will be made within the context of a Mixed Model Repeated Measures (MMRM) analysis where the EASI scores over time are treated as repeated measures within a given patient. Treatment group, time (study visit), treatment by time interaction, and baseline severity of AD will enter the model as categorical factors, baseline EASI score 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 p-values. If the MMRM model will not converge or if there is strong collinearity between the baseline EASI score and the baseline severity of AD, one or both of the covariates may be excluded from the primary analysis.

For the primary efficacy analysis on the FAS population, missing data will be imputed using LOCF. Missing data will not be imputed for the analyses that are based on the PP population.

The null hypothesis is that the LSM contrast between ATI-1777 and vehicle at Week 4 equals zero. Significance tests will be based on least-squares means using a one-sided test at $\alpha = 0.05$ (one-sided p-value compared to 0.05). A symmetric two-sided 90% confidence interval will accompany the corresponding p-value. The MMRM will be fit with covariance matrices of UN (unstructured), CS (compound symmetry), TOEPH (Heterogeneous Toeplitz) and ARH(1) (Heterogeneous auto-regressive 1). The analysis with the lowest Akaike's information criterion (AIC) will be reported in the table. Other covariance matrix structures may be used if none of these converge. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

The estimates at the timepoint Week 4 will be considered as primary. Least squares mean, Standard Errors, for each treatment group, least squares mean difference (ATI-1777 minus vehicle), and 90% confidence intervals for the

difference between the treatment groups and the corresponding one-sided p-value will be reported. The following SAS code will be used.

```
proc mixed data= datain method=ml;
        class treatment visit baseline  ADseverity;
        model pchg_EASI = baseline_EASI baseline_ADseverity visit treatment treatment*visit
                          / cl solution ddfm=kr alpha=0.10;
        repeated /type=un subject=usubjid;
        slice treatment * visit /sliceby=visit means diff nof cl;
        ods output slices = lsm sliceDiffs = diffs;
run;
```

Summary statistics (n, mean, SD, minimum, Q1, median, Q3, and maximum) of the baseline value, the value at Week 4 and the corresponding change from baseline for EASI score will be presented by treatment group and overall using the FAS..

12.4.3.5. Sensitivity Analyses

The population-level summary for the primary estimand based on the FAS population will be repeated using the Per-Protocol population to assess the sensitivity of the analysis to compliance to treatment administration and adherence to protocol specified procedures. Other secondary efficacy analyses and summaries are intended to support the primary estimand and do not qualify as sensitivity analyses.

12.4.4. Secondary Analyses

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 the analysis window scheme described in Section 10.1.1. Change from baseline is calculated as described in section 10.1.3.

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 and baseline severity of AD as a factor, and the baseline value as a covariate. Model-based point estimates for the treatment proportions will be provided as well as model-based differences and corresponding symmetric 90% confidence intervals and one-sided p-values. If the Logistic model will not converge or if there is strong collinearity between the baseline EASI score and the baseline severity of AD, one or both of the covariates may be excluded from the secondary analysis.

The secondary efficacy 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

12.4.4.1. EASI, EASI-50, EASI-75 and EASI-90

The analysis of percent change from baseline in EASI score at each visit for FAS will be in the same model as the primary efficacy analysis. The estimates at the timepoint other than Week 4 will be considered as secondary endpoints.

EASI-50, EASI-75 and EASI-90 are the proportions of patients achieve 50%, 75%, 90% improvement in EASI score respectively within 4 weeks of the start of the treatment. The follow is an example of EASI-50 definition.

EASI-50 = “YES” If (EASI score at Day 28 – baseline EASI)/baseline EASI ≥ 50%

The follow SAS code is an example for the analysis of EASI-50 at Day 28.

```
proc logistic data= datain;
        class treatment baseline_ADseverity;
        model EASI_50 = baseline_EASI treatment baseline_ADseverity / expb;
        oddsratio treatment;
        lsmeans treatment / e diff oddsratio cl adjust = bon;
run;
```

12.4.4.2. Investigator's Global Assessment (IGA)

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 6 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. 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 6 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

The change from baseline in IGA score at each study visit is analyzed using similar MMRM model as the primary efficacy endpoint except the baseline IGA score will be included as a covariate.

The patient achieves an IGA score of 0 or 1 combined with an improvement of 2 or more points from baseline within 4 weeks of the start of treatment is analyzed as categorical variable using logistic regression.

12.4.4.3. Body Surface Area (BSA)

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.

BSA results and corresponding change from study baseline values will be summarized at each time point using descriptive statistics by treatment group. The change from baseline in AD BSA at each study visit is analyzed using similar MMRM model as the primary efficacy endpoint.

12.4.4.4. Peak Pruritus Numerical Rating Scale (PP-NRS)

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.

The PP-NRS score on Day 1 prior to study medication application is the baseline. The PP-NRS scores just prior to study medication application on Day 8, Day 15 and Day 28 will be flagged and used in the efficacy analysis. PP-NRS results and corresponding change from study baseline values will be summarized at each time point using descriptive statistics by treatment group. The change from baseline in PP-NRS is analyzed using similar MMRM model as the primary efficacy endpoint.

All PP-NRS score data will be presented in a data listing, the values included in the efficacy analysis will be flagged.

12.5. PK Analyses

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

Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Individual and mean plasma concentrations at each nominal sampling time point or time window for ATI-1777 will be listed and summarized in a tabular form including means, geometric means, ranges, SD, and coefficients of variation. Mean concentrations will be plotted versus nominal time on linear and semilogarithmic scales.

Plasma concentration-time profiles of ATI-1777 will be plotted on semi-log and linear scales for each individual patient as spaghetti plots using actual collection times by visit day. For ease of presentation, mean plasma concentration-time data of ATI-1777 will be plotted by nominal time on both linear and semi-logarithmic scales by visit day. Plasma PK concentrations of ATI-1777 for each patient will be reported to the precision of the raw data in listing presentations. In addition, concentration-time profiles will be plotted by patient.

If concentration data show that sufficient samples are available with quantifiable levels of ATI-1777, scatterplots of plasma concentration values versus EASI scores or baseline BMI values will be generated by visit and PK time. For Day 28, separate scatterplots will be produced by subgroup and PK time.

12.6. Safety Analyses

All safety analyses will be completed for the FAS. All safety data will be listed and summarized. No formal statistics will be performed for the safety analysis.

12.6.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

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.

An SAE is defined as any AE that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The severity of AEs will be classified by the investigator as mild, moderate, or severe.

The causality of AEs will be classified by the investigator as related and not related.

An overall AE summary will be generated presenting the frequency and percentage of patients and the number of AEs using FAS for the following:

- Any TEAE
- Any treatment-related TEAE
- Any severe TEAE
- Any treatment-related severe TEAE
- Any SAE
- Any treatment-related SAE
- Any TEAE leading to study discontinuation
- Any death
- Any Suspected Unexpected Serious Adverse Reaction
- Any Adverse Events of Special Interest

All AEs will be coded using MedDRA (version to be delineated in the clinical study report [CSR]). The TEAEs will also be summarized by SOC, PT, by severity and relationship to study treatment. Missing or partial medication start/stop date will be imputed as described in Appendix 3.

The TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A patient with 2 or more events within the same level of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of patients in the FAS.

A TEAE summary table by prevalence will also be provided. The preferred terms will be sorted by decreasing frequency in the active arm.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment related AEs, SAEs, and AEs leading to study discontinuation.

12.6.1.1. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) 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 Investigator Brochure (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.

The SUSAR will be summarized by SOC and PT. The SUSAR will also be presented in a data listing.

12.6.1.2. Adverse Events of Special Interest

The adverse events of special interest (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)

The AESI will be summarized by SOC and PT. The AESI will also be presented in a data listing.

12.6.2. Laboratory Data

Laboratory parameters will be summarized for FAS. Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to Système International units for reporting and processing purposes. Summaries by visit will include data from scheduled assessments, and all data will be reported according to the visit window for which it was recorded. Absolute values and changes from baseline will be presented descriptively.

Hematology, serum chemistry, and urinalysis will be summarized using descriptive statistics for numeric variables and numbers and percentages for categorical variables at each scheduled assessment. Numeric hematology, chemistry, and urinalysis results will be summarized using change from baseline as well. Where it is applicable to categorize a laboratory assessment by normal, high, or low according to the normal range provided by the central laboratory, the status at the final value at the end of the treatment period will be compared with that at the study baseline and the "shifts" from study baseline will be summarized using the number and percentage of patients in each shift category by treatment group.

All clinical laboratory test results will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

12.6.3. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature, and will be measured at Screening, Day 1, Day 8, Day 15 and Day28/ET. Patients will be resting for at least 5 minutes before taking vital signs.

Body weight will be measured and recorded at each study visit. Height will be measure at Screening visit.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the visit window . Vital sign results and corresponding change from study baseline values will be summarized at each scheduled visit using descriptive statistics by treatment group.

All vital sign, body weight, and height measurements will be presented in a data listing. The actual values and change from baseline values at each time point will be summarized for the FAS.

12.6.4. Physical Examinations

Full physical examinations will be performed at Screening and abbreviated physical examinations will be performed at Day 1 and Day 28 visits.

All physical examination results will be presented in a data listing.

12.6.5. Electrocardiograms

Triplicate 12-lead electrocardiograms (ECGs) will be obtained after the patient has been resting for at least 5 minutes at Screening and Day 28/ET.

Heart rate, PR interval, QRS axis, QRS duration, QT interval, RR interval, as well as the interpretation of the ECG will be collected in eCRF. All ECG results along with the interpretation by the central reader, including the average of triplicate measurements at each timepoint, will be presented in data listings.

QTcF values will be presented with the implementation of corrections (i.e., Fridericia's) as defined in ICH Guidelines E14 by the following categories:

Absolute QTcF interval prolongation:

- QTcF interval > 450 ms

- QTcF interval > 480 ms
- QTcF interval > 500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms.

The actual values and change from baseline values at each time point will be summarized for the FAS. An average of the triplicates at each timepoint will be used in the summaries. Baseline will be defined as the average of the last triplicate measurements before the first dose of study drug.

13. References

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Yosipovitch G, Reaney M, Mastey V, et al. Peak pruritus numerical rating scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019; 181(4):761-769.

14. Glossary of Abbreviations

Glossary 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
BSA	body surface area
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
GGT	gamma glutamyltransferase
HDL-C	high-density lipoprotein cholesterol
IB	Investigator 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
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
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	total cholesterol
TG	triglycerides
TEAE	treatment-emergent adverse event
WBC	white blood cell
WOCBP	women of childbearing potential

Appendix 1 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.

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.

Appendix 2 Study Medication Interruption Criteria

Laboratory Test	Hold Study Medication if:	Resume Study Medication if:
WBC count	$< 2\times10^9$/L	$\geq 2.5\times10^9$/L
ANC	$< 1\times10^9$/L	$\geq 1.5\times10^9$/L
Lymphocyte count	$< 0.5\times10^9$/L	$\geq 0.75\times10^9$/L
Platelet count	$< 75\times10^9$/L	$\geq 100\times10^9$/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

Appendix 3 Adverse Event Start/Stop Date Study Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Study Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 4 Prior and Concomitant Medication Start/Stop Date Study imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Study imputation
Start date for con meds	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date for con meds	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.