CLINICAL STUDY PROTOCOL

Title:	A Phase 2a, Open-Label, Single-Arm Study to Investigate the Safety and Efficacy of ATI-450 for the Maintenance of Remission in Patients with Cryopyrin-Associated Periodic Syndrome (CAPS) Previously Managed with Anti-IL-1 Therapy.
Protocol number:	ATI-450-CAPS-201
Study phase:	Phase 2a
Test product:	ATI-450
Sponsor:	Aclaris Therapeutics, Inc 640 Lee Road, Suite 200 Wayne, PA 19087, US
Protocol version and date:	2.0; 24 Sep 2020

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(s) 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:

[redacted]

Print Name

Title

[redacted]

Signature

Date

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by Aclaris Therapeutics, Inc. (Aclaris), and given approval/favorable opinion by the Institutional Review Board (IRB) /Independent Ethics Committee (IEC), 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, 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. 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, patient to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonization guidelines on Good Clinical Practice (ICH 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, and inspection by the appropriate regulatory authorities.

I agree to make my patients' study records available to Aclaris, 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 indicates that they are no longer needed. I am aware of my responsibilities as an investigator as provided by Aclaris I understand that Aclaris, 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 to Aclaris.

Print Name Title

Institution

Signature Date

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In the event of an 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 following changes have been introduced in Version 2.0 of the protocol

Sections Affected	Changes
Synopsis and Section 4.1 – Inclusion Criteria	Revised: 2. Patients with a PGA score of "minimal" or less ~~and a hsCRP and SAA value within the normal range (≤10 mg/L),~~ and who are considered to have achieved that response as a result of successful anti-IL-1 therapy.
Synopsis and Section 4.2 – Exclusion Criteria	Revised: 4. History of being immunocompromised, including a positive HIV test result at screening. ~~(ELISA and Western blot) test result.~~
Synopsis, Section 5.2.1.1 – Maintenance of Disease Remission and Clinical Remission, Section 8.4.1 – Efficacy Analyses	Revised and Added: Revised definition of disease remission and added clinical remission.
Synopsis, Table 1 – Schedule of Assessments, and Section 5.4 – Pharmacokinetics and Pharmacokinetics	Added: Pharmacokinetics added as an exploratory endpoint.
Table 1 – Schedule of Assessments and Section 3.1 – Overall Study Design and Plan	Revised: Clarified that the patient diary will be completed beginning 7 days prior to the administration of ATI-450 (Day 1), or immediately beginning at the screening visit if Day 1 is scheduled to occur less than 7 days after baseline. Reduced requirement for patient to complete the patient diary from completion of the study to the completion of the follow up Day 7 visit
Table 1 – Schedule of Assessments	Added: KSS to be calculated during the screening period.
Table 1 – Schedule of Assessments	Revised: Visit 6 and 7 physical examinations have been changed from full physical exams to brief physical exams.

Table 1 – Schedule of Assessments	Added: Administration of morning dose of ATI-450 in clinic.
Appendix 1 – Possible Hy's Law Liver Chemistry Action and Follow-up Assessments	Revised: Serum acetaminophen to be tested using enzyme immunoassay instead of high liquid chromatography assay.
Appendix 2 – Daily Health Assessment Form	Revised: Daily Health Assessment Form revised because the symptom severity scoring incorrectly ranged from 0 to 9.5 instead of 0 to 10.

PROTOCOL SYNOPSIS

Protocol Number: ATI-450-CAPS-201

Protocol Title: A Phase 2a, Open-Label, Single-Arm Study to Investigate the Safety and Efficacy of ATI-450 for the Maintenance of Remission in Patients with Cryopyrin-Associated Periodic Syndrome (CAPS) Previously Managed with Anti-IL-1 Therapy.

Sponsor: Aclaris Therapeutics, Inc.

Study Phase: Phase 2a

Study Sites: [redacted]

Rationale:
CAPS is a rare hereditary autoinflammatory disease caused by a gain-of-function mutation of the NLRP3 gene coding for cryopyrin, which is a component of the NLRP3 inflammasome. Dysregulation of the NLRP3 inflammasome results in an overproduction of interleukin-1 (IL-1), and consequently the inflammatory symptoms seen in CAPS [1]. Current anti-IL-1 therapies have been shown to induce rapid and sustained disease remission in CAPS patients and are generally well tolerated [2, 3, 4].

ATI-450 has been shown to cause a marked inhibition of IL-1 in both pre-clinical and clinical studies. Current anti-IL-1 therapies for treatment of CAPS are biologics that are administered either intravenously or subcutaneously. ATI-450, an orally administered small molecule, has the potential to have a similar safety and efficacy profile compared to currently available therapies with a differentiated route of administration that may be preferred by some CAPS patients.

This study is being conducted to determine the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of ATI-450 in patients with CAPS. The results of this study may support further investigation of ATI-450 in patients with CAPS.

Objectives and Endpoints:

Objectives		Endpoints
Primary	• To assess the safety and tolerability of ATI-450 to maintain remission in patients with CAPS previously managed with anti-IL-1 therapy	• Number and percent of adverse events (AEs) and serious adverse events (SAEs); mean change from baseline in laboratory values, vital signs, and electrocardiograms (ECGs)

Secondary	• To assess the efficacy of ATI-450 to maintain remission in patients previously managed with anti-IL-1 therapy	• Proportion of participants in disease remission over time. Disease remission is defined as having a Physician Global Assessment (PGA) score of absent or minimal and a high sensitivity C-reactive protein (hsCRP) and serum amyloid A (SAA) value within the normal range (≤10 mg/L) or within 30 percent of the baseline value. • Proportion of participants in clinical remission over time. Clinical remission is defined as having a PGA score of absent or minimal. • Time to relapse; where relapse is defined as a two-point worsening on the PGA scale. • Proportion of participants who experience re-emergence of disease symptoms after discontinuation of ATI-450. Re-emergence is defined as a daily Key Symptom Score (KSS) ≥ 3 points higher than baseline for at least 2 consecutive days. KSS is derived from the patient-administered daily health assessment form (DHAF). • Proportion of participants with a mean KSS no more than 2 points higher than baseline for at least 6 out of 8 weeks during the treatment period. • Change from baseline in PGA. • Change from baseline in KSS. • Change from baseline in hsCRP and SAA.
Exploratory	• To assess the Pharmacodynamics (PD) of ATI-450 in patients with CAPS • To assess the Pharmacokinetics (PK) of ATI-450 in patients with CAPS	• Change from baseline in serum cytokines IL-1β, IL-1α, IL-6, IL-18, and TNF-α • ATI-450 concentrations at trough

Study Design:

This is a Phase 2a, open-label, single-arm, study to investigate the safety, tolerability, efficacy, and PD of ATI-450 to maintain remission in patients ≥ 18 years old with CAPS previously managed with anti-IL-1 therapy.

Patients with a PGA score of "minimal" or less and a hsCRP and SAA value within the normal range, and are considered to have achieved remission (i.e., those values for PGA, hsCRP, and SAA) as a result of successful anti-IL-1 therapy, will be eligible for study entry.

Patients will be entered into the study at the time of their next scheduled dose of anti-IL-1 therapy. Rather than receiving anti-IL-1 therapy, ATI-450 will be dosed at 50 mg twice daily (BID) orally for 12 weeks. Patients will be assessed for safety and disease activity at 2 weeks, 4 weeks, 8 weeks, and 12 weeks.

At the end of 12-weeks, Day 84 (+/- 1 day), patients will stop ATI-450 and conduct end of study assessments.

Patients will complete safety follow-up visits on site 7 Days (+4 days) after the last dose of ATI-450 and via a phone call 30 Days (+/-3 days) after the last dose.

Patients should not start their anti-IL-1 therapy until all safety follow-up Day 7 assessments have been completed. However, in the event of a safety concern, patients will be allowed to return early or restart their anti-IL-1 therapy prior to completing the safety follow-up Day 7 visit at the discretion of the investigator.

The study will consist of up to an 8-week screening period, a 12-week treatment period, and a 4-week safety follow-up period. The total duration of the study for patients remaining until their final follow-up assessment will be up to 24 weeks.

Up to 10 patients whose eligibility is confirmed at baseline will be enrolled in the study.

Study Duration:

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. It is anticipated that total duration could be up to 24 weeks.

Planned Number of Patients: It is planned to enroll up to 10 patients.

Target Population:

Inclusion Criteria

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

1. Diagnosis of Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, or Neonatal Onset Multisystem Inflammatory Disease. Prior agreement between the Investigator and Aclaris for study eligibility is required for patients who do not have a molecular diagnosis of NALP3 mutations available (either testing not performed, or testing performed, but negative) upon study entry. For those patients who have not been molecularly tested for NALP3 mutations, molecular testing should be performed during the study.
2. Patients with a PGA score of "minimal" or less and who are considered to have achieved that response as a result of successful anti-IL-1 therapy.
3. Continuous Treatment with anti-IL-1 therapy for at least 6 months.
4. Able to understand and comply with study procedures and able to provide informed consent.
5. Male or non-pregnant, non-nursing female patients at least 18 years of age, inclusive.
    - Female patients who are of childbearing potential must use 2 methods of highly effective contraception* - one of which must be a physical barrier- for the duration of the study and for 30 days after the last dose.

- Male patients of childbearing potential with a female partner of childbearing potential must agree to use a condom plus another highly effective form of birth control for the duration of the study and for 90 days after the last dose.

6. Female patients must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to dosing on Day 1.
7. Willing and capable of taking appropriate Covid-19 risk mitigation precautions (e.g. wearing a mask in public, adhering to social distancing, etc.) as required by local, state, or federal guidelines during participation in the study.

*Highly effective birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices, heterosexual abstinence, or vasectomized.

Exclusion Criteria

A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Participation in any clinical study with an investigative agent within 12 weeks prior to entry or within 5 half-lives of the investigational agent.
2. Being treated with another immuno-suppressive agent (i.e., in addition to an anti-IL-1 product) for CAPS syndrome (anti- IL-1 therapy will have been used for at least 6 months and will be stopped at study entry).
3. Use of any of the following treatments within the indicated washout period prior to the baseline visit:
    a. Systemic immunosuppressant or immunomodulatory therapy (e.g., etanercept, alefacept, infliximab, methotrexate) within 16 weeks prior to Visit 2 (excluding anti-IL-1 therapy for CAPS).
    b. Janus Kinase (JAK) inhibitors (systemic or topical) within 4 weeks prior to Visit 2.
    c. Systemic corticosteroids within 4 weeks prior to Visit 2 (Intranasal, inhaled, and topical ocular corticosteroids are allowed).
4. History of being immunocompromised, including a positive HIV test result at screening. [Previous treatment with anti-IL-1 therapy is not an exclusion]
5. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody test result.
6. Live vaccinations within 3 months prior to the start of the trial, or during the trial.
7. History of recurrent and/or evidence of active bacterial, fungal, or viral infections.
8. History or evidence of active or latent tuberculosis (TB).
9. Tests performed at a central laboratory at screening that meet any of the criteria below (out of range labs may be rechecked one time, after consultation with sponsor or designee, before patient is considered a screen failure):
    - White blood cell (WBC) count $<3.0\times10^3$ cells/mm^3
    - Absolute neutrophil count (ANC) $<1.5\times10^3$ cells/mm^3
    - Lymphocyte count $<0.5\times10^3$ cells/mm^3
    - Platelet count $<100\times10^3$ cells/mm^3
    - Hemoglobin <10 g/dL
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq$ 2×upper limit of normal (ULN)
    - Total bilirubin level >2×ULN, unless patient has been diagnosed with Gilberts' disease and this is clearly documented

- Estimated glomerular filtration rate Estimated glomerular filtration rate (eGFR), <40 mL/min/1.73m2 based on Modification of Diet and Renal Disease formula

10. Any clinically significant laboratory abnormality that would affect interpretation of study data or safety of the patient's participation in the study, per the judgment of the investigator.
11. Patient has clinically significant abnormal findings other than CAPS from physical examination that may affect the interpretation of study data or the safety of the patient's participation in the study, per the judgment of the investigator.
12. Patient has a clinically important history of a medical disorder that would compromise patient safety or data quality, per the judgement of the investigator.
13. Blood pressure (BP) levels (in supine position after at least 5 minutes rest): <90 mmHg or >140 mmHg for systolic BP or <40 mmHg or >90 mmHg for diastolic blood pressure.
14. Patients with history of stroke.
15. Significant cardiac disease that would affect interpretation of study data or the safety of the patient's participation in the study, per the judgment of the investigator, including recent myocardial infarction or unstable angina, or heart failure with New York Heart Association Class III or IV symptoms.
16. Patients with the following screening or pre-dose ECG findings, specifically:
    - Evidence of atrial fibrillation, atrial flutter, complete right or left bundle branch block, Wolff-Parkinson-White Syndrome, or other significant rhythm disturbance
    - Evidence of acute ischemia
    - Screening or pre-dose baseline mean QTcF >450 msec for males or >470 msec for females (use of the ECG algorithm is acceptable for this purpose)
    - Personal or family history of congenital long QT syndrome or sudden death
    - Any other finding that is considered clinically significant
17. A confirmed diagnosis of Covid-19 at baseline or at any time during the study.

Test Product:

Name: ATI-450

Dose: 50 mg BID

Mode of administration: Oral tablets

Control Product:

None

Statistical Methods:

Determination of Sample Size

The sample size for this study was determined based upon feasibility constraints as opposed to a formal power computation. Up to 10 patients are planned to be enrolled.

Analysis Populations.

- The Intent-to-treat (ITT) population will include all patients who have been administered at least one dose of study medication.
- The Per-Protocol (PP) population will include all patients who complete 12-weeks of treatment and 4-weeks of safety follow-up and have completed study assessments.

Efficacy Analyses

All efficacy summaries will be conducted on both the ITT and PP populations.

- Proportion of participants in disease remission over time; where disease remission is defined as having a PGA score of minimal or better and a hsCRP and SAA value within the normal range or within 30 percent of the baseline value (ITT and PP population).
- Proportion of participants in clinical remission over time; where clinical remission is defined as having a PGA score of minimal or better (ITT and PP population).
- Proportion of participants who experience an increase over baseline in daily KSS of ≥ 3 for at least two days after discontinuation of ATI-450 over time (PP population).
- Proportion of participants who maintain a mean KSS of no more than 2 points higher than baseline in at least 6 out of 8 weeks in the ITT and PP population.
- Change from baseline in PGA and KSS scores will be reported descriptively over time (ITT and PP population).
- Change from baseline in hsCRP and SAA and percent change from baseline in hsCRP and SAA will be summarized over time using continuous statistical summary measures. Determination of sustained treatment effect for hsCRP and SAA will be based upon the median percent change from baseline in the ITT and PP population.

Safety Analyses

The ITT population will be used for the analysis of safety data (AEs, exposure to study medication, clinical laboratory values, vital signs, and ECG).

AEs will be coded with the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as AEs with an onset date on or after the date of first administration of study medication and before the date of last administration of study medication + 30 days. 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.

Handling of Missing Data
Missing data will not be imputed for the safety summaries or the efficacy summaries conducted on the PP population. For efficacy summaries conducted on the ITT population, a model based multiple imputation procedure will be used to impute missing data, where appropriate.

Protocol version and date: 2.0, 24 Sep 2020

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Assessment	Screening	12-Week Treatment Period					4-Week Safety Follow-up	
	Visit 1 Day -56 to Day -1	Visit 2 Baseline Day 1	Visit 3 Day 14	Visit 4 Day 28	Visit 5 Day 56	Visit 6 Day 84 EOS	Visit 7 Day 7[6]	Visit 8 Phone Call Day 30
		(+/-1 day)					(+4 days)	(+/-3 days)
Informed Consent	X							
Eligibility Review	X	X						
CAPS and Other Medical History and Demographics	X							
QuantiFERON Gold Test for TB	X							
Height	X							
Weight	X							
Physical Exam[1]	X							
Limited Physical Exam		X	X	X	X	X	X	
Physicians Global Assessment of Disease Activity[2]	X	X	X	X	X	X	X	
Patient Diary (daily)[2, 8]	X	X	X	X	X	X	X	
Key Symptom Score[2, 8]	X	X	X	X	X	X	X	
HIV and Hep Screen	X							
SARS-CoV-2 Testing by RT-PCR		X						
Vital Signs[2, 3]	X	X	X	X	X	X	X	
12-Lead ECG[2, 4]	X	X				X		
Hematology, Coagulation, Chemistry, Lipids, and Urinalysis	X	X	X	X	X	X	X	

Assessment	Screening	12-Week Treatment Period					4-Week Safety Follow-up	
	Visit 1 Day -56 to Day -1	Visit 2 Baseline Day 1	Visit 3 Day 14	Visit 4 Day 28	Visit 5 Day 56	Visit 6 Day 84 EOS	Visit 7 Day 7[6]	Visit 8 Phone Call Day 30
		(+/-1 day)					(+4 days)	(+/-3 days)
PD Blood Sampling[2]		X	X	X	X	X	X	
PK Blood Sampling[2]		X	X	X	X	X	X	
Serum Pregnancy	X							
Urine Pregnancy		X	X	X	X	X	X	
Dispense Study Medication		X	X	X	X			
Administration of Morning Dose of ATI-450 in Clinic[7]		X	X	X	X	X		
Drug Accountability			X	X	X	X		
Adverse Events[5]	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X

ECG=electrocardiogram, Hep=hepatitis, PD=pharmacodynamic, TB=tuberculosis, EOS=end of study

[1]A full physical examination will be performed at screening. The brief physical examination (including signs of CAPS) will be performed at visit 6 and follow-up. Body mass index will be derived in the eCRF.

[2]On dosing day(s), patient diary, PGA, KSS, vitals, clinical laboratory parameters, PK, and PD will be performed before the administration of study medication.

[3]Vital signs will be measured prior to dosing and immediately following dosing in a semi supine position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

[4] A triplicate 12-lead ECG will be recorded after the subject has been resting for at least 5 minutes in a supine position.

[5]Serious adverse event reporting will start at the time of consent. Any AE that occurs between the time of consent and dosing on Day 1 will be recorded as medical history. Treatment-emergent AEs will be collected following the first dose of study medication on Day 1.

[6]Patients should not start their anti-IL-1 therapy until all safety follow-up Day 7 assessments have been completed. However, in the event of a safety concern, patients will be allowed to return early or restart their anti-IL-1 therapy early prior to completing the safety follow-up Day 7 visit at the discretion of the investigator.

[7] The last dose of ATI-450 will be administered in clinic on Day 84. The second dose of ATI-450 is not to be administered on Day 84.

[8] Patients will be instructed on how to complete their patient diary at the screening visit. Patients will begin completing the patient diary 7 days prior to beginning ATI-450 administration (Day 1), or immediately beginning at the screening visit if the Day 1 visit is scheduled to occur less than 7 days after screening.

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LIST OF TABLES

LIST OF ABBREVIATIONS

Aclaris	Aclaris Therapeutics, Inc.
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATF2	activating transcription factor 2
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
β-hCG	beta human chorionic gonadotrophin
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
CAPS	Cryopyrin-Associated Periodic Syndrome
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CRF	case report form
hsCRP	high sensitivity C-reactive protein
DHAF	daily health assessment form
ECG	electrocardiogram
FSH	follicle-stimulating hormone
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IC	inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
JAK	janus kinase
KSS	Key Symptom Score
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MK2	MAPK-activated protein kinase 2
NOMID	neonatal-onset multisystem inflammatory disease
PD	pharmacodynamic(s)
PGA	Physician Global Assessment
PK	pharmacokinetic(s)
PP	per-protocol
PRAK	p38α-related/activated protein kinase
QTL	quality tolerance limits
SAA	serum amyloid A
SAE	serious adverse event
SAP	statistical analysis plan
$t_{1/2}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
TMF	trial master file
TNFα	tumor necrosis factor-α
ULN	upper limit of normal
WBC	white blood cell

1 INTRODUCTION AND RATIONALE

1.1 Background

1.1.1 Background

Aclaris is developing ATI-450 Tablet, an orally available, small molecule inhibitor of the p38α mitogen-activated protein kinase (MAPK)/MAPK-activated protein kinase 2 (MK2) inflammatory signaling pathway. This pathway drives the expression of multiple cytokines, chemokines, matrix metalloproteases, and other inflammatory signals. Key inflammatory cytokines driven by this pathway include tumor necrosis factor-α (TNF-α), interleukin-1α and β (IL-1α and β), and interleukin-6 (IL-6).

ATI-450 has a novel mechanism of action. It targets the high affinity docking interaction between p38α MAPK and MK2. Upon binding to the interface created upon formation of this bimolecular complex, ATI-450 blocks MK2 phosphorylation by p38 MAPK and thereby the downstream MK2-mediated inflammatory drive. ATI-450 shows low potency for inhibition of p38α phosphorylation/activation of alternate substrates and is selective across the human kinome.

Aclaris is developing ATI-450 for potential treatment of inflammatory disorders.

1.1.2 Nonclinical Experience

1.1.2.1 Nonclinical Pharmacology

ATI-450 was developed to selectively block p38α activation of the proinflammatory kinase MK2 while sparing inhibition of p38α alone or other substrates such as p38α-related/activated protein kinase (PRAK) and activating transcription factor 2 (ATF2). The activity and selectivity of ATI-450 has been measured in a variety of in vitro assays, including functional assays directly measuring the phosphorylation of MK2. In all assays, ATI-450 showed high potency and, at high concentrations, resulted in full blockade of measured response.

ATI-450 reduced lipopolysaccharide (LPS)-induced production of TNF-α and IL-6 in vivo rat and mouse models. Oral administration of 1 mg/kg of ATI-450 resulted in ≥80% inhibition of LPS-induced TNF-α and IL-6 levels in rats. Oral administration (1000 ppm dietary admixture) of ATI-450 to mice for 3 days prior to the investigational product challenge with LPS (0.5 mg/mouse) resulted in >87% inhibition of circulating TNF-α levels. Inhibition was maintained in mice treated for up to 4 weeks.

To determine whether p38α-MK2 regulates inflammasome priming signals, neonatal-onset multisystem inflammatory disease (NOMID) mice, expressing consecutively activated NLRP3 in myeloid cells driven by lysozyme M-Cre were used. The phenotype of these mice resembles that of mice globally expressing a NLRP3 mutant, although the disease is less severe in mice with myeloid-restricted expression of the transgene. LPS markedly induced IL-1β, IL-6, and TNF-α expression in wild-type and NOMID bone marrow macrophages; these responses correlated with

p38α and MK2 activation and were inhibited by ATI-450. MK2 phosphorylation peaked at 30 minutes before returning to baseline levels 180 minutes after stimulation. ATI-450 inhibited the transient LPS-stimulated MK2 phosphorylation at 15 and 30 minutes but had little effect at 180 minutes when MK2 activation returned to baseline state. ATI-450 was not cytotoxic at an efficacious concentration tested in the study.

NOMID mice were used to evaluate the in vivo role of p38α–MK2 in NOMID pathogenesis. Because constitutive activation of the NLRP3 inflammasome caused premature lethality, *Nlrp3*$^{fl(D301N)/+}$*; CreER* mice were generated for postnatal conditional tamoxifen-induced NLRP3 activation and generation of viable adult NOMID mice. ATI-450 was formulated in chow with the inhibitor level (parts per million) selected based on achieving sustained >60% inhibition of LPS-induced TNF-α expression. WT mice fed with normal chow or ATI-450 chow gained body weight undistinguishably. NOMID mice fed ATI-450 chow lost significantly less body weight than untreated NOMID mice. Furthermore, approximately 35% of untreated NOMID mice developed skin lesions, and 20% of these mice died over the 7-wk period, but neither occurred in ATI-450–treated mice.

Inflammation in NOMID mice was associated with increased p38α phosphorylation, over-production of IL-1β and IL-18 in bone marrow, and splenomegaly. These responses correlated with an increased number of WBC accompanied by neutrophilia, anemia, thrombocytosis, and inflammation in multiple organs including liver, spleen, and brain. All inflammatory responses in NOMID mice were attenuated by ATI-450.

Skeletal complications including low bone mass are hallmarks of NOMID [8]. Osteopenia caused by increased osteoclast differentiation was also observed in NOMID mice [9. 10.]. An increased number of osteoclasts was observed on trabecular bone surfaces and on cortical bone surfaces in NOMID mice—a phenotype that was prevented by ATI-450. Consistent with in vivo results, ATI-450 inhibited in vitro osteoclast formation induced by RANKL, the obligatory osteoclastogenic cytokine that activates p38α among other pathways in osteoclast precursors [11. 12. 13.]. These results indicate that treatment with ATI-450 prevents osteopenia in NOMID mice through inhibition of osteoclastogenesis.

1.1.2.2 Nonclinical Pharmacokinetics and Metabolism

The pharmacokinetics (PK) of ATI-450 was studied in mouse, rat, dog, monkey, and mini-pigs. The single dose intravenous PK in all nonclinical species is characterized by a mono-exponential pattern of elimination with mean half-lives ranging from 0.5 to 3.1 hours. After oral dosing, the mean half-life ($t_{1/2}$) was observed to be up to 6.33 hours in the monkey. Clearance was low in dog and monkey; and high in rat and mouse. Oral bioavailability was high in mouse; moderate in rat, dog, and monkey; and lower in mini-pig.

ATI-450 has the potential to translate the observed pre-clinical efficacy into the clinic based upon its oral drug-like properties. Metabolic stability and PK properties of ATI-450 (e.g., long $t_{1/2}$, low clearance, high oral bioavailability, high volume of distribution) are consistent with oral, 1 to 2 times per day dosing in humans.

1.1.2.3 Toxicology and Safety Pharmacology

In vitro, no appreciable off-target interactions were observed in broad profile screening against receptors, enzymes, and transporters relevant for safety evaluation. No significant inhibition of the human ether-a-go-go-related gene potassium channel current was observed in vitro. In a standard battery of in vivo safety pharmacology studies, no AEs of ATI-450 were found on the respiratory and central nervous systems following single dose oral administration up to 45 mg/kg in rat. In a cardiovascular study in mini-pig, no ATI-450-related changes in ECG waveform (PR interval, QRS interval, and corrected QT interval [QTcB]) were observed; however, ATI-450 administration at a dose level of 45 mg/kg was associated with a decrease in arterial BP approximately 2 through 6 hours post-dose, and an elevated heart rate and body temperature approximately 7 through 18 hours post-dose. Arterial BP returned to baseline by 8 hours post-dose, with heart rate and body temperature returning to baseline by 24 hours post-dose. No effects were noted in animals given 5 or 15 mg/kg.

ATI-450 was not genotoxic in the bacterial reverse mutagenicity assay or in the in vitro chromosomal aberration assay using cultured human peripheral blood lymphocytes, or in an in vivo micronucleus assay in the rat.

Thirteen-week oral toxicity studies were conducted in rats and mini-pigs at dose levels of 3, 10, and 30 mg/kg/day and 10, 30, and 60 mg/kg/day, respectively. There were no ATI-450-related adverse effects noted in either species. ATI-450-related findings in rats given oral doses up to 30 mg/kg/day included a mild to moderate myocyte degeneration, which did not have any effect on the health and well-being of the animals and was not observed after a 4-week non-dosing recovery period. There were no adverse effects on clinical pathology (hematology, clinical chemistry, coagulation, urinalysis). In mini-pigs given oral doses up to 60 mg/kg/day, sporadic and transient clinical signs of warm to touch and hypoactivity were observed once or twice during the 13-week dosing period in 1 or 2 animals given 30 or 60 mg/kg/day. As these were isolated incidences, they were not considered to be adverse. No adverse effects of treatment were observed on clinical pathology (hematology, clinical chemistry, coagulation, urinalysis), nor were there any gross post-mortem or histopathologic findings observed in mini-pigs after 13 weeks of daily oral treatment.

Based on the results of the 13-week oral toxicity studies in rats and mini-pigs, the No-Observed-Adverse-Effect Level was considered to be 30 mg/kg/day in rats and 60 mg/kg/day in mini-pigs.

In conclusion, ATI-450 selectively blocks p38α activation of the proinflammatory kinase MK2 while sparing p38α activation of other effectors such as PRAK and ATF2. Through this mechanism, ATI-450 inhibits inflammatory pathways (such as TNF-α and IL-1β), implying it has potential in a broad range of inflammatory indications. By avoiding direct inhibition of p38, which could lead to inhibition of anti-inflammatory substrates of p38, ATI-450 has the potential to avoid transient efficacy associated with global p38 inhibitors.

1.1.3 Clinical Studies

A single and multiple dose ascending study of ATI-450 in healthy volunteers has been conducted: ATI-450-PKPD-101.

ATI-450-PKPD-101 consisted of multiple parts. A total of 32 male and female subjects were enrolled into Part A of the study where 4 ascending single doses (10 mg, 30 mg, 50 mg, and 100 mg) were explored. Eight subjects were randomized at each dose level to receive a single oral dose of ATI-450 (n=6) or placebo (n=2). The 50 mg cohort was repeated following a high fat, high calorie breakfast to explore the fed-fasting PK of ATI-450.

In Part B, 3 ascending multiple doses (10 mg BID, 30 mg BID, and 50 mg BID) were explored in 30 male and female subjects. Ten subjects were randomized to receive multiple oral doses (6.5 days) of ATI-450 (n=8) or placebo (n=2) at each dose level.

Data demonstrates that ATI-450 was well tolerated at all doses in the study. No SAEs or severe intensity events were reported. The most common AEs (reported by 2 or more subjects who received ATI-450) were dizziness, headache, upper respiratory tract infection, constipation, and abdominal pain. All events were of mild intensity. A trend of a decrease in ANC was observed concurrent with dosing of ATI-450 without correlated clinical sequelae. No subject had an ANC value <500 cells/μL. Other laboratory findings were generally unremarkable.

After single oral doses (10 mg to 100 mg), ATI-450 was rapidly absorbed with median time to maximum plasma concentration (t_{max}) values ranging from 2.0 to 4.0 hours. Systemic exposure to ATI-450 (as measured by mean maximum plasma concentration [C_{max}] and area under the concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$]) increased approximately proportionally with dose between 10 and 100 mg, suggesting that the PKs of ATI-450 are dose-independent (i.e., linear) over the dose range evaluated. Elimination of ATI-450 from plasma was moderately slow, with mean terminal half-life $t_{1/2}$ values ranging from approximately 9 to 11 hours. After oral administration of ATI-450 at 100 mg with a standardized high fat, high-calorie breakfast, the median t_{max} was delayed (6.0 hours versus 2.0 hours), but there did not appear to be any appreciable impact on systemic exposure to ATI 450 (C_{max} was ~14% lower and $AUC_{0-\infty}$ was ~10% higher in the fed state).

The PK behavior of ATI-450 after multiple dose administration was consistent with that observed following single doses. Trough concentrations of ATI-450 were generally similar on Days 2 through 7, suggesting that the subjects were at or near steady-state by Day 2 of BID administration. Systemic exposure to ATI-450 on Day 7 of dosing was approximately dose-proportional between 10 and 50 mg. A small amount of accumulation (up to 1.4-fold) was observed following multiple dosing, which was not unexpected given the $t_{1/2}$ of ATI-450 and the length of the dosing interval.

The PD of ATI-450 were explored by investigating the inhibition of cytokines of interest in blood samples collected from subjects in ATI-450-PKPD-101. For 10 mg BID, mean trough drug levels were below the 80% inhibitory concentration (IC80) for IL-1β and TNFα. At 30 mg BID, mean trough drug levels were above the IC80 for IL-1β, but not for TNFα. At 50 mg BID,

mean trough drug levels were above the IC80 for IL-1β and TNFα. No dose level achieved mean trough levels above the IC80 for IL-6, but the 50 mg BID dose level produced drug levels that were higher than the IC50 for IL-6 for at least part of the dosing interval.

The safety, PK, and PD data support the 50 mg BID dose level as the most appropriate for investigation in this study.

1.2 Study Rationale

The assessment of 12-weeks of ATI-450 treatment in patients with CAPS will provide important data to initially explore the safety and efficacy of ATI-450 in patients with CAPS.

CAPS is a rare hereditary autoinflammatory disease caused by a gain-of-function mutation of the NLRP3 gene coding for cryopyrin, which is a component of the NLRP3 inflammasome. Dysregulation of the NLRP3 inflammasome results in an overproduction of IL-1, and consequently the inflammatory symptoms seen in CAPS[1]. Current anti-IL-1 therapies have been shown to induce rapid and sustained disease remission in CAPS patients and are generally well tolerated [2, 3, 4].

ATI-450 has been shown to cause a marked inhibition of IL-1 in both pre-clinical and clinical studies. Current anti-IL-1 therapies for treatment of CAPS are biologics that are administered either intravenously or subcutaneously. ATI-450, an orally administered small molecule, has the potential to have a similar safety and efficacy profile compared to currently available therapies with a differentiated route of administration that may be preferred by some CAPS patients.

This study is being conducted to determine the safety, tolerability, PD, and preliminary efficacy of ATI-450 in patients with CAPS. The results of this study may support further investigation of ATI-450 in patients with CAPS.

1.3 Benefit/Risk Assessment

Efficacy data for ATI-450 in the intended indication of CAPS are not yet available.

In non-clinical repeat-dose toxicology studies, incidence of skeletal muscle degeneration was noted in 3 muscles (psoas, quadriceps femoris, and soleus) in 1 species only, and was attributed to ATI-450 treatment. However, there was no evidence of persistence of these findings, suggesting that the lesions were fully reversible following discontinuation of dosing. The risk to humans associated with these toxicology findings are anticipated to be very low in this short clinical study. There are also theoretical risks similar to what has been observed for other anti-cytokine therapies, such as serious infections, malignancy, cytopenia(s), and hypersensitivity reactions. Data from the first-in-human study ATI-450-PKPD-101 demonstrate ATI-450 was generally well tolerated with no SAEs, severe adverse events, or AEs that led to discontinuation of study medication. The most common AEs (reported by 2 or more subjects who received ATI-450) observed during the trial were dizziness, headache, upper respiratory tract infection, constipation, nausea, and abdominal pain. All AEs were mild. A trend of a decrease in ANC was

observed without correlated clinical sequelae. This effect is consistent with the PD profile of certain anti-TNF therapies[7]. Other laboratory findings were generally unremarkable.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of ATI-450 can be found in the Investigator's Brochure (IB).

2 STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints for this study are provided in Table 2 below.

Table 2 Study Objectives and Endpoints

Objectives		Endpoints
Primary	• To assess the safety and tolerability of ATI-450 to maintain remission in patients with CAPS previously managed with anti-IL-1 therapy	• Number and percent of adverse events (AEs) and serious adverse events (SAEs); mean change from baseline in laboratory values, vital signs, and electrocardiograms (ECGs).
Secondary	• To assess the efficacy of ATI-450 to maintain remission in patients previously managed with anti-IL-1 therapy	• Proportion of participants in disease remission. Disease remission is defined as having a Physician Global Assessment (PGA) score of absent or minimal and a high sensitivity C-reactive protein (hsCRP) and serum amyloid A (SAA) value within the normal range (≤10 mg/L) or within 30 percent of the baseline value. • Proportion of participants in clinical remission. Clinical remission is defined as having a PGA score of absent or minimal. • Time to relapse; where relapse is defined as a two-point worsening on the PGA scale. • Proportion of participants who experience a re-emergence of disease symptoms after discontinuation of ATI-450. Re-emergence is defined as an increase in daily Key Symptom Score (KSS) ≥3 for at least two consecutive days. KSS is derived from the patient-administered daily health assessment form (DHAF). • Proportion of participants with a mean KSS no more than 2 points higher than baseline for at least 6 out of 8 weeks during the treatment period. • Change from baseline in PGA. • Change from baseline in KSS.

		• Change from baseline in hsCRP and SAA.
Exploratory	• To assess the Pharmacodynamics (PD) of ATI-450 in patients with CAPS • To assess the pharmacokinetics (PK) of ATI-450 in patients with CAPS	• Change from baseline in serum cytokines IL-1β, IL-1α, IL-6, IL-18 and TNF-α • ATI-450 concentrations at trough

3 STUDY PLAN

3.1 Overall Study Design and Plan

The study visit schedule and planned assessments at each visit are detailed in Table 1.

This is a Phase 2a, open-label, single-arm study to investigate the safety, tolerability, efficacy, PK, and PD of ATI-450 to maintain remission in patients with CAPS previously managed with anti-IL-1 therapy. Up to 10 patients are planned to be enrolled in the study. The study will consist of an up to 8-week screening period, a 12-week treatment period, and a 4-week safety follow-up period. The total duration of the study for patients remaining in the study until their final safety follow-up assessment will be up to 24 weeks.

The investigator will obtain signed informed consent from the patient before any study procedures are performed. For further details regarding the informed consent process, see Section 9.3. During the screening visit each patient will be required to have all assessments performed as outlined in the Schedule of Assessments (Table 1).

Patients whose eligibility is confirmed at baseline will begin dosing ATI-450 tablets (50 mg BID). Such patients will be in protocol-defined remission due to prior treatment with an anti-IL-1 biologic. Dosing will begin on the day that the next dose of their anti-IL-1 therapy is scheduled at which time anti-IL-1 therapy will be discontinued.

The first dose of ATI-450 (50 mg BID) will be taken at the following times (based on anti-IL-1 therapy):

- Anakinra: 24 hours (+/- 1 hour) after last administration or at approximate time of regular anakinra dose.
- Canakinumab: 8 weeks (+/- 1 week) after last administration.
- Rilonacept: 1 week (+/- 1 day) after last administration.

ATI-450 will be administered orally for 12-weeks. Patients will attend clinic visits on Days 14, 28, 56, and 84 (+/-1 day) for safety, efficacy, PK and PD assessments. Patients will begin recording disease symptoms in their daily diary card 7 days prior to beginning administration of ATI-450, or immediately starting at the screening visit if the Day 1 visit is scheduled to occur less than 7 days after the screening visit. Patients will continue to complete their diary until completion of the safety follow up Day 7 visit.

At the end of 12-weeks, Day 84 (+/- 1 day), patients will stop ATI-450 and conduct end of study assessments. Patients will complete safety follow-up visits on site 7 Days (+4 days) after the last dose of ATI-450 and via a phone call 30 Days (+/-3 days) after the last dose.

Patients should not start their anti-IL-1 therapy until all safety follow-up Day 7 assessments have been completed. However, in the event of a safety concern, patients will be allowed to return

early or restart their anti-IL-1 therapy prior to completing the safety follow-up Day 7 visit at the discretion of the investigator.

3.2 Discussion of Study Design

The study is designed to assess the safety, tolerability, efficacy, PK, and PD of ATI-450 in patients with CAPS.

Many patients with CAPS achieve complete or near complete disease remission with currently available anti-IL-1 therapies. Therefore, the study is designed to minimize patient's time off anti-IL-1 therapy due to potentially harmful long-term complications that can result from prolonged relapse of disease symptoms.

The study is open-label and there is no washout period for anti-IL-1 therapy; patients enrolled in the trial will begin treatment with study medication (Day 1) on the day of their next scheduled dose of anti-IL-1 therapy. At the end of the 12-week treatment period, ATI-450 administration will be discontinued, and patients will delay administration of anti-IL-1 therapy until 7 days (+4 days) after the last dose of ATI-450.

The 12-week treatment period was selected to allow sufficient time to explore the efficacy of ATI-450 in maintaining disease remission, and to adequately rule out the potential for prolonged disease remission caused by the last dose of anti-IL-1 therapy. Due to its long $t_{1/2}$, this is particularly relevant in instances when canakinumab is used.

3.3 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 date of last procedure of the last patient in the study.

4 STUDY POPULATION

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

4.1 Inclusion Criteria

The following inclusion criteria must be met for a patient to be eligible for inclusion in the study:

1. Diagnosis of Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, or Neonatal Onset Multisystem Inflammatory Disease. Prior agreement between the Investigator and Aclaris for study eligibility is required for patients who do not have a molecular diagnosis of NALP3 mutations available (either testing not performed, or testing performed but negative) upon study entry. For those patients who have not been molecularly tested for NALP3 mutations, molecular testing should be performed during the course of the study.
2. Patients with a PGA score of "minimal" or less and who are considered to have achieved that response as a result of successful anti-IL-1 therapy.
3. Continuous treatment with anti-IL-1 therapy for at least 6 months.
4. Able to understand and comply with study procedures and was able to provide informed consent.
5. Male or non-pregnant, non-nursing female patients at least 18 years of age, inclusive.
    - Female patients who are of childbearing potential must use 2 methods of highly effective contraception* - one of which must be a physical barrier- for the duration of the study and for 30 days after the last dose
    - Male patients of childbearing potential with a female partner of childbearing potential must agree to use a condom plus another highly effective form of birth control for the duration of the study and for 90 days after the last dose
6. Female patients must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to dosing on Day 1.
7. Willing and capable of taking appropriate Covid-19 risk mitigation precautions (e.g. wearing a mask in public, adhering to social distancing, etc.) as required or recommended by local, state, or federal guidelines during participation in the study.

*Highly effective birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices, heterosexual abstinence, or vasectomized.

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Participation in any clinical study with an investigative agent within 12 weeks prior to entry or within 5 half-lives of the investigational agent.

2. Being treated with another immuno-suppressive agent (i.e., in addition to an anti-IL-1 product) for CAPS syndrome (anti- IL1 therapy will have been used for at least 6 months and will be stopped at study entry).
3. Use of any of the following treatments within the indicated washout period prior to the baseline visit:
    a. Systemic immunosuppressant or immunomodulatory therapy (e.g., etanercept, alefacept, infliximab, methotrexate) within 16 weeks prior to Visit 2 (excluding anti-IL-1 therapy for CAPS).
    b. Janus Kinase (JAK) inhibitors (systemic and topical) within 4 weeks prior to Visit 2.
    c. Systemic corticosteroids within 4 weeks prior to Visit 2. (Intranasal, inhaled, and topical ocular corticosteroids are allowed).
4. History of being immunocompromised, including a positive HIV test result at screening.
5. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody test result is not allowed.
6. Live vaccination within 3 months prior to the start of the trial, or during the trial.
7. History of recurrent and/or evidence of active bacterial, fungal, or viral infections.
8. History or evidence of active or latent tuberculosis (TB).
9. Tests performed at a central laboratory at screening that meet any of the criteria below (out of range labs may be rechecked one time, after consultation with sponsor or designee, before patient is considered a screen failure):
    - White blood cell (WBC) count $<3.0\times10^3$ cells/mm^3
    - Absolute neutrophil count (ANC) $<1.5\times10^3$ cells/mm^3
    - Lymphocyte count $<0.5\times10^3$ cells/mm^3
    - Platelet count $<100\times10^3$ cells/mm^3
    - Hemoglobin <10 g/dL
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq$1.5×upper limit of normal (ULN)
    - Total bilirubin level $\geq$2×ULN unless the patient has been diagnosed with Gilberts' disease and this is clearly documented
    - Estimated glomerular filtration rate (eGFR), <40 mL/min/1.73m^2 based on Modification of Diet and Renal Disease formula
10. Any clinically significant laboratory abnormality that would affect interpretation of study data or safety of the patient's participation in the study, per judgment of investigator.
11. Patient has clinically significant abnormal findings other than CAPS from physical examination conducted at screening visit (Visit 1) and at baseline visit (Visit 2) that may affect the interpretation of study data or the safety of the patient's participation in the study, per the judgment of the investigator.
12. Patient has a clinically important history of a medical disorder that would compromise patient safety or data quality, per the judgment of the investigator.

13. Blood pressure (BP) levels (in supine position after at least 5 minutes rest) <90 mmHg or >140 mmHG for systolic BP or <40 mmHG or >90 mmHg for diastolic blood pressure.
14. Patients with history of stroke.
15. Significant cardiac disease that would affect interpretation of study data or the safety of the patient's participation in the study, per the judgment of the investigator, including recent myocardial infarction or unstable angina, or heart failure with New York Heart Association Class III or IV symptoms.
16. Patients with the following screening or pre-dose ECG findings, specifically:
    - Evidence of atrial fibrillation, atrial flutter, complete right or left bundle branch block, Wolff-Parkinson-White Syndrome, or other significant rhythm disturbance
    - Evidence of acute ischemia
    - Screening or pre-dose baseline mean QTcF >450 msec for males or >470 msec for females (use of the ECG algorithm is acceptable for this purpose)
    - Personal or family history of congenital long QT syndrome or sudden death
    - Any other finding that is considered clinically significant
17. A confirmed diagnosis of Covid-19 at baseline or at any time during the study.

4.3 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 progressed to treatment 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(s).

Individuals who are screen failures due to out of range laboratory values can be rescreened once. Rescreened individuals retain the same screening number as used for the initial screening.

4.4 Premature Discontinuation

4.4.1 Premature Discontinuation of Investigational Product

Patients should discontinue ATI-450 if any of the following occurs:

- Serious infection
- Invasive fungal infection
- Malignancy (except for non-melanoma skin cancer)
- Hepatitis B virus reactivation

- Demyelinating disease
- Heart failure
- Lupus-like syndrome
- Hypersensitivity reaction
- Gastrointestinal perforation
- WBC count: $<1\times10^3/\mu L$
- ANC: $<0.5\times10^3/\mu L$
- Lymphocyte count: $<0.3\times10^3/\mu L$
- Platelet count: $<50\times10^3/\mu L$
- Hemoglobin: <6.5 g/dL
- 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 international normalized ratio [INR] >1.5
    - ≥3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Serum creatinine: >2×ULN persisting for 2-weeks after study medication interruption or second occurrence of >2×ULN
- Confirmed, active infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus)

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

- Severe AEs or SAEs
- Any other reason relating to the patient's safety

The investigator will make every effort to ensure that patients who prematurely discontinue ATI-450 complete the end of study assessments.

Patients who discontinue ATI-450 prematurely may be replaced at discretion of the sponsor.

4.4.2 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.

The investigator has the right to terminate participation of a patient for any of the following reasons:

- Difficulties in obtaining blood samples
- Violation of the protocol
- Any other reason relating to integrity of the study data

If a patient is withdrawn from the study, the study monitor/sponsor will be informed immediately. If there is a medical reason for withdrawal, the patient will 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.

At the time of premature study discontinuation, the investigator should make every effort to ensure the patient completes the assessments indicated at the end of study (Day 84) and safety follow-up visit (Day 7); see Table 1.

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 14.

4.4.3 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, two telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's research record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

5 DESCRIPTION OF STUDY ASSESSMENTS

Refer to Table 1 for the Schedule of Assessments.

5.1 Demographics and Other Screening Assessments

Screening assessments that are also part of the safety assessments are described in Section 5.3.

5.1.1 Medical History

Relevant medical history and current medical condition, including CAPS disease phenotype and duration as well as date of first diagnosis and previous treatments including any previous biologic or non-biologic therapy for CAPS will be recorded in the eCRF.

At the baseline visit, inclusion/exclusion criteria will be reviewed and updated to ensure the patient remains qualified for the study. Findings that are observed after the patient has signed the Informed Consent Form (ICF) and prior to the first dose of ATI-450 will be recorded as medical history on the eCRF. Any adverse event observed after the patient has signed the ICF that meets the definition of a SAE (See Section 7.1.2), in which case, all applicable safety reporting procedures will be followed by the site.

5.1.2 Demographics

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

5.1.3 Tuberculosis Test

An interferon-gamma release assay/QuantiFERON TB Gold test for active/latent TB will be performed at screening with analysis conducted by the sponsor's designated central laboratory. Patients with a negative test result will be eligible for the study.

In case of indeterminate results, the test may be repeated once. The patient can be included in the study if the repeat test is negative; however, if the repeat test is positive or indeterminate, the patient will be excluded from the study.

5.1.4 Screening Clinical Laboratory Assessments

Blood samples will be collected for clinical chemistry, coagulation, hematology, hsCRP, SAA, and lipids, follicle-stimulating hormone (FSH), HBsAg, hepatitis B core antibody, hepatitis C antibody, and HIV-1/HIV-2. A serum pregnancy test will be performed on women of childbearing potential. All laboratory analyses will be performed by the sponsor's designated central laboratory.

5.1.5 COVID-19 Monitoring

At Baseline Visit 2, all patients entering the treatment phase of the study must have a nasopharyngeal (preferred) or oropharyngeal swab collected prior to the first dose of ATI-450 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 (RT-PCR) 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 Baseline Visit 2 (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 ATI-450 in the absence of central laboratory or locally equivalent testing being performed.

Patients are allowed to dose with ATI-450 in the interval between sample collection at Baseline Visit 2 and result reporting as long as there is no clinical suspicion of COVID-19 infection or recent exposure 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 Visit 2, the patient will need to be notified immediately upon receipt of the results and treatment with ATI-450 will be permanently discontinued. The patient should 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 safety follow-up Visit 7 (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 7.1.2), 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 Adverse Event per the requirements of Section 7 of this protocol.

5.2 Efficacy Assessments

5.2.1 Physician Completed Efficacy Questionnaire

The Physician's Global Assessment of Autoinflammatory Disease Activity (PGA) is a measure to be completed by the investigator or designee. The PGA uses a 5-point rating scale: absent, minimal, mild, moderate, and severe. The investigator will select a rating based on the patient's current disease activity at the time of the visit.

5.2.1.1 Maintenance of Disease Remission and Clinical Remission

Maintenance of disease remission will be assessed during the treatment period. Disease remission is defined as having a PGA score of absent or minimal and a hsCRP and SAA value within the normal range (≤10 mg/L) or within 30 percent of the baseline value.

Maintenance of clinical remission will be assessed during the treatment period. Clinical remission is defined as having a PGA score of absent or minimal.

5.2.1.2 Time to Relapse

Time to relapse will be assessed during the treatment period. Relapse is defined as a two-point worsening on the PGA scale.

5.2.2 Patient Completed Efficacy Questionnaires

When these assessments are required at the times outlined in Table 1, they should be the first tasks done at any visit, and prior to study medication dosing.

The KSS is derived from the patient-administered DHAF (Appendix 2), and is the average on a 0 to 10 scale (0 = None, 10 = Very Severe) of 5 separate scales – rash, feeling of fever and chills, joint pain, eye redness and pain, and fatigue.

The DHAF is designed using a linear rating scale of circles in half-step units (e.g. 0.5, 1.0, 1.5, 2.0, etc.), which are marked 0 (none, no severity) to 10 (very severe) [2, 5]. Patients will select the circle on the scale that they determine most accurately represents severity of the symptom that they have experienced during the last 24 hours.

The DHAF will be completed daily by the patient. Daily KSS will be calculated by averaging the sum of the 5 individual symptom scores. KSS during a specified time period will further be calculated by averaging the sum of daily KSS scores during the time period.

Patients will be provided a quiet, private place to complete the assessments. Patients will be instructed to answer all the questions to the best of their ability and without help from others (study staff, family, or friends). The study staff should review the questionnaires after they are completed and encourage patients to complete any missing information. Patients can refrain from answering any question. Study staff will record the refusal of patients to answer any question in the source documents.

5.2.2.1 Re-emergence of CAPS Symptoms

Re-emergence of CAPS symptoms will be assessed after ATI-450 is discontinued following completion of the treatment period. Re-emergence is defined as an increase in daily KSS of ≥ 3 from baseline for at least two consecutive days.

5.2.3 High Sensitivity C-reactive Protein and Serum Amyloid A

Blood samples for evaluation of hsCRP and SAA will be collected at the times specified in Table 1. Samples will be shipped to a central laboratory. Specific instructions for collection, processing, storage and shipment of blood samples will be provided in a separate laboratory manual.

The normal range for serum hsCRP and SAA is defined as ≤ 10mg/L for both.

5.3 Safety Assessments

5.3.1 Adverse Events

AEs will be followed, recorded, and reported in line with the procedures described in Section 7.

5.3.2 Clinical Laboratory Evaluations

Laboratory assessments during treatment will be performed by a central laboratory. 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.

Unless indicated otherwise, all laboratory samples will be processed and shipped to the central laboratory, as described in the central 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.

The following parameters will be assessed:

Hematology: hemoglobin, hematocrit, red blood cells, platelets, total WBC count, differential WBC count, and ANC

Coagulation: INR, partial thromboplastin time, and prothrombin time

Biochemistry: albumin, alkaline phosphatase (ALP), ALT, amylase, AST, blood urea nitrogen (BUN), calcium, creatine phosphokinase, hsCRP, creatinine, gamma glutamyltransferase, glucose, inorganic phosphatase, lactate dehydrogenase, lipase, magnesium, potassium, SAA, sodium, chloride, bicarbonate, total bilirubin, total protein, and uric acid

Lipids: total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides

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

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. If known, the underlying etiology of the clinically relevant laboratory changes should be reported as the AE, rather than the abnormal laboratory result 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 under study, 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 30 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 sponsor should be notified.

5.3.2.1 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 1 Possible Hy's Law Liver Chemistry Action and Follow-up Assessments Possible Hy's Law Liver Chemistry Action and Follow-up Assessments for further information.

5.3.3 Pregnancy

All patients are required to meet the requirements relating to pregnancy and use of contraception described in the inclusion and exclusion criteria (see Section 4.1 and Section 4.2, respectively).

Serum beta human chorionic gonadotrophin (β-hCG) testing will be performed for female patients of childbearing potential at screening (within 28 days of Day -1), and a urine pregnancy test will be performed on Day 1 (prior to dosing) and throughout the study.

The pregnancy test must be negative for the patient to be eligible. The serum pregnancy tests will be analyzed by the central laboratory, and the urine pregnancy tests will be analyzed locally.

Monitoring for pregnancies in female patients will continue from the patient's inclusion in the study until the follow-up visit. 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 sponsor (or designee).

If a patient becomes pregnant, study medication will be permanently discontinued and she will be withdrawn from the study after completing the assessments planned for the end of study visit (see Table 1). Any pregnant 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. Generally, follow-up will be required for no longer than 6 to 8 weeks beyond the estimated delivery date.

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.

For any male study patient whose partner becomes pregnant, the investigator will attempt to collect pregnancy information on the male patient's partner while the male patient is in this study.

The investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The investigator will obtain

informed consent from the female partner to collect information about the pregnancy and its outcome. Information on the status of the pregnant partner and the fetus will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

5.3.4 12-lead Electrocardiogram

Triplicate 12-lead ECG will be recorded after the subject has been resting for at least 5 minutes in the supine position. as outlined in Table 1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The ECG tracing should clearly identify the patient, include the date and time of the assessment and the signature and date of the person who made the interpretation; the tracing will be archived at the study site. Abnormal, clinically significant ECG results will be recorded as AEs.

5.3.5 Vital Signs

Vital signs will be measured prior to dosing and immediately following dosing in a semi-supine position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate. Abnormal, clinically significant vital sign results will be recorded as AEs. If known, the underlying etiology for the abnormal clinically significant vital sign will be recorded as an AE rather than the vital sign itself.

5.3.6 Physical Examination

The complete physical examination will include assessments of the standard physical examination items, including general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems, if applicable, for describing the status of the patient's health.

The brief physical examination will include, at a minimum, signs of CAPS.

Body weight and height will also be measured and recorded. The patient should be dressed in lightweight clothing, without shoes.

Investigators should pay attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as AEs, as appropriate (see Section 7).

5.4 Pharmacokinetics and Pharmacodynamics

Blood samples for PK and PD evaluation will be collected at the times specified in Table 1. Samples will be shipped to a central laboratory. Specific instructions for collection, processing, storage, and shipment of blood samples will be provided in a separate laboratory manual.

6 TREATMENTS

6.1 Investigational Product(s)

6.1.1 Description of Investigational Product(s)

Test Product

Substance:	ATI-450
Strength:	50 mg
Mode of administration:	Oral tablets
Manufacturer:	Emerson Resources

6.1.2 Preparation, Handling, and Storage

The investigator (or designee) is responsible for the safe and proper storage of study medication at the site. ATI-450 and placebo will be stored under controlled conditions according to the storage requirements described on the label(s). Study medications should be stored at 15°C to 25°C (59°F to 77°F), away from heat moisture and direct light. The investigator (or designee) will instruct the patients to store the study medication in accordance to the instructions on the label(s).

6.1.3 Packaging, Labeling, and Shipment

ATI-450 will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

ATI-450 will be supplied in high-density polyethylene bottles.

Study medication 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.

6.2 Blinding

This is an open-label trial.

6.3 Dose and Administration

ATI-450 will be administered as oral tablets for a total of 100 mg daily. Doses will be administered twice daily (50 mg BID).

6.4 Precautions and/or Lifestyle Considerations

There are no lifestyle considerations (such as dietary or physical activity restrictions) for this study.

6.5 Prior Medication and Procedures

The following are considered exclusionary if taken within the defined period prior to the screening visit:

1. Systemic immunosuppressant or immunomodulatory therapy (e.g., etanercept, alefacept, infliximab, methotrexate) within 16 weeks prior to Visit 2 (excluding anti-IL-1 therapy for treatment of CAPS).

2. JAK inhibitors (systemic and topical) within 4 weeks prior to Visit 2.

3. Systemic corticosteroids within 4 weeks prior to Visit 2 (Intranasal, inhaled, and topical ocular corticosteroids are allowed).

6.6 Concomitant Medication

The following medications are prohibited during the duration of the study:

1. Systemic immunosuppressant or immunomodulatory therapy (excluding anti-IL-1 therapy for treatment of CAPS during screening and follow-up period). See section 3.1 for washout information.

2. JAK inhibitors (systemic and topical).

3. Systemic corticosteroids (Intranasal, inhaled, and topical ocular corticosteroids) are allowed.

All medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken from 30 days before start of screening 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.

6.7 Overdose

There is limited clinical experience with ATI-450. In the event of an overdose, patients should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved ATI-450) must be communicated to the sponsor (or a specified designee) within 24 hours of its occurrence.

Any overdose associated with clinical symptoms will be recorded as an AE or SAE, as appropriate. Details of any signs or symptoms and their management should be recorded, including details of any treatments administered for the overdose. All overdoses with clinical symptoms meeting the SAE criteria must be reported as described in Section 7.4.

6.8 Compliance

The investigator (or designee) will explain the correct use of the study medication to each patient and will check that each patient is following the instructions properly. Compliance will be assessed at each visit by counting returned tablets and will be documented in the source documents and eCRF. Any deviation from the correct use of the study medications will be recorded in the eCRF.

A record of the number of tablets dispensed to and taken by each patient will be maintained and reconciled with study medication and compliance records. The study medication start and stop dates, including dates for study medication delays and/or dose reductions, will also be recorded in the eCRF.

6.9 Accountability

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

The site 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 (TMF). 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.

The investigator (or designee) will administer the study medication only to the identified patients in this study, according to the procedures described in this study protocol.

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.

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study 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.

7.1.2 Serious Adverse Events

An SAE is any untoward medical occurrence 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 or prolongation of 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 or SAE as per the definitions.

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.

7.1.3 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, coagulation, lipids, 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 7.1.1 and 7.1.2. If the underlying cause for the laboratory abnormality is known, record the etiology or diagnosis (e.g., anemia), rather than the laboratory result (i.e., decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities, see Section 5.3.2.

7.2 Assessment of Adverse Events

7.2.1 Severity

The investigator will determine the intensity of the AE according to the definitions below:

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of the event; both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, not when it is rated as severe.

7.2.2 Causality

The investigator is obligated to assess the relationship between study medication and each occurrence of an AE/SAE. The investigator will use her/his best clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. The investigator will also consult the IB in his/her assessment. The investigator will define the relationship of an AE to the study medication by selecting one of the following categories:

Related:

- There is a reasonable possibility that there is a causal relationship between the study medication and the AE

Not Related:

- There is no reasonable possibility that there is a causal relationship between the study medication and the AE

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.

7.3 Documenting and Reporting Adverse Events

Reporting of SAEs will begin when the patient has provided informed consent and will continue up to the end of study visit or 30 days after the last ATI-450administration whichever is later. Reporting of AEs will begin when the patient receives the first dose of ATI-450 and will continue up to the end of study visit or 30 days after the last study drug administration, whichever is later. Any clinical AE that occurs between the time of consent and dosing Day 1 will be recorded as medical history.

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 CRF 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 administration if the AE started on a dosing day], 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.

7.4 Reporting of Serious Adverse Events

Upon becoming aware of a SAE whether or not related to the study medications, the investigator must:

1. Take the appropriate medical action to ensure the patient's safety.
2. Immediately, and no longer than within 24-hours, report the SAE to the safety monitor, ensuring that the patient information is de-identified to (Aclaris safety monitor):

   ProPharma Group

   - **Email**: [redacted]
   - **Fax:** [redacted]
3. Print a copy of the email confirmation from ProPharma and place in the study file.
4. Within 24-hours, complete, as fully as possible an SAE form; email the forms and any other relevant information (e.g., concomitant medication eCRF, medical history eCRF, laboratory test results) to ProPharma.
5. Monitor and document the progress of the SAE until it resolves or, if not resolved after the patient's last study visit, until in the opinion of the investigator the AE reaches a clinically stable outcome with or without sequelae AND the investigator and Aclaris safety and medical monitor agree that the SAE is satisfactorily resolved.
6. Report any SAE updates within 24-hours of knowledge to the safety monitor via email (or fax) and update the SAE form.
7. Comply with the appropriate regulatory requirements and Aclaris instructions regarding reporting of the SAE to the responsible IRB.

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.

7.5 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.

7.6 Safety Reporting Oversight

In accordance with ICH GCP, 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/IEC approval/favorable opinion to continue the trial."

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study medication under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, 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/IEC, if appropriate, according to local requirements.

8 STATISTICS

8.1 General Procedures

Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) by the sponsor or its representatives.

The statistical analysis plan (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.

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.

8.2 Analysis Populations

- The ITT population will include all patients who have been administered at least one dose of study medication.
- The PP population will include all patients who complete 12-weeks of treatment and 4-weeks of follow up and have completed assessments.

8.3 Sample Size

The sample size for this study was determined based upon feasibility constraints as opposed to a formal power computation. Up to 10 patients are planned to be enrolled.

8.4 Statistical Methods

8.4.1 Efficacy Analyses

All efficacy summaries will be conducted on both the ITT and PP populations.

- Proportion of participants in disease remission over time; where disease remission is defined as having a PGA score of minimal or better and a hsCRP and SAA value within the normal range or within 30 percent of the baseline value (ITT and PP population).
- Proportion of participants in clinical remission over time; where clinical remission is defined as having a PGA score of minimal or better (ITT and PP population).
- Time to relapse; where relapse is defined as a two-point worsening on the PGA scale in the ITT population.

- Proportion of participants who experience a daily increase in KSS ≥ 3 on at least two consecutive days after discontinuation of ATI-450 over time (PP population).

- Proportion of participants who maintain a mean KSS of no more than 2 higher than baseline for at least 6 out of 8 weeks in the ITT and PP population.

- Change from baseline in PGA and KSS scores will be reported descriptively over time (ITT and PP population).

- Change from baseline in hsCRP and SAA and percent change from baseline in hsCRP and SAA will be summarized over time using continuous statistical summary measures. Determination of sustained treatment effect for hsCRP and SAA will be based upon the median percent change from baseline in the ITT and PP population.

8.4.2 Safety Analyses

The Safety population will be used for the analysis of safety data (AEs, exposure to study medication, clinical laboratory, vital signs, and ECG).

AEs will be coded with the MedDRA. TEAEs are defined as AEs with an onset date on or after the date of first administration of study medication and before the date of last administration of study medication + 30 days. 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, lipids, 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.

8.4.3 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex at birth, ethnicity, and race) and baseline characteristics (including height, weight, body mass index (derived in eCRF), and disease characteristics) will be presented descriptively.

8.4.4 Pharmacodynamic Analyses

The assessment of cytokine PD parameters will be described and provided in a separate report(s).

8.4.5 Handling of Missing Values

Missing data will not be imputed for the safety summaries or the efficacy summaries conducted on the PP population.

For efficacy summaries conducted on the ITT population a model based multiple imputation procedure will be used to impute missing data, where appropriate. Rules for imputation of missing efficacy data will be detailed 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 withdrawal visit will be used as an end of study assessment for these patients. If the withdrawal visit was performed >1 day after the last dose was administered, then the previous visit will be used as the end of study assessment.

8.5 Interim Analysis

This is an open-label study. The safety will be assessed on an ongoing basis during the conduct of the trial. No formal interim analyses will be conducted.

9 ETHICS AND RESPONSIBILITIES

9.1 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), requirements for the conduct of clinical studies as provided in the EU Directive 2001/20/EC, the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

9.2 Institutional Review Board/Independent Ethics Committee

Before initiating a study, the investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC 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 IRB/IEC 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/IEC.

The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/IEC 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/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Notifying the IRB/IEC of SAEs or other significant safety findings, including adverse drug reactions that are both serious and unexpected, as required by IRB/IEC 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

9.3 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/IEC 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 (HIPAA) requirements in the US, and the IRB/IEC 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/IEC 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.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days of the previous ICF signature date.

9.4 Data Monitoring Committee

There is no data monitoring committee for this study.

9.5 Financing and Insurance

9.5.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the site's 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.

9.5.2 Insurance, Indemnity, and Compensation

Aclaris will maintain an appropriate clinical study insurance policy.

9.5.3 Financial Disclosure

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

10 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.

10.1 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 persons. The investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC 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/IEC review, and regulatory inspection.

10.2 Electronic 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.

10.3 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.

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-450. 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 subject 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.

11 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.

The CRFs 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 CRFs 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.

11.1 Risk and Quality Tolerance Limits

The sponsor will review risk control measures outlined within 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 CSR.

11.2 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/IEC 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.

12 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/IEC, 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/IEC, 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.

13 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 Clinical Study Reports (ICH E3).

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.

14 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 date of the last patient's last assessment.

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/IEC 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/IEC. The investigator/site personnel should also provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

15 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/IEC personnel, 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 level of disclosure must also be explained to the patient, who will be required to give consent for their data to be used as described in the ICF. 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/IEC members, and by inspectors from regulatory authorities.

Identification of patients and eCRFs shall be by unique patient identification numbers (such as screening or randomization number) only. All personal identifiers according to applicable regulations (e.g., name, phone 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 sponsor designees.

16 APPENDICES

16.1 Appendix 1 Possible Hy's Law Liver Chemistry Action and Follow-up Assessments

Suggested Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study medication. • Report the event to the sponsor or designee **within 24 hours.** • Complete a 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**). • **Do not restart/re-challenge** participant with study treatment unless allowed per-protocol and sponsor approval **is granted**. • If restart/re-challenge is either **not allowed per-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 ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Repeat liver chemistry tests (ALT, AST, ALP, 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 ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, ALP, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.**	• Viral hepatitis serology[3] • Obtain INR and recheck with each liver chemistry assessment until the transaminase's values show downward trend • Obtain blood sample for ATI-450 drug concentration[4] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin if total bilirubin ≥2xULN • 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 CRF **If ALT ≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct enzyme immunoassay(quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week.[6])

• Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment if ALT ≥3xULN **and** bilirubin ≥2xULN. 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 ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **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 IgM antibody; HBsAg and hepatitis B Core Antibody (HBcAb); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM 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 on the CRF. 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.

16.2 Appendix 2 Daily Health Assessment Form

Protocol: ATI-450-CAPS-201

Daily Health Assessment Form

Initials: __ __ __ Subject #: __ __ __ Today's Date: ___/___/_____

Please rate the severity of the following symptoms over the last 24 hours:

	None, No Severity 0																				Very Severe 10
Rash:	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Fatigue: (Tiredness)	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Joint Pain:	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Feeling of Fever/Chills:	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Eye Redness/Pain:	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O

Other CAPS Symptoms (if any, please describe):

_____
_____
_____
_____

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