CLINICAL STUDY PROTOCOL

Title:	A Phase 2a, Randomized, Investigator and Patient-blind, Sponsor-unblinded, Parallel Group, Placebo-controlled Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ATI-450 Plus Methotrexate (MTX) vs MTX Alone in Patients with Moderate to Severe Active Rheumatoid Arthritis with Inadequate Response to MTX
Protocol number:	ATI-450-RA-201
Study phase:	Phase 2a
Test product:	ATI-450
Sponsor:	Aclaris Therapeutics, Inc 640 Lee Road, Suite 200 Wayne, PA 19087, US
[redacted]	[redacted]
Protocol version and date:	3.0, 27July2020

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] [redacted]

Print Name Title

[redacted] [redacted]

Signature Date

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by Aclaris Therapeutics, Inc., and given approval/favorable opinion by the 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 Therapeutics, Inc., or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study. I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Aclaris Therapeutics, Inc. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, patient to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regional regulatory requirements. I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by Aclaris Therapeutics, Inc., and inspection by the appropriate regulatory authorities.

I agree to make my patients' study records available to Aclaris Therapeutics, Inc., personnel, their representatives and relevant regulatory authorities in order to verify data that I have entered into the case report forms (CRFs). I will retain the study-related essential documents until Aclaris Therapeutics, Inc indicates that they are no longer needed. I am aware of my responsibilities as an investigator as provided by Aclaris Therapeutics, Inc. I understand that Aclaris Therapeutics, Inc., may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Aclaris Therapeutics, Inc.

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:

[redacted]

[redacted]

[redacted]

PROTOCOL SUMMARY

Protocol Number: ATI-450-RA-201

Protocol Title: A Phase 2a, Randomized, Investigator and Patient-blind, Sponsor-unblinded, Parallel Group, Placebo-controlled Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ATI-450 Plus Methotrexate (MTX) vs MTX Alone in Patients with Moderate to Severe Active Rheumatoid Arthritis with Inadequate Response to MTX

Sponsor: Aclaris Therapeutics, Inc.

Study Phase: Phase 2a

Study Sites: [redacted]

Objectives and Endpoints:

Objectives		Endpoints
Primary	• To assess the safety and tolerability of ATI-450 plus MTX in patients with moderate to severe rheumatoid arthritis (RA)	• 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 pharmacodynamics (PD) of ATI-450 plus MTX in patients with moderate to severe RA	• Median percent change from baseline in high sensitivity C-reactive protein (hsCRP) levels over time • Mean change from baseline in Disease Activity Score using 28 joint count-C-reactive protein (CRP) (DAS28-CRP) over time • Proportion of patients with DAS28-CRP below 2.6 • Mean change from baseline in Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) Hand-Wrist assessments of synovitis or osteitis at Week 12 • Proportion of patients with American College of Rheumatology (ACR)20/50/70 over time
	• To assess the pharmacokinetics (PK) of ATI-450 in patients with moderate to severe RA who are receiving concomitant MTX	• ATI-450 concentrations at trough and 2 hours post-dose

Exploratory	• To assess the PD of ATI-450 plus MTX in patients with moderate to severe RA	• Mean change from baseline in endogenous cytokine levels (e.g., tumor necrosis factor-α [TNF-α], interleukin [IL]-1β, IL-6, IL-8, IFNγ, IL-17, IL-18, IL-10, IL-1α and IL-1RA) • Mean change from pre-dose in ex vivo stimulated cytokine levels (e.g., TNF-α, IL-1β, IL-6, IL-8, IFNγ, IL-17, IL-18, IL-10, IL-1RA, and IL-1α) • Ex vivo stimulated phosphoprotein modulation • Mean change from baseline in the cartilage loss score (CARLOS) Hand-Wrist magnetic resonance imaging (MRI) assessment of cartilage loss

Study Design:

This is a Phase 2, randomized, investigator and patient-blind, sponsor-unblinded, parallel group, placebo-controlled study to investigate the safety, tolerability, PK, and PD of ATI-450 plus MTX versus MTX alone in patients with moderate to severe RA.

The study will consist of an up to 28-day screening period, a 12-week treatment period, and a 4-week follow-up period. The total duration of the study for patients remaining until their final follow-up assessment will be up to 20 weeks.

The investigator will obtain signed informed consent from the patient before any study procedures are performed.

During the screening period, each patient will be required to have all assessments performed as outlined in the Schedule of Assessments. The MRI is not to be performed until the site obtains the results of the patient's hsCRP level to ensure that this assessment meets the entry criteria prior to performing the MRI. The patient will have the RAMRIS Hand-Wrist MRI assessment performed at their local institution and evaluated by a central radiology review team to determine if they meet the radiological inclusion criteria. Results for all of the screening assessments must be available at the time patient eligibility is reconfirmed prior to randomization and dosing.

Patients whose eligibility is confirmed at baseline will be randomized in a 3:1 ratio to receive either ATI-450 tablets (50 mg twice daily [BID]) plus MTX, or matching placebo tablets plus MTX. Study medications will be administered orally for 12 weeks. Patients will be required to remain on a stable dose of MTX (7.5 mg to 25 mg/week) for the duration of the study.

Patients will attend clinic visits on Days 7, 14, 28, 42, 56, and 84 (±1 day) for safety, efficacy, PK, and PD assessments. The morning dose of study medication will be administered in the clinic on each study visit day.

At the completion of 4 weeks of treatment (Day 28), each patient's safety data (e.g., AEs, laboratory values, vital signs, and ECGs) will be reviewed by the Aclaris medical monitor and Aclaris safety physician to ensure that the patient is tolerating the treatment regimen and is deemed suitable to continue treatment for the next 8 weeks.

On Day 84 (Week 12), patients will complete the end of study assessments. A safety follow-up visit will be conducted 30 days (+7) after the last dose of study medication.

The study is randomized and blinded to the investigator, patient, site personnel, and sponsor representatives responsible for clinical monitoring at the investigational to prevent bias in treatment allocation and in the assessment of treatment effect. The Aclaris statistician, medical and safety monitor will be unblinded to each patient's treatment assignment.

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.

Planned Number of Patients: It is planned to enroll 25 patients in order to obtain 15 evaluable patients. An evaluable patient is a patient who meets all entry criteria and completes 12 weeks of treatment.

Target Population:

Inclusion Criteria

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

1. Able to comprehend and be willing to sign the Institutional Review Board (IRB)-approved subject informed consent form (ICF) prior to administration of any study-related procedures.
2. Diagnosis of adult-onset RA as defined by the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria.

[redacted]

6. Patients must have definitive intra-articular synovitis or osteitis defined as a score of 1 or greater on a Hand-Wrist MRI as assessed by central imaging reader (using RAMRIS).
7. On a stable MTX dose (defined as 7.5 mg to 25 mg weekly) and a stable dose of folic or folinic acid (defined as ≥ 5mg/week) for at least 4 weeks prior to the screening visit.
8. Male or non-pregnant, non-nursing female patients between 18 and 70 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
9. Female patients must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to dosing on Day 1.
10. Screening laboratory evaluations (hematology, chemistry, coagulation, and urinalysis) must fall within the normal range of the central laboratory's reference ranges unless the results have been determined by the investigator to not be clinically significant.
11. Willing and capable of taking appropriate coronavirus disease 2019 (COVID-19) risk mitigation precautions (e.g., wearing a mask in public, adhering to social distancing, etc.) as recommended or required by local, state, or federal guidelines during participation in the study.

*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. The requirements for highly effective birth control do not apply to female patients of nonchildbearing potential (i.e., physiologically incapable of becoming pregnant) defined as:

- Has had a complete hysterectomy greater than or equal to 3 months prior to dosing or
- Has had a bilateral oophorectomy (ovariectomy) or
- Has had a bilateral tubal ligation or fallopian tube inserts or
- Is postmenopausal (i.e., cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level >40 mIU/mL) or
- Medically documented ovarian failure

Exclusion Criteria

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

1. Patient has a current acute or chronic immunoinflammatory disease other than RA which may impact the course or assessment of RA.
2. Patient has an uncontrolled non-immunoinflammatory disease that may place the patient at increased risk during the study or impact the interpretation of results.
3. History or evidence of active or latent tuberculosis.
4. Known hypersensitivity to MTX or ATI-450.
5. Patient has a history of either alcoholism/current alcoholic, alcoholic liver disease, or other chronic liver disease.
6. Active infection requiring treatment with antibiotics.
7. Positive for HIV, hepatitis B or C. Patients with serologic evidence of hepatitis B vaccination (hepatitis B surface antibody without the presence of hepatitis B surface antigen) will be allowed to participate.
8. 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 count $<3.0\times10^3$ cells/mm^3
    - Absolute neutrophil count $<1.5\times10^3$ 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) ≥1.5×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 (eGFR), <40 mL/min/1.73 m^2 based on Modification of Diet and Renal Disease formula

9. 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 the investigator.
10. Patient has clinically significant abnormal findings other than RA 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.
11. Patient has a clinically important history of a medical disorder that would compromise patient safety or data quality (per investigator's judgment).
12. Blood pressure levels (in supine position after at least 5 minutes rest): <90 mmHg or >140 mmHg for systolic blood pressure or <40 mmHg or >90 mmHg for diastolic blood pressure.
13. [redacted]
14. Are currently receiving corticosteroids at doses greater than 10 mg per day of prednisone (or equivalent) or have been receiving an unstable dosing regimen of corticosteroids within 2 weeks of the screening visit.
15. Have started treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or have been receiving an unstable dosing regimen of NSAIDs within 2 weeks of the screening visit.
16. Patients with history of stroke.
17. Significant cardiac disease that would affect interpretation of study data or the safety of the patient's participation in the study, per judgment of the investigator, including recent myocardial infarction or unstable angina, or heart failure with New York Heart Association Class III or IV symptoms.
18. 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

19. Any joint procedure in the past 90 days prior to screening.
20. Known exposure to an individual with a confirmed diagnosis of COVID-19 at any time during the screening period.
21. Vaccination with a live or attenuated vaccine within 6 weeks prior to Baseline (Visit 2) or planned vaccination with these vaccines at any time during treatment or within 6 weeks following discontinuation of study medication.

Test Product:

Name: ATI-450 (50 mg)

Dose: 50 mg BID

Mode of administration: Oral tablets

Concomitant Product

Name: Methotrexate (MTX)

Dose: Patients are to remain on their stable dose of MTX (defined as 7.5 mg to 25 mg per week) throughout the 12-week treatment period

Mode of administration: Oral tablets

Control Product:

Name: Placebo

Dose: 0 mg; administered BID

Mode of administration: Oral tablets

Statistical Methods:

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

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

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

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

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

Determination of Sample Size

The sample size for this study was determined based upon feasibility constraints as opposed to a formal power computation. Approximately 25 patients are planned to be enrolled with the expectation that at least 15 patients will complete the 12-weeks of treatment.

Interim Analyses

This study is being conducted as a sponsor-unblinded study. The safety and efficacy will be assessed on an ongoing basis during the conduct of the trial via multiple unblinded interim analyses. The frequency of the interim analyses will be approximately weekly depending upon the rate of enrollment. Since there is no formal statistical hypothesis, there will be no alpha spending adjustment made for multiple analyses. There is no scenario for which the study would be stopped early for efficacy.

Analysis Populations

- The Safety population will include all patients who have been administered at least one dose of study medication.
- The Intent-to-treat (ITT) population will include all randomized patients.
- The Per-Protocol population will include all patients who have completed their Day 84 visit and have valid hsCRP values for at least 6 of the 7 scheduled collection times.
- The PK population will include all patients who receive at least 1 dose of ATI-450 and provide at least one plasma concentration value.

Efficacy Analyses

All efficacy summaries will be conducted on both the ITT and Per-Protocol populations.

- The hsCRP levels, change from baseline in hsCRP and percent change from baseline in hsCRP will be summarized over time using continuous statistical summary measures. Determination of sustained treatment effect for hsCRP will be based upon the median percent change from baseline in hsCRP over time in the Per-Protocol population.
- The DAS28-CRP, RAMRIS and CARLOS Hand Assessments, 66/68 swollen/tender joint count, Patient's Global Assessment of Disease Activity, Patient's Assessment of Arthritis Pain, and Physicians Global Assessment of Disease Activity, as well as their corresponding changes from baseline will be summarized over time (for all scheduled timepoints) using continuous statistical summary measures. The focus of the MRI analyses will be the synovitis and osteitis scores.
- The number and proportion of patients with DAS28-CRP <2.6 and the number and proportion of patients meeting American College of Rheumatology (ACR) 20/50/70 will be tabulated at each scheduled visit, separately.

Safety Analyses

The Safety 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 through the completion of the last follow up visit or the date of last administration of study medication + 30 days (whichever occurs later). 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.

ATI-450 Drug Concentrations and Pharmacokinetic Analyses
Plasma concentrations of ATI-450 will be summarized by nominal timepoint and day. Trough concentration versus time (Days 7, 14, 28, 42, 56, and 84) and concentration versus time (0 and 2 hours post-dose) by day (Days 1 and 84) will be displayed by linear scale.

Pharmacodynamic Analyses
The assessment of cytokines and phosphoprotein PD parameters will be described and provided in a separate report(s).

[redacted]

Protocol version and date: 3.0, 27July2020

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Assessment	**Screening Visit 1 Day -28 to Day -1**	**Visit 2 Baseline Day 1**	**Visit 3 Day 7**	**Visit 4 Day 14**	**Visit 5 Day 28**	**Visit 6 Day 42**	**Visit 7 Day 56**	**Visit 8 Day 84 (Week 12)**	**Visit 9 Follow-up 30 days (+ 7 days)**
			+/-1 day						
Informed Consent	X								
Eligibility Review	X	X							
RA and Other Medical History and Demographics	X								
QuantiFERON Gold Test for TB	X								
Height	X								
Weight	X								X
Full Physical Exam[1]	X							X	X
Limited Physical Exam		X	X	X	X	X	X		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SARS-CoV-2 Testing by RT-PCR		X							
HIV and Hep Screen	X								
Vital Signs	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X			X			X	X
Hematology, Coagulation, Chemistry, Lipids, and Urinalysis	X	X	X	X	X	X	X	X	X
hsCRP	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Assessment	Screening Visit 1 Day -28 to Day -1	Visit 2 Baseline Day 1	Visit 3 Day 7	Visit 4 Day 14	Visit 5 Day 28	Visit 6 Day 42	Visit 7 Day 56	Visit 8 Day 84 (Week 12)	Visit 9 Follow-up 30 days (+ 7 days)
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAMRIS and CARLOS Hand-Wrist MRI Assessments	X[6]							X[10]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]	[redacted]
Serum Pregnancy	X								
Urine Pregnancy		X	X	X	X	X	X	X	X
Randomization		X							
Dispense Study Medication		X	X	X	X	X	X[7]		
Administration of Morning Dose of Study Medication in Clinic		X	X	X	X	X	X	X[8]	
Drug Accountability			X	X	X	X	X	X	
Adverse Events[9]	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X

[redacted]

[1]A complete physical examination will be performed at screening, Week 12, and follow-up.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATF2	activating transcription factor 2
AUC	area under the concentration-time curve
$AUC_{0-\alpha}$	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
CARLOS	cartilage loss score
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score using 28 joint count-C-reactive protein
DMARD	disease-modifying antirheumatic drugs
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

HAQ-DI	Health Assessment Questionnaire – Disability Index
HIPAA	Health Insurance Portability and Accountability Act
hsCRP	high sensitivity C-reactive protein
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
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MK2	MAPK-activated protein kinase 2
MRI	magnetic resonance imaging
MTX	methotrexate
NOMID	neonatal-onset multisystem inflammatory disease
NSAIDS	non-steroidal anti-inflammatory drugs
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRAK	p38α-related/activated protein kinase
QTL	quality tolerance limits
RA	rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Score
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
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
VAS	visual analog scale
WBC	white blood cell

1 INTRODUCTION AND RATIONALE

1.1 Background

1.1.1 Background

Aclaris Therapeutics, Inc. is developing ATI-450, 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 p38MAPK 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 Therapeutics, Inc is developing ATI-450 for potential treatment of inflammatory disorders.

[redacted]

[redacted]

ATI-450-related adverse effects noted in either species. ATI-450-related findings in rats

[redacted]

[redacted]

1.2 Study Rationale

The assessment of 12-weeks of ATI-450 exposure in patients with RA will provide important data to initially describe the safety and tolerability of ATI-450 in a relevant patient population.

The p38 MAPK pathway offers great potential in the treatment of inflammatory diseases such as RA. Unfortunately, this potential has not been realized in clinical studies where it has been hypothesized that the lack of efficacy resulted from the development of tachyphylaxis. [1, 2, 3]

The tachyphylaxis hypothesis has been supported by the consistent observation in the studies cited above, that C-reactive protein (CRP) showed an initial rapid reduction, followed by a return to baseline within 4 to 8 weeks. It is thought this may be a result of p38 MAPK inhibitors inhibiting anti-inflammatory downstream substrates in addition to proinflammatory substrates.

By targeting MK2, which is downstream from p38, it is believed that ATI-450 can inhibit the inflammatory pathways without a significant impact on anti-inflammatory pathways, which could lead to the avoidance of tachyphylaxis. This hypothesis is supported by pre-clinical models.

The consistent pattern of CRP tachyphylaxis with p38 inhibition provides an efficient model to test the potential of MK2 inhibition to avoid tachyphylaxis, i.e., if a reduction in CRP is achieved and maintained over 12 weeks, MK2 inhibition will have been shown to have a PD profile that is distinct from p38 inhibition and one that could offer potential for efficacy in RA. This study will assess the CRP profile.

This study is being conducted to determine the safety, tolerability, PK, PD and preliminary efficacy of ATI-450 in combination with MTX in patients with moderate to severe RA. The results of this study may benefit patients with RA.

[redacted]

[redacted]

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 plus MTX in patients with moderate to severe RA	• Number and percent of AEs and SAEs; mean change from baseline in laboratory values, vital signs, and ECGs
Secondary	• To assess the PD of ATI-450 plus MTX in patients with moderate to severe RA	• Median percent change from baseline in high sensitivity C-reactive protein (hsCRP) levels over time • Mean change from baseline in Disease Activity Score using 28 joint count-C-reactive protein (DAS28-CRP) over time • Proportion of patients with DAS28-CRP below 2.6 • Mean change from baseline in Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) Hand-Wrist assessments of synovitis or osteitis at Week 12 • Proportion of patients with American College of Rheumatology (ACR)20/50/70 over time
	• To assess the PK of ATI-450 in patients with moderate to severe RA who are receiving concomitant MTX	• ATI-450 concentrations at trough and 2 hours post-dose
Exploratory	• To assess the PD of ATI-450 plus MTX in patients with moderate to severe RA	• Mean change from baseline in endogenous cytokine levels (e.g. TNF-α, IL-1β, IL-6, IL-8. IFNγ, IL-17, IL-18, IL-10, IL-1α, and IL-1RA) • Mean change from pre-dose in ex vivo stimulated cytokine levels (e.g. TNF-α, IL-1β, IL-6, IL-8, IFNγ, IL-17, IL-18, IL-10, IL-1RA and IL-1α) • Ex vivo stimulated phosphoprotein modulation

		• Mean change from baseline in the cartilage loss score (CARLOS) Hand-Wrist magnetic resonance imaging (MRI) assessment of cartilage loss

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, randomized, investigator- and patient-blind, sponsor-unblinded, parallel group, placebo-controlled study to investigate the safety, tolerability, PK, and PD of ATI-450 plus MTX versus MTX alone in patients with moderate to severe RA.

Approximately 25 patients are planned to be enrolled with the expectation that at least 15 patients will complete the 12-weeks of treatment. The study will consist of an up to 28-day screening period, a 12-week treatment period, and a 4-week follow-up period. The total duration of the study for patients remaining in the study until their final follow-up assessment will be up to 20 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 period each patient will be required to have all assessments performed as outlined in the Schedule of Assessments (Table 1). The MRI is not to be performed until the site obtains the results of the patient's hsCRP level to ensure that this assessment meets entry criteria prior to performing the MRI. The patient will have the RAMRIS Hand-Wrist assessment performed at their local institution and evaluated by a central radiology review team to determine if they meet the radiological inclusion criteria. Results for all of the screening assessments must be available at the time patient eligibility is reconfirmed prior to randomization and dosing.

Patients whose eligibility is confirmed at baseline will be randomized in a 3:1 ratio to receive either ATI-450 tablets (50 mg BID) plus MTX, or matching placebo tablets plus MTX. Study medications will be administered orally for 12 weeks. Patients will be required to remain on a stable dose of MTX (7.5 mg to 25 mg/week) and a stable dose of folic or folinic acid (≥ 5mg/week) for the duration of the study.

Patients will attend clinic visits on Days 7, 14, 28, 42, 56, and 84 (±1 day) for safety, efficacy, PK, and PD assessments. The morning dose of study medication will be administered in the clinic on each study visit day.

After 4 weeks of treatment (Day 28), each patient's safety data (e.g., AEs, laboratory values, vital signs, ECGs) will be reviewed by the Aclaris medical monitor and the Aclaris safety physician to ensure that the patient is tolerating the treatment regimen and is deemed suitable to continue treatment for the next 8 weeks. This review is described in more detail in the study-specific safety management plan.

End of study assessments will be conducted on Day 84 (Week 12). A safety follow-up visit will be conducted 30 days (+7 days) after the last dose of study medication.

The study is randomized and blinded to the investigator, patient, site personnel and Aclaris clinical monitors involved in site and patient monitoring with regard to ATI-450 and placebo to prevent bias in treatment allocation and in the assessment of treatment effect. See Section 6.2 for details on access to the treatment codes in the event of emergency unblinding. The Aclaris statistician, medical and safety monitor will be unblinded to each patient's treatment assignment.

3.2 Discussion of Study Design

The study is designed to assess the safety and tolerability of ATI-450 in a relevant patient population (i.e., patients with RA).

The study will also describe the PK and PD of ATI-450 in a relevant disease. The efficacy hypothesis to be explored is described in Section 1.2 and provides justification for recruiting a population with active RA and elevated hsCRP.

Investigator and patient blinding will maintain integrity for assessments of safety and AEs. The 3:1 randomization schedule will maximize the number of patients receiving active drug to allow for a more robust assessment for the change from baseline in hsCRP.

The 12-week treatment period is sufficient to explore the tachyphylaxis signal (observed within that timeframe by p38 MAPK inhibitors). Treatment of all patients with MTX ensures that all patients will receive active treatment for their RA throughout the study.

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. Able to comprehend and be willing to sign the Institutional Review Board (IRB) approved subject informed consent form (ICF) prior to the administration of any study-related procedures.
2. Diagnosis of adult-onset RA as defined by the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria.

[redacted]

6. Patients must have definitive intra-articular synovitis or osteitis defined as a score of 1 or greater on a Hand-Wrist MRI as assessed by central imaging reader (using RAMRIS).
7. On a stable MTX dose (defined as 7.5 mg to 25 mg weekly) and a stable dose of folic or folinic acid (defined as ≥ 5mg/week) for at least 4 weeks prior to the screening visit.
8. Male or non-pregnant, non-nursing female patients between 18 and 70 years of age, inclusive.
    - Female patients that 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
9. Female patients must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to dosing on Day 1.
10. Screening laboratory evaluations (hematology, chemistry, coagulation, and urinalysis) must fall within the normal range of the central laboratory's reference ranges unless the results have been determined by the investigator to not be clinically significant.
11. Willing and capable of taking appropriate coronavirus disease 2019 (COVID-19) risk mitigation precautions (e.g., wearing a mask in public, adhering to social

distancing, etc.) as recommended or required by local, state, or federal guidelines during participation in the study.

*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. The requirements for highly effective birth control do not apply to female patients of nonchildbearing potential (i.e., physiologically incapable of becoming pregnant) defined as:

- Has had a complete hysterectomy greater than or equal to 3 months prior to dosing or
- Has had a bilateral oophorectomy (ovariectomy) or
- Has had a bilateral tubal ligation or fallopian tube inserts or
- Is postmenopausal (i.e., cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level >40 mIU/mL) or
- Medically documented ovarian failure

4.2 Exclusion Criteria

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

1. Patient has a current acute or chronic immunoinflammatory disease other than RA which may impact the course or assessment of RA.
2. Patient has an uncontrolled non-immunoinflammatory disease that may place the patient at increased risk during the study or impact the interpretation of results.
3. History or evidence of active or latent tuberculosis (TB).
4. Known hypersensitivity to MTX or ATI-450.
5. Patient has either a history of alcoholism/current alcoholic, alcoholic liver disease, or other chronic liver disease.
6. Active infection requiring treatment with antibiotics.
7. Positive for HIV, hepatitis B or C. Patients with serologic evidence of hepatitis B vaccination (hepatitis B surface antibody without the presence of hepatitis B surface antigen) will be allowed to participate.
8. 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

- 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) ≥1.5×upper limit of normal (ULN)
- Total bilirubin level ≥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

9. 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.
10. Patient has clinically significant abnormal findings other than RA 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.
11. Patient has a clinically important history of a medical disorder that would compromise patient safety or data quality (per investigator's judgment).
12. Blood pressure levels (in supine position after at least 5 minutes rest): <90 mmHg or >140 mmHg for systolic blood pressure or <40 mmHg or >90 mmHg for diastolic blood pressure.
13. Has taken any of the following within the defined time period prior to screening visit:

    - Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) (leflunomide, cyclosporine, azathioprine): 30 days
    - Rituximab or other B cell inhibitors: 6 months
    - Biologic DMARDs (infliximab, golimumab, adalimumab, certolizumab pegol, abatacept, and tocilizumab): 8 weeks
    - Etanercept and anakinra: 4 weeks
    - Janus kinase (JAK) inhibitors: 30 days
    - Investigational small molecules: 30 days

- Intra-articular corticosteroid injection: 30 days

14. Are currently receiving corticosteroids at doses greater than 10 mg per day of prednisone (or equivalent) or have been receiving an unstable dosing regimen of corticosteroids within 2 weeks of the screening visit.
15. Have started treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or have been receiving an unstable dosing regimen of NSAIDs within 2 weeks of the screening visit.
16. Patients with history of stroke.
17. Significant cardiac disease that would affect interpretation of study data or the safety of the patient's participation in the study, per judgment of the investigator, including recent myocardial infarction or unstable angina, or heart failure with New York Heart Association Class III or IV symptoms.
18. 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
19. Any joint procedure in past 90 days prior to screening
20. Known exposure to an individual with a confirmed, active diagnosis of COVID-19 at any time during the screening period.
21. Vaccination with a live or attenuated vaccine within 6 weeks prior to Baseline (Visit 2) or planned vaccination with these vaccines at any time during treatment or within 6 weeks following discontinuation of study medication.

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 randomized 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 retested once during the 28-day screening period. If the repeated lab values remain exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since the previous result was never obtained.

Patients that screen fail for the study may be re-screened at a later date (i.e., after the 28-day screening window has expired) following re-consent. A new patient ID must be assigned in this instance.

4.4 Premature Discontinuation

4.4.1 Premature Discontinuation of Investigational Product

Patients should discontinue the study medication if any of the following occurs:

- Confirmed, active infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus
- 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
- 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.

The investigator will make every effort to ensure that patients who prematurely discontinue study medication complete the Day 84, end of study assessments.

Patients who discontinue study medication 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
- Severe AEs or SAEs
- Any other reason relating to the patient's safety or 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 (Week 12) visit; 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, 2 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 RA disease phenotype and duration as well as date of first diagnosis and previous treatments including any previous biologic or non-biologic therapy for RA will be recorded in the electronic case report form (eCRF).

At the baseline visit, inclusion/exclusion criteria will be reviewed and updated to ensure the patient remains qualified for the study. Significant findings that are observed after the patient has signed the ICF and prior to the first dose of study medication will be recorded as medical history on the eCRF. Any event observed after the patient has signed the ICF that meets the definition of a SAE will be recorded on the SAE eCRF.

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, lipids, FSH, hepatitis B surface antigen, 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 study medication to test for the presence of the SARS-CoV-2 virus. The sample will be sent to the study's central lab for analysis by reverse transcription polymerase chain reaction (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 study medication treatment in the absence of central laboratory or locally equivalent testing being performed.

Patients are allowed to dose with study medication 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 study medication 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 post-treatment follow-up Visit 9 (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 SAEs 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 AE per the requirements of Section 7 of this protocol.

5.2 Efficacy Assessments

[redacted]

[redacted]

[redacted]

5.2.4 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.

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.

[redacted]

[redacted]

5.2.5 *Physician Completed Efficacy Questionnaire*

When this assessment is required at the times indicated in Table 1, it should be one of the first assessments done at the visit, and must be completed prior to drug dosing.

[redacted]

5.2.6 *High Sensitivity C-reactive Protein*

Blood samples for evaluation of hsCRP 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 samples for hsCRP will be provided in a separate laboratory manual.

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 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, creatinine, hsCRP, gamma glutamyltransferase, glucose, inorganic phosphatase, lactate dehydrogenase, lipase, magnesium, potassium, 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 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 8 (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

12-lead ECG will be obtained as outlined in Table 1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

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 BP, 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 RA.

Body weight and height (height at screening only) 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).

[redacted]

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
[redacted]	[redacted]

Placebo

Substance:	Placebo
Strength:	Not applicable
Mode of administration:	Matching oral tablets
[redacted]	[redacted]

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). [redacted]

6.1.3 Packaging, Labeling, and Shipment

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

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

Study medications 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.

The sponsor or designee will supply the study medications. MTX and folic/folinic acid will be obtained locally by the site.

6.2 Blinding

The investigators, study personnel, and the study patients will remain blinded to treatment allocation as will sponsor personnel responsible for monitoring the clinical data. The Aclaris statistician, medical and safety monitor will be unblinded to each patient's treatment allocation.

6.4 Dose and Administration

ATI-450 will be administered as oral tablets for a total of 100 mg daily. Doses will be administered BID (50 mg×2). Matching placebo tablets will be administered in the same manner.

6.5 Precautions and/or Lifestyle Considerations

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

[redacted]

6.7 Concomitant Medication

See Section 4 for details of medication that is permitted or prohibited according to the inclusion and exclusion criteria.

[redacted]

[redacted]

6.8 Vaccine Guidelines

Vaccination with live or attenuated components is prohibited during the study and for 6 weeks after the last dose of study medication. Similarly, current routine household contact with children and others vaccinated with live or attenuated vaccine components should be avoided during treatment and for 6 weeks following completion of the study.

Some of these vaccines include varicella ("chickenpox") vaccine, oral polio vaccine, and the inhaled flu vaccine.

Following vaccination with live or attenuated component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted. General guidelines suggest that exposure should be avoided following vaccination with these vaccines for the stated time period:

- Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination;
- Oral polio vaccination for 6 weeks following vaccination;
- Attenuated rotavirus vaccine for 10 days following vaccination;
- Inhaled flu vaccine for 1 week following vaccination.

6.9 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.

6.10 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 (ATI-450 or placebo) 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.

Weekly dose of MTX and folic/folinic acid will be recorded at the clinic visits in the eCRF.

6.11 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 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 study drug administration whichever is later. Reporting of AEs will begin when the patient receives the first dose of study medication 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:

   [redacted]

   [redacted]
3. Print a copy of the email confirmation from [redacted] 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 [redacted] (Aclaris Therapeutics, Inc. safety monitor).
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 Therapeutics, Inc. 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 Therapeutics, Inc. 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/Independent Ethics Committee (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.

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

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

[redacted]

8.4 Statistical Methods

[redacted]

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. 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 through the completion of the last follow up visit or before the date of last administration of study medication + 30 days (whichever is later). 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, and disease characteristics) will be presented descriptively.

8.4.4 Drug Concentration

Plasma concentrations of ATI-450 will be summarized by nominal timepoint and day. Trough concentration versus time (Days 7, 14, 28, 42, 56, and 84) and concentration versus time (0 and 2 hours post-dose) by day (Days 1 and 84) will be displayed by linear scale.

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.

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 Therapeutics, Inc., 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 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 CRFs, verification of CRF data against original source documents, and occurrence of AEs. The investigator must agree to sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the investigator will assist with the sponsor's monitoring activities.

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

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/rechallenge** participant with study treatment unless allowed per-protocol and sponsor approval **is granted**. • If restart/rechallenge 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, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and	• Viral hepatitis serology[3] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for ATI-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 high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or

perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	likely acetaminophen use in the preceding week.[9])

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; hepatitis B surface antigen (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.

17 REFERENCES

1 Genovese MC, Cohen SB, Wofsy D, Weinblatt, ME, Firestein, GS, Brahn E, Strand V, Baker DG, Tong SE. 2011. A 24-week, randomized, double-blind, placebo-controlled, parallel group study of the efficacy of oral SCIO-469, a p38 mitogen-activated protein kinase inhibitor, in patients with active rheumatoid arthritis. J Rheumatol 38(5):846-54.

2 Alten RE, Zerbini C, Jeka S, Irazoque F, Khatib F, Emery P, Bertasso A, Rabbia M, Caulfield JP. Efficacy and safety of pamapimod in patients with active rheumatoid arthritis receiving stable methotrexate therapy. 2010. Ann Rheum Dis, 69(2):364-7.

3 Cohen SB, Cheng TT, Chindalor V, Damjanov N, Burgos-Vargas R, DeLora P, et al. 2009. Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis. Arthritis Rheum 60:335-44.

4 Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, Kirkpatrick J. 1995. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 38(1):38-43.

5 Prevoo MLL, van T Hof MA, Kuper HH, van Keeuwen MA, van de Putte LBA, van Riel PLCM. 1995. Modified Disease Activity Scores that include twenty-eight joints. Arthritis & Rheumatism 38(1):44-48.

6 Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T. Michaud K, Saag KG, O'Dell JR, Kazi S. 2012. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken) 64(5):640-7.

7 Perterfy CG, Olech E, DiCarlo JC, Merrill JT, Countryman PJ, Gaylis NB. 2013. Monitoring cartilage loss in the hands and wrists in rheumatoid arthritis with magnetic resonance imaging in a multi-center clinical trial: IMPRESS (NCT00425932). Arthritis Research & Therapy, 15:R44.

8 Beals C, Baumgartner R, Peterfy C, Balanescu A, Mirea G, Harabagiu A, et al. 2017. Magnetic resonance imaging of the hand and wrist in a randomized, double-blind, multicenter, placebo-controlled trial of infliximab for rheumatoid arthritis: Comparison of dynamic contrast enhanced assessments with semi-quantitative scoring. PLoS ONE 12(12):e0187297.

9 James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. 2009. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 37:1779-1784.