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Protocol ATI-450-RA-202 - Version 7.0

NCT #: NCT05279417

TITLE PAGE

Protocol Title: A Phase 2b, Randomized, Multicenter, Double-blind, Parallel Group, Placebo Controlled, Dose Ranging Study to Investigate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ATI-450 Plus Methotrexate (MTX) Versus Placebo Plus MTX in Patients with Moderate to Severe Active Rheumatoid Arthritis (RA) who have had an Inadequate Response to MTX Alone

Protocol Number: ATI-450-RA-202

Version Number: Version 7 (Amendment 6)

Product: ATI-450

Short Title: ATI-450 Plus Methotrexate (MTX) Versus Placebo Plus MTX in Patients with Moderate to Severe Active Rheumatoid Arthritis (RA) who have had an Inadequate Response to MTX Alone

Study Phase: Phase 2b

Sponsor Name: Aclaris Therapeutics, Inc.

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Regulatory Agency Identifying Number(s): IND No. 139858
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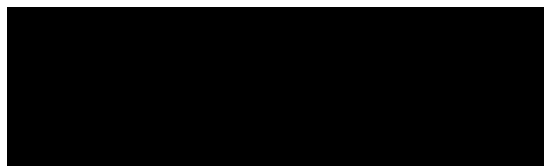
Date of Protocol: 06 June 2022 (Version 7.0)

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Sponsor Signatory

I have read this protocol in its entirety and agree to conduct the study accordingly:



6/6/2022

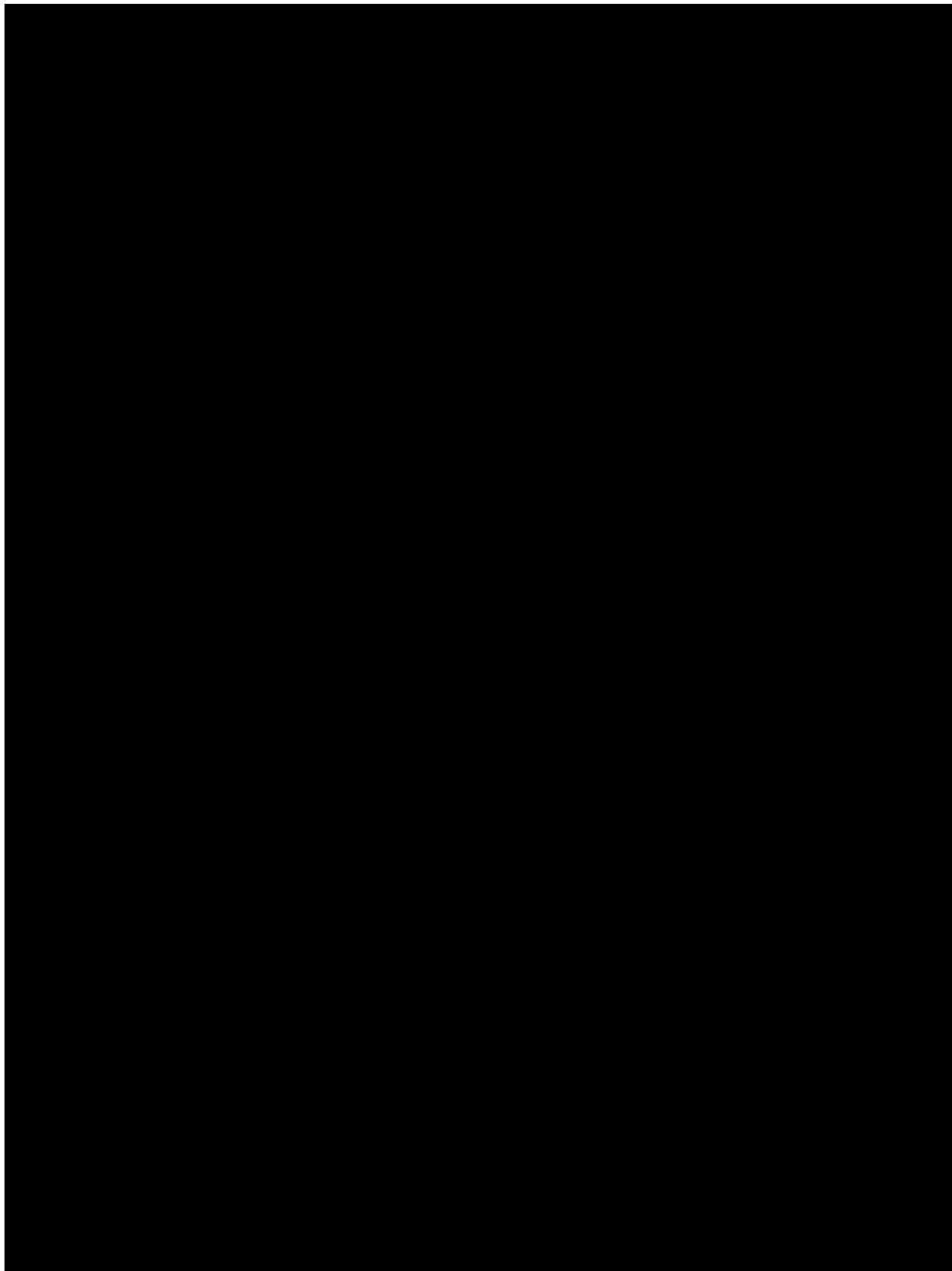
Date

Aclaris Therapeutics, Inc.

Medical Monitor name and contact information can be found in [Appendix 2](#).

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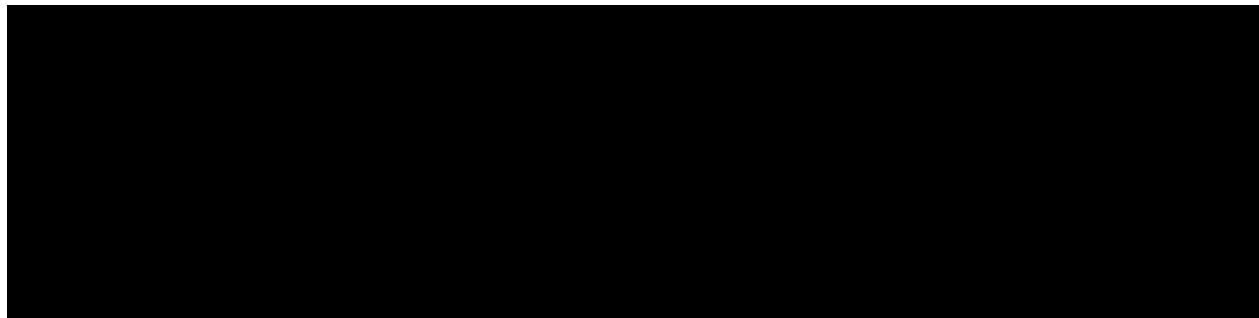


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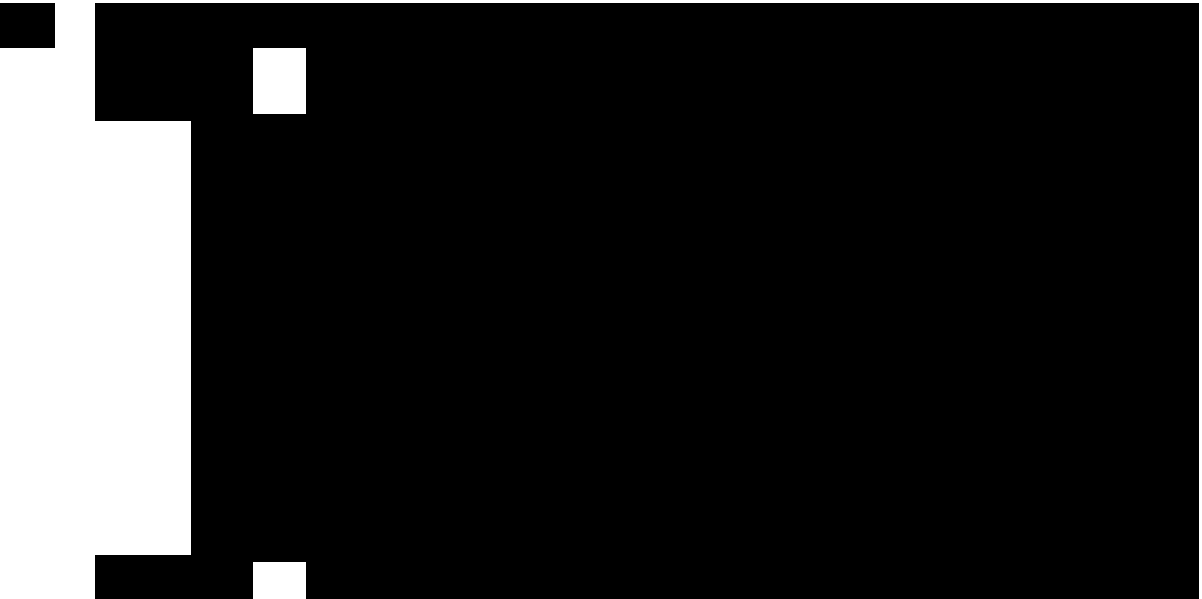
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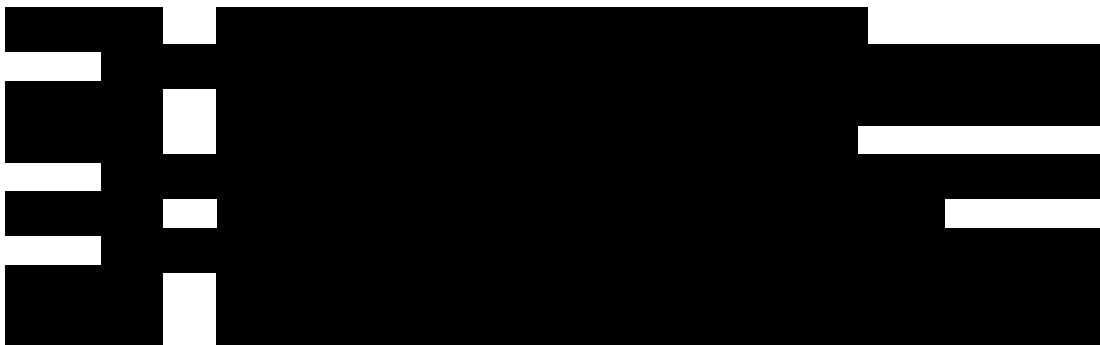
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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b, Randomized, Multicenter, Double-blind, Parallel Group, Placebo Controlled, Dose Ranging Study to Investigate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ATI-450 Plus Methotrexate (MTX) Versus Placebo Plus MTX in Patients with Moderate to Severe Active Rheumatoid Arthritis (RA) who have had an Inadequate Response to MTX Alone

Short Title: ATI-450 Plus Methotrexate (MTX) Versus Placebo Plus MTX in Patients with Moderate to Severe Active Rheumatoid Arthritis (RA) who have had an Inadequate Response to MTX Alone

Rationale: ATI-450 is an orally available, novel, potent, and selective small molecule inhibitor of the p38 α mitogen-activated protein kinase (MAPK)/MAPK-activated protein kinase 2 (MK2) inflammatory signaling pathway being developed for treatment of inflammatory disorders. The p38 MAPK pathway offers great potential in the treatment of inflammatory diseases such as RA. By targeting MK2, which is downstream from p38, it is believed that ATI-450 can effectively and safely inhibit the inflammatory pathways without substantially impacting anti-inflammatory pathways. This study is being conducted to determine the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of 12 weeks of ATI-450 exposure in combination with MTX in patients with moderate to severe active RA. These important data will further describe the efficacy and safety of ATI-450 in a relevant patient population.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of multiple doses of ATI-450 plus MTX versus placebo plus MTX in patients with moderate to severe active RA	Proportion of patients achieving ACR20 at Week 12 (see Section 8.1.10)
Secondary	
To assess the efficacy and safety of ATI-450 plus MTX in patients with moderate to severe active RA	- Proportion of patients achieving ACR50/70 at Week 12 (see Section 8.1.10) - Proportion of patients achieving ACR20/50/70 at each scheduled timepoint (Section 8.1.10) - Mean change from baseline in DAS28-CRP over time (see Section 8.1.11) - Proportion of patients achieving DAS28-CRP remission (score < 2.6) at each scheduled timepoint (see Section 8.1.11) - Proportion of patients achieving DAS28-CRP low disease activity (score $\leq$ 3.2) at each scheduled timepoint (see Section 8.1.11) - Mean change from baseline in CDAI over time (see Section 8.1.9) - Proportion of patients achieving CDAI remission (score $\leq$ 2.8) at each scheduled timepoint (see Section 8.1.9) - Percent change from baseline in hsCRP level at each scheduled timepoint (see Section 8.1.6) - HAQ-DI score over time (see Section 8.1.3)

	- SF-36v2 score over time (see Section 8.1.4) - FACIT-Fatigue score over time (see Section 8.1.5) - AEs, SAEs, vital signs, laboratory values, PEs, and ECGs (see Sections 8.2 and 8.3)
To assess the PK of ATI-450 in patients with moderate to severe active RA who are receiving concomitant MTX	Trough ATI-450 and metabolite (CDD-2164) concentrations at clinic visits. On Day 1, 8, and 85, trough and 2-hour post dose will be collected. (see Section 8.5)
To conduct dose response modeling of ATI-450 in patients with moderate to severe RA who are receiving concomitant MTX	- Proportion of patients achieving ACR20/50/70 at Week 12 (see Section 8.1.10) - Change from baseline to Week 12 in DAS28-CRP (see Section 8.1.11)
Exploratory	
To assess the PD of ATI-450 plus MTX in patients with moderate to severe active RA	

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%/50%/70% improvement criteria; AE = adverse event; CDAI = Clinical Disease Activity Index; DAS28-CRP = Disease Activity Score using 28 Joint Count-C-reactive Protein; ECG = electrocardiogram; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; HAQ-DI = Health Assessment Questionnaire Disability Index; hsCRP = high sensitivity C-reactive protein;  MTX = methotrexate; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; RA = rheumatoid arthritis; SAE = serious adverse event; SF-36v2 = Short Form-36 Health Status Survey Questionnaire Version 2; 

Overall Design:

This is a Phase 2b, randomized, multicenter, double-blind, parallel group, placebo controlled, dose ranging study to investigate the efficacy, safety, tolerability, PK, and PD of multiple doses of ATI-450 plus MTX versus placebo plus MTX in patients with moderate to severe active RA.

The study will consist of an up to 28-day Screening Period, a 12-week Treatment Period, and a 30-day Follow-up Period. Patients will attend clinic visits on Days 1, 8, 15, 29, 43, 57, and 85 (± 1 day) for safety, efficacy, PK, and PD assessments. Patients will be evaluated at a final clinic visit 30 days (+ 7 days) after the last study treatment dose to assess PD and safety.

Number of Investigators and Study Centers:

Approximately 51 Investigators and study centers are expected to participate in this study.

Number of Patients:

Approximately 240 participants will be enrolled to achieve 80 randomized patients per treatment arm.

Treatment Groups and Duration:

Eligible patients will be randomized in a 1:1:1 ratio to receive either ATI-450 tablets (20 or 50 mg twice daily [BID]) plus MTX, or matching placebo tablets BID plus MTX. The randomization of patients to treatment groups will be stratified by 2 separate factors: (1) positive for rheumatoid factor (RF) and/or anti-cyclic citrullinated protein (anti-CCP) at screening, and (2) prior biologic or Janus kinase (JAK) RA treatment. Enrollment will be limited such that $\leq 20\%$ of the study population has prior experience with either a biologic RA therapy or a JAK RA therapy. Patients with prior biologic or a JAK exposure should

have the medication name, start date, stop date, and reason for discontinuation of those therapies recorded.

Study drug will be administered orally BID for 12 weeks. Patients will be required to remain on a stable dose of MTX for the duration of the study. The dose of MTX will be 15 to 25 mg/week (10 mg/week is acceptable for patients with documented intolerance) and will have been maintained at a stable dose for 4 weeks prior to screening.

The total duration of the study for patients remaining until their final follow-up assessment will be up to 21 weeks.

Statistical Methods:

The primary statistical hypothesis to be tested in this study is the hypothesis that at least one of the ATI-450 treatment groups is superior to placebo for the treatment of RA based upon the 12-week American College of Rheumatology 20% improvement criteria (ACR20) assessment versus the null hypothesis of no difference in any of the treatment groups. Note that each ATI-450 treatment group will be compared to placebo separately (ATI-450 treatment groups will not be pooled) requiring 2 separate hypothesis tests. These hypotheses will be conducted using a two-sided testing procedure with an alpha level of 0.05. No adjustment for multiplicity will be made.

Secondary superiority hypotheses will be tested on the secondary efficacy endpoints to gather supportive evidence for the primary hypothesis. These secondary assessments will have the same null and alternatives hypotheses as the primary and will be tested using a two-sided procedure with an alpha level of 0.05.

The primary efficacy endpoint (proportion of patients achieving ACR20 at Week 12) will be analyzed using logistic regression. The statistical model will include fixed factors for treatment group and the stratum used in the randomization (positive for RF and/or anti-CCP at screening and prior biologic or JAK RA treatment). Patients with missing ACR20 values at Week 12 will be considered non-responders as will patients with confounding intercurrent events. Each study treatment dose will be compared with placebo; model-based point estimates for the treatment difference, 95% confidence intervals (CIs), and p-values will be calculated.

Secondary efficacy endpoints of the proportion of patients achieving ACR50/70 at Week 12, the proportion of patients achieving ACR20/50/70 over time, and the proportion of patients achieving Disease Activity Score using 28 Joint Count-C-reactive Protein (DAS28-CRP) remission (score < 2.6) over time and at Week 12, will be assessed using the same analysis method as used for the primary efficacy endpoint.

Continuous secondary efficacy endpoints (mean change from baseline over time in DAS28-CRP, Clinical Disease Activity Index [CDAI], Health Assessment Questionnaire Disability Index [HAQ-DI] score, Short Form-36 Health Status Survey Questionnaire Version 2 [SF-36v2] score, and Functional Assessment of Chronic Illness Therapy – Fatigue Scale [FACIT-Fatigue] score) will be analyzed using mixed model repeated measures. This model will include fixed factors for treatment group, time, treatment-by-time interaction, and the stratum used in the randomization, as well as a random effect for patient. Patients with missing continuous efficacy measures or measures following negative intercurrent events will be imputed in the Intent-to-treat (ITT) analysis using a model-based multiple imputation procedure, where applicable. Model-based point estimates and 95% CIs will be provided for treatment effects. Point estimates, 95% CIs, and p-values will be provided for treatment differences versus placebo at each time point separately.

For high sensitivity C-reactive protein (hsCRP), standard summary statistics for continuous variables will be provided, as well as the change from baseline and percent change from baseline at each post-baseline time point.

Dose response modeling will be conducted for ACR20/50/70 responder rates, the change from baseline in DAS28-CRP, and other efficacy parameters as deemed appropriate.

Safety endpoints (adverse events [AEs], exposure to study drug, clinical laboratory values, vital signs, physical examinations [PEs], and electrocardiogram [ECG] parameters) will be summarized by treatment group using the Safety Analysis Population.

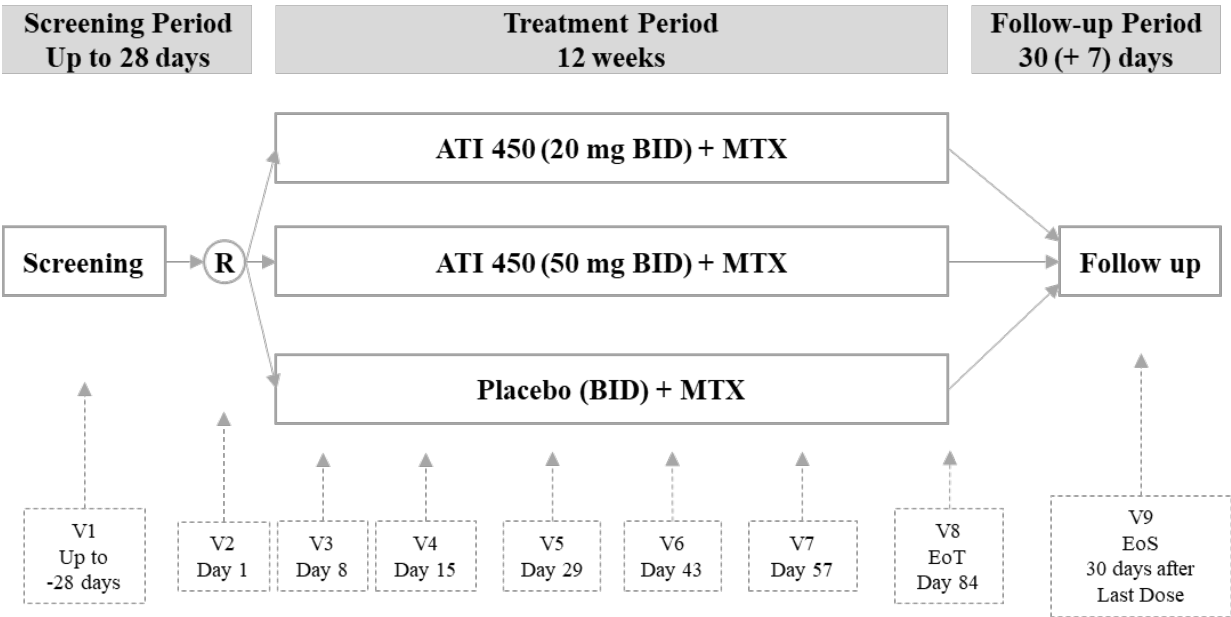
Plasma concentrations of ATI-450 and its primary circulating metabolite, CDD-2164, will be summarized by day and sample time using the PK Population. Concentration versus time since dose (Days 1, 8, 15, 29, 43, 57, and 85) will be displayed by linear scale. Population PK modeling and related exposure response modeling may be explored, as appropriate.

The exploratory PD analyses of [REDACTED] will be reported in a descriptive analysis.

Data Monitoring Committee: Yes

1.2 Schema

Figure 1 Study Schema



Abbreviations: BID = twice daily; EoT = End of Treatment; EoS = End of Study; MTX = methotrexate; R = Randomization; V = Visit

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1.3 Schedule of Activities

Table 1 Schedule of Assessments

Study Period ⁸	Screening Period	Treatment Period								Follow-up Period
Visit Number (Visit Name)	Visit 1	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 (EoT/ET)	Visit 9 (EoS)	
Visit Day (Visit Week)	Day -28 to Day -1	Day 1 ⁹	Day 8 ⁹	Day 15	Day 29	Day 43	Day 57	Day 85 (Week 12)	30 Days After Last Dose	
Visit Window	NA	NA	± 1 Day						+ 7 Days	
Assessment										
Informed Consent	X									
Eligibility Review	X	X								
Randomization		X								
Demographics	X									
Medical History; RA and Other Current Medical Conditions	X									
Patient’s Global Assessment of Disease Activity	X	X	X	X	X	X	X	X		
Patient’s Assessment of Arthritis Pain		X			X		X	X		
Patient’s Assessment of Physical Function as Measured by the HAQ-DI		X			X		X	X		
SF-36v2		X			X		X	X		
FACIT-Fatigue		X			X		X	X		
12-lead ECG ¹	X	X	X	X	X	X	X	X		
Vital Signs ²	X	X	X	X	X	X	X	X	X	
Body Weight, BMI (derived)	X							X		

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Table 1 Schedule of Assessments (Continued)

Study Period ⁸	Screening Period	Treatment Period							Follow-up Period
Visit Number (Visit Name)	Visit 1	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 (EoT/ET)	Visit 9 (EoS)
Visit Day (Visit Week)	Day -28 to Day -1	Day 1 ⁹	Day 8 ⁹	Day 15	Day 29	Day 43	Day 57	Day 85 (Week 12)	30 Days After Last Dose
Visit Window	NA	NA	± 1 Day						+ 7 Days
Assessment									
Full Physical Exam Including Height	X								
Targeted Physical Exam		X	X	X	X	X	X	X	X
Swollen (66) and Tender (68) Joint Assessment	X	X	X	X	X	X	X	X	
DAS28-CRP	X	X	X	X	X	X	X	X	
CDAI	X	X	X	X	X	X	X	X	
Physician’s Global Assessment of Disease Activity	X	X	X	X	X	X	X	X	
Laboratory Assessments: Hematology, Coagulation, Chemistry, Lipids, Urinalysis	X	X	X	X	X	X	X	X	X
hsCRP	X	X	X	X	X	X	X	X	X
Rheumatoid factor and anti-CCP	X								
HIV and Hepatitis B & C Screen	X								
SARS-CoV-2 Testing	X	X							
QuantiFERON Gold Test for TB	X								
Serum Pregnancy Test (WOCBP Only)	X								
Urine Pregnancy Test (WOCBP Only)		X	X	X	X	X	X	X	X

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Table 1 Schedule of Assessments (Continued)

Study Period ⁸	Screening Period	Treatment Period								Follow-up Period
Visit Number (Visit Name)	Visit 1	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 (EoT/ET)	Visit 9 (EoS)	
Visit Day (Visit Week)	Day -28 to Day -1	Day 1 ⁹	Day 8 ⁹	Day 15	Day 29	Day 43	Day 57	Day 85 (Week 12)	30 Days After Last Dose	
Visit Window	NA	NA	± 1 Day						+ 7 Days	
Assessment										
Blood Sampling for PK		X ³	X ³	X ⁴	X ⁴	X ⁴	X ⁴	X ³		
Dispense Study Drug		X	X	X	X	X	X			
Dispense and Review Patient Diary	X	X	X	X	X	X	X	X		
Administration of Morning Dose of Study Drug in Clinic		X	X	X	X	X	X	X ⁶		
Drug Accountability			X	X	X	X	X	X		
Adverse Events ⁷	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; anti-CCP = anti-cyclic citrullinated peptide; BMI = body mass index; CDAI = Clinical Disease Activity Index; DAS28-CRP = Disease Activity Score using 28 Joint Count-C-reactive protein; ECG = electrocardiogram; EoS = End of Study; EoT = End of Treatment; ET = Early Termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; HAQ-DI = Health Assessment Questionnaire Disability Index; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; RA = rheumatoid arthritis; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SF-36v2 = Short Form-36 Health Status Survey Questionnaire Version 2; TB = tuberculosis; WOCBP = women of childbearing potential.

¹ Triplicate 12-lead ECGs will be performed at the indicated timepoints at least 30 seconds apart, in a supine position, after resting for at least 10 minutes without external stimulation, e.g., talking, TV, noise, and submitted for central reading. Screening ECGs should be performed prior to collection of vital signs and blood samples for laboratory tests. On Days 1 and 8, ECGs will be taken predose and 2 hours postdose. Patients not fasting on Days 1 and 8 will have an additional 4-hour postdose ECG. On Days 15, 29, 43, 57, and 85 ECGs will be performed as the last assessment in the clinic (as close to Cmax). See Section 8.2.3 for additional details on collection parameters.

² Vital signs are to be taken before blood collection for laboratory tests. See Section 8.2.2 for additional details on collection parameters.

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- ³ PK [REDACTED] blood sampling times on Days 1, 8 [REDACTED], and 85 will occur predose and 2 hours after the morning dose. Patients not fasting on Days 1 and 8 will have an additional PK sample collected at 4 hours postdose. If the patient objects to both blood draws at the 2-hour and 4-hour timepoint, the 4-hour PK sample is more important to collect. Patients must remain in the clinic until 30 minutes after the morning postdose PK blood sampling is completed.
- ⁴ PK [REDACTED] blood sampling will occur prior to the morning dose on Days 15, 29, 43, and 57.
- ⁶ The last dose of study drug will be administered in the clinic on Day 85. The second dose of study drug is not to be administered on Day 85.
- ⁷ Serious AE reporting will start at the time of consent. Any AE that occurs between the time of consent and prior to dosing on Day 1 will be recorded as medical history. Treatment-emergent AEs will be collected following the first dose of study drug on Day 1 through the Follow-up Visit (30 days after the last administration of study drug).
- ⁸ Unscheduled visits are allowed, as deemed necessary by the Investigator, in the event that assessments need to be repeated (eg, lab draws), safety follow-up needs to be conducted, or additional dispensing activities need to occur.
- ⁹ Patient should be fasted for visits on Days 1 and 8, defined as no food in previous 8 hours. A snack is permitted 2 hours after the morning dose.

2.0 INTRODUCTION

ATI-450 is an orally available, novel, potent, and selective small molecule inhibitor of the p38 α mitogen-activated protein kinase (MAPK)/MAPK-activated protein kinase 2 (MK2) inflammatory signaling pathway being developed for treatment of inflammatory disorders.

2.1 Study Rationale

The p38 MAPK pathway offers great potential in the treatment of inflammatory diseases such as rheumatoid arthritis (RA). By targeting MK2, which is downstream from p38, it is believed that ATI-450 can effectively and safely inhibit the inflammatory pathways without substantially impacting anti-inflammatory pathways. This study is being conducted to determine the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of 12 weeks of ATI-450 exposure in combination with methotrexate (MTX) in patients with moderate to severe active RA. These important data will further describe the efficacy and safety of ATI-450 in a relevant patient population.

2.2 Background

RA affects 0.5% to 1.0% of the adult population ([Sparks 2019](#)) and is characterized by the polyarticular synovitis with a prominent inflammatory and mesenchymal tissue reaction in the synovium, causing pain, swelling, stiffness and bone and cartilage destruction. In patients with RA, synovial fluid is enriched with neutrophils, macrophages, T cells and dendritic cells. Many of these cells have an activated phenotype, expressing high levels of human leukocyte antigen class II antigens and adhesion molecules, and produce most of the known cytokines and chemokines.

The Sponsor is developing ATI-450, an orally available, small molecule inhibitor of the p38 α MAPK/MK2 inflammatory signaling pathway. The p38 MAPK signaling pathway has long been a target for therapeutic intervention for inflammatory diseases owing to its involvement in the regulation and the expression of multiple cytokines and other inflammatory signals ([Saklatvala 2004](#); [Schett et al., 2008](#)). Key inflammatory cytokines driven by this pathway include tumor necrosis factor- α (TNF- α) as well as interleukins (IL) IL-1 α , IL-1 β , and IL-6. The involvement of these cytokines in a variety of diseases, including RA, has been demonstrated by successful treatment of inflammatory disease with anti-TNF- α monoclonal antibodies, antagonists of the IL-1 receptor, anti-IL-1 β monoclonal antibodies, and anti-IL-6 receptor monoclonal antibodies ([Ruocco et al., 2009](#); [Patel et al., 2015](#); [Kimball et al., 2016](#); [Kullenberg et al., 2016](#); [Broderick et al., 2015](#); [Kanni et al., 2018](#); [Maarouf et al., 2018](#)). However, a drawback of biologics is that they require self-administered injections, and many patients prefer oral options. Thus, identification of orally available small molecule therapeutics would add to the available treatment modalities.

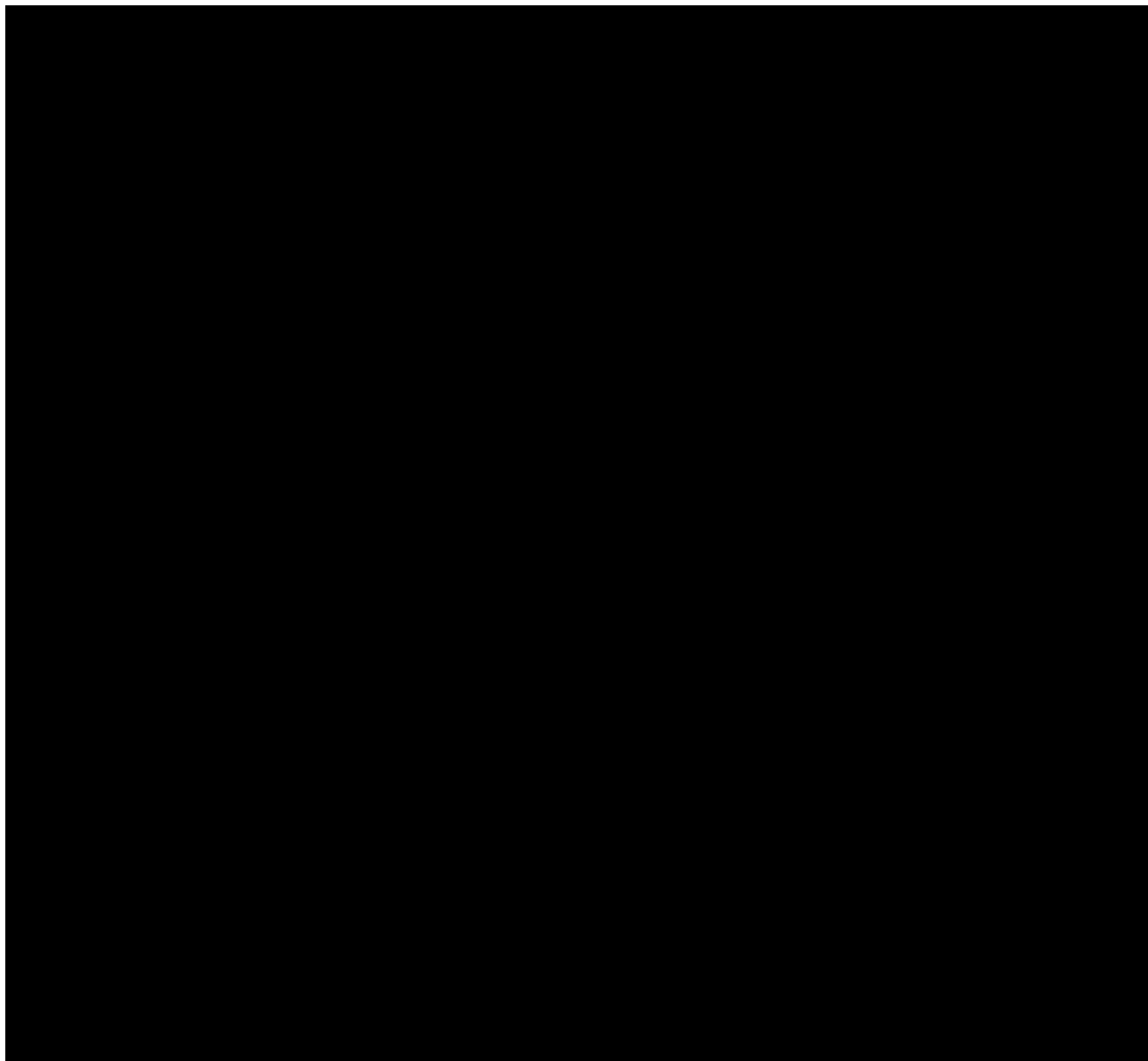
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ATI-450 has a novel mechanism of action in that it targets the high affinity docking interaction between p38 α MAPK and MK2 ([Wang et al., 2018](#)). Upon binding to the interface created upon formation of this bimolecular complex, ATI-450 blocks MK2 phosphorylation by p38 MAPK and thereby the downstream MK2-mediated inflammatory drive. ATI-450 shows low potency for inhibition of p38 α phosphorylation/activation of alternate substrates and is selective across the human kinome.

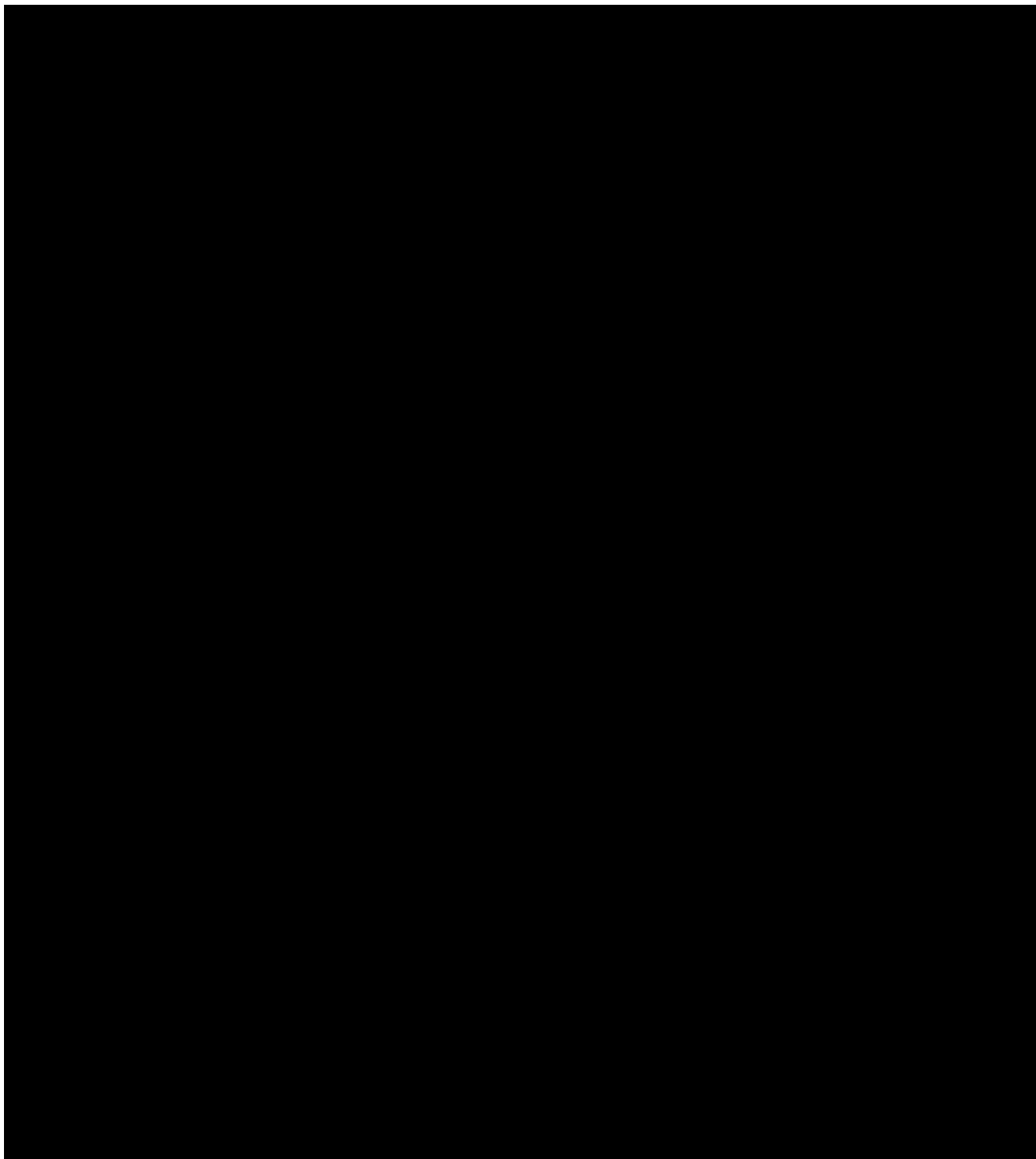
The Sponsor is developing ATI-450 for potential treatment of inflammatory disorders such as RA in which anti-TNF- α and anti-IL-1 β biotherapeutics have shown themselves to be efficacious. Additional information regarding nonclinical and clinical experience with ATI-450 can be found in the Investigator's Brochure (IB).

2.3



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3.0 OBJECTIVES AND ENDPOINTS

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of multiple doses of ATI-450 plus MTX versus placebo plus MTX in patients with moderate to severe active RA	Proportion of patients achieving ACR20 at Week 12 (see Section 8.1.10)
Secondary	
To assess the efficacy and safety of ATI-450 plus MTX in patients with moderate to severe active RA	- Proportion of patients achieving ACR50/70 at Week 12 (see Section 8.1.10) - Proportion of patients achieving ACR20/50/70 over time (Section 8.1.10) - Mean change from baseline in DAS28-CRP over time (see Section 8.1.11) - Proportion of patients achieving DAS28-CRP remission (score < 2.6) over time and at Week 12 (see Section 8.1.11) - Proportion of patients achieving DAS28-CRP low disease activity (score ≤ 3.2) over time and at Week 12 (see Section 8.1.11) - Mean change from baseline in CDAI over time (see Section 8.1.9) - Proportion of patients achieving CDAI remission (score ≤ 2.8) over time and at Week 12 (see Section 8.1.9) - Percent change from baseline in hsCRP level over time (see Section 8.1.6) - HAQ-DI score over time (see Section 8.1.3) - SF-36v2 score over time (see Section 8.1.4) - FACIT-Fatigue score over time (see Section 8.1.5) - AEs, SAEs, vital signs, laboratory values, PEs, and ECGs (see Sections 8.2 and 8.3)
To assess the PK of ATI-450 in patients with moderate to severe active RA who are receiving concomitant MTX	Trough ATI-450 and metabolite (CDD-2164) concentrations at clinic visits. On Days 1, 8, and 85, trough and 2-hour post dose will be collected. (see Section 8.5)
To conduct dose response modeling of ATI-450 in patients with moderate to severe RA who are receiving concomitant MTX	- Proportion of patients achieving ACR20/50/70 at Week 12 (see Section 8.1.10) - Change from baseline to Week 12 in DAS28-CRP (see Section 8.1.11)

Table 2 Study Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
To assess the PD of ATI-450 plus MTX in patients with moderate to severe active RA	

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%/50%/70% improvement criteria; AE = adverse event; CDAI = Clinical Disease Activity Index; DAS28-CRP = Disease Activity Score using 28 Joint Count-C-reactive Protein; ECG = electrocardiogram; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; HAQ-DI = Health Assessment Questionnaire Disability Index; hsCRP = high sensitivity C-reactive protein; [REDACTED]; MTX = methotrexate; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; RA = rheumatoid arthritis; SAE = serious adverse event; SF-36v2 = Short Form-36 Health Status Survey Questionnaire Version 2; [REDACTED]

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 2b, randomized, multicenter, double-blind, parallel group, placebo controlled, dose ranging study to investigate the efficacy, safety, tolerability, PK, and PD of multiple doses of ATI-450 plus MTX versus placebo plus MTX in patients with moderate to severe active RA.

The study will consist of an up to 28-day Screening Period, a 12-week Treatment Period, and a 30-day Follow-up Period. The total duration of the study for patients remaining until their final follow-up assessment will be up to 21 weeks.

The Investigator will obtain the signed informed consent form (ICF) 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 (SoA; [Table 1](#)). Results of all 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 1:1:1 ratio to receive either ATI-450 tablets (20 or 50 mg BID) plus MTX, or matching placebo tablets BID plus MTX. The randomization of patients to treatment groups will be stratified by 2 separate factors: (1) positive for rheumatoid factor (RF) and/or anti-cyclic citrullinated protein (anti-CCP) at screening, and (2) prior biologic or Janus kinase (JAK) RA treatment. Enrollment will be limited such that $\leq 20\%$ of the study population has prior experience with either a biologic RA therapy or a JAK RA therapy. Patients with prior biologic or a JAK exposure should have the medication name, start date, stop date, and reason for discontinuation of those therapies recorded.

Study drug will be administered orally BID for 12 weeks. Patients will be required to remain on a stable dose of MTX for the duration of the study. The dose of MTX will be 15 to 25 mg/week (10 mg/week is acceptable for patients with documented intolerance) and will have been maintained at a stable dose for 4 weeks prior to screening.

Patients will attend clinic visits on Days 1, 8, 15, 29, 43, 57, and 85 (± 1 day) for safety, efficacy, PK, and PD assessments. The morning dose of study drug will be administered in the clinic on each study visit day.

On Day 85 (± 1 day; Week 12), patients will complete the End of Treatment Period assessments. A safety Follow-up Visit will be conducted 30 days (+ 7 days) after the last dose of study drug for patients who complete the Treatment Period as well as those who discontinue early. See [Section 7.0](#) for specific considerations to be taken with patients that discontinue study drug prematurely.

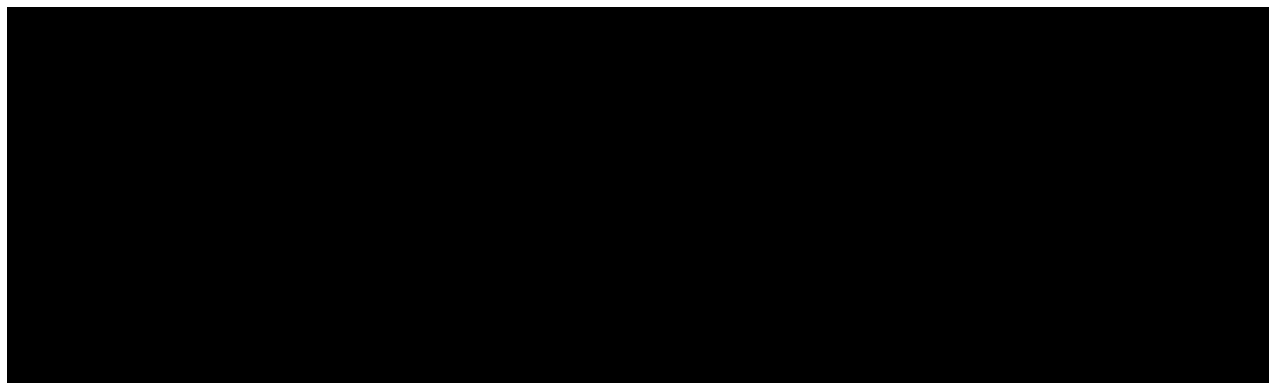
4.2 Scientific Rationale for Study Design

A parallel group, randomized, double-blind, placebo controlled study design is a conventional and well-established design to assess efficacy and safety of new treatments in RA. The study design, including dosing, endpoints, and timing of assessments follows the US Food and Drug Administration (FDA) Draft Guidance for Industry (May 2013, Revision 1): “*Rheumatoid Arthritis: Developing Drug Products for Treatment*”. The study design is also consistent with the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (14 December 2017) “*Guideline on Clinical Investigation of Medicinal Products for the Treatment of Rheumatoid Arthritis*” (CPMP/EWP/556/95 Rev. 2).

Sample size justification is provided in Section [9.3](#).

4.3





4.4 End of Study Definition

A patient is considered to have completed the study if he/she has completed all study visits. For the purposes of this study, the End of Study (EoS) date for an individual patient will be the last date of successful contact for study purposes including non-clinic follow-ups (eg, phone call for patients lost to follow-up, continued follow-up on outstanding AE/SAE post Visit 9, etc.). 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.

5.0 STUDY POPULATION

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

5.1 Inclusion Criteria

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

1. Able to comprehend and be willing to sign the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved patient 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.
3. Have active moderate to severe RA defined by DAS28-CRP ≥ 3.2 (moderate to high disease activity) at Screening.
4. Have active moderate to severe RA as defined by the following minimum disease activity criteria:
 - ≥ 6 swollen joints (based on 66 joint counts) at Screening and Baseline Visits; and
 - ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
 - hsCRP $>$ ULN OR positive for both RF and anti-CCP at screening.
5. A minimum of 12 weeks on MTX with a stable MTX dose (defined as 15 to 25 mg/week or 10 mg/week for patients with documented intolerance) for ≥ 4 weeks prior to screening.
6. Stable dose of folic acid or folinic acid (defined as ≥ 5 mg/week) for ≥ 4 weeks prior to screening.
7. Male or non-pregnant, non-nursing female patients between 18 and 75 years of age, inclusive, at the time of signing the ICF.
 - Heterosexually active female patients who are of childbearing potential must use 2 methods of highly effective contraception, 1 of which must be a physical barrier for the duration of the study and for 180 days after the last dose consistent with the MTX product label (see [Appendix 7](#)).
 - Heterosexually active 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 (see [Appendix 7](#)).
8. Female patients of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to dosing on Day 1.

9. Screening laboratory evaluations (hematology, coagulation, chemistry, 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.

5.2 Exclusion Criteria

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

1. Current acute or chronic immunoinflammatory disease other than RA which may impact the course or assessment of RA.
2. Uncontrolled non-immunoinflammatory disease that may place the patient at increased risk during the study or impact the interpretation of results (eg, previous malignancy, recurrent infection, previous venous thromboembolism).
3. History or evidence of active tuberculosis, irrespective of prior or current treatment status; or current or prior untreated latent tuberculosis. Note: Prior latent tuberculosis with completed treatment is not an exclusion.
4. Known hypersensitivity to MTX or ATI-450.
5. History of either alcoholism/current alcoholic, alcoholic liver disease, or other chronic liver disease.
6. Active infection requiring treatment with antibiotics.
7. Active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.
8. Positive for human immunodeficiency virus (HIV) or hepatitis B or C. Note: Patients with hepatitis B surface antibody without the presence of hepatitis B surface antigen will be allowed to participate. Patients with hepatitis C antibody positive can have Hepatitis C viral load tested, if the Hepatitis C virus is undetectable and the patient has been off antivirals for 6 months, he/she may be enrolled in the study.
9. Tests performed at a central laboratory at screening that meet any of the criteria below (out of range values may be rechecked once, after consultation with the study Medical Monitor, before the patient is considered a screen failure [see Section 5.4]):
 - White blood cell count $< 3.0 \times 10^3$ cells/mm³;
 - Absolute neutrophil count $< 1.5 \times 10^3$ cells/mm³;
 - Lymphocyte count $< 0.5 \times 10^3$ cells/mm³;
 - Platelet count $< 100 \times 10^3$ cells/mm³;
 - Hemoglobin < 10 g/dL;
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 1.5 \times$ ULN;
 - Total bilirubin level $\geq 2 \times$ ULN unless patient has been diagnosed with Gilberts' syndrome and this is clearly documented; and
 - Estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m² based on Modification of Diet and Renal Disease formula.

10. Any clinically significant laboratory abnormality that would affect interpretation of study data or safety of the patient's participation in the study, per judgment of the Investigator.
11. Clinically significant abnormal findings other than RA from physical examination (PE) conducted at the Screening Visit (Visit 1) and at the Baseline Visit (Visit 2) that may affect the interpretation of study data or the safety of the patient's participation in the study, per the judgment of the Investigator.
12. Clinically important history of a medical disorder that would compromise patient safety or data quality, per judgment of the Investigator.
13. Blood pressure (BP) (in semi-supine position after ≥ 5 minutes rest): < 90 mm Hg or > 150 mm Hg for systolic BP or < 40 mm Hg or > 90 mm Hg for diastolic BP at Screening and Baseline Visits.
14. Patient has experience with > 2 biologics, > 1 JAK inhibitor, or a combination of 1 biologic experience and 1 JAK inhibitor.

[REDACTED]

[REDACTED]

16. Currently receiving corticosteroids at doses > 10 mg/day of prednisone (or equivalent) or have been receiving an unstable dosing regimen of corticosteroids within 2 weeks of screening.
17. Have started treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or have been receiving an unstable dosing regimen of NSAIDs within 2 weeks of screening. Any concomitant NSAIDs or other analgesics must be at a stable dose for at least 2 weeks prior to screening.

[REDACTED]

20. History of stroke.
21. Significant active cardiac disease, in the past 6 months, that would affect interpretation of study data or the safety of the patient's participation in the study, per judgment of the Investigator. This includes myocardial infarction, acute coronary syndrome, unstable angina, or heart failure with New York Heart Association Class II, III, or IV symptoms. In addition, patients with a personal or family history of congenital long QT syndrome, Torsades de Pointes, sustained or symptomatic VT, or unexpected sudden cardiac death, are excluded.
22. Any of the following electrocardiogram (ECG) findings at the Baseline Visits:
- Mean QTcF > 450 msec as averaged on triplicate ECGs;
 - ECG or historical evidence of Wolff-Parkinson-White Syndrome (unless ablated);
 - If atrial fibrillation or flutter is present, the mean ventricular response must be < 90 BPM and the patient must be anticoagulated according to national guidelines; and/or
 - Any other finding that is considered clinically significant.
23. Any joint surgery or procedure in the 90 days prior to screening.
24. Known exposure to an individual with a confirmed, active diagnosis of COVID-19 at any time during the Screening Period.
25. Participated in another ATI-450 clinical study.
26. History of clinically significant drug abuse within 2 years prior to screening. Note: Marijuana use is allowed, if not considered substance abuse by the investigator. If a patient uses marijuana, it is recommended that patient refrain from all marijuana use for 24 hours prior to any study site visit.
27. Uncontrolled hypokalemia (<3.8 mmol/L), or uncontrolled hypomagnesemia (< LLN).

5.3 Lifestyle Considerations

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

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1 Retesting During Screening

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

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

5.4.2 Rescreening

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

For tests to be conducted at rescreening, the medical monitor should be contacted. In general, the following guidance is recommended: If patient is rescreened within 28 days of the screening visit, the 12-lead ECG, Vital Signs, Body Weight, BMI (derived), Swollen (66) and Tender (68) Joint Assessment, DAS28-CRP, Laboratory Assessments: Hematology, Coagulation, Chemistry, Lipids, Urinalysis, hsCRP, Rheumatoid factor and anti-CCP, Serum Pregnancy Test (WOCBP Only) should be repeated and any Adverse Events and Prior and Concomitant Medications should be recorded. If rescreening is more than 28 days past the initial screening visit, all screening assessments should be repeated.

5.5 COVID-19 Guidance

5.5.1 COVID-19 Vaccination and Treatment Guidance

Prior to the Study:

While not a precondition for study participation, it is strongly recommended that patients receive vaccination against COVID-19 prior to enrolling in the study and initiation of study treatment. If possible, the first dose of study treatment should be given at least 4 weeks after completion of the patient's COVID-19 vaccination regimen (or booster shot, if applicable).

During the Study:

Prior to proceeding with COVID-19 vaccination during the study period, each patient's specific situation should be discussed with and approved by the study medical monitor. Where possible, the timing of vaccination should be planned so that a vaccination is not administered during the study treatment period.

Investigators and patients should consider the schedule of their COVID-19 vaccination (if applicable), including potential booster shots, when planning the timing of their study participation. Consideration should be given to current practice guidance (ACR or EULAR) concerning administration of COVID-19 vaccination in patients with Rheumatic and Musculoskeletal diseases. Administration of a COVID-19 vaccine should be particularly avoided during the final month of the treatment period, if possible. The effect of ATI-450 on the response to COVID-19 vaccination is unknown. The COVID-19 vaccine may lead to adverse events (fever, chills, etc.), which will need to be captured and distinguished as related to vaccine versus ATI-450.

Patient's may be treated for COVID-19 infections as needed, including with monoclonal antibody therapy, as long as the treatment is not a prohibited medication per protocol [Appendix 5](#). If a patient is treated with a protocol prohibited medication, then the study drug should be discontinued.

5.5.2 COVID-19 Testing Guidance

At the Screening Visit (Visit 1) and Baseline Visit (Visit 2) prior to the first dose of study drug, all patients must have a nasopharyngeal (preferred) or oropharyngeal swab collected 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 an acceptable diagnostic assay. Patients with positive test results at Visit 1 will be considered screen failures per the exclusion criteria for the study but may be considered for re-screening at a later date following consultation with the study Medical Monitor.

Patients are allowed to dose with study drug in the interval between sample collection at the Baseline Visit 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. The patient should be advised to begin self-isolation and self-monitoring procedures according to any applicable local, state, and/or country-specific health recommendations. Referral to an appropriate health care provider for management of the patient's COVID-19 diagnosis should also be made. The patient's COVID-19 diagnosis will be reported as medical history unless the patient's clinical course progresses such that criterion for SAE reporting is met (see [Appendix 4](#)), 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 drug administration be reported as an AE per the requirements of [Appendix 4](#) of this protocol.

In the event that a patient tests positive for the SARS-CoV-2 virus at or after Visit 2, the Investigator must consult with the study Medical Monitor to determine if the patient should continue with study medication treatment or discontinue from treatment. Determinations will be made on a case-by-case basis with the intent to minimize any increased risk for the patient.

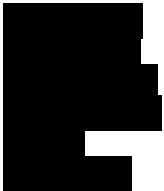
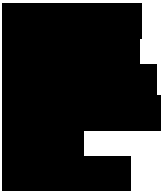
6.0 STUDY TREATMENT

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

6.1 Study Treatment(s) Administered

Study treatments are described in [Table 3](#).

Table 3 Study Treatment Details

Study Treatment Name	ATI-450	Placebo	Methotrexate	Folic Acid or Folinic Acid
Dosage Formulation	Tablet	Tablet	Tablet or Injectable Solution	Tablet/Capsule
Unit Dose Strength(s)/Dosage Level(s)	20 and 50 mg	Not applicable	Per stable dose (15 to 25 mg/week for 4 weeks prior to screening or 10 mg/week for 4 weeks prior to screening for patients with documented intolerance)	Per stable dose (≥ 5 mg/week) for 4 weeks prior to screening
Route of Administration	Oral	Oral	Oral or Subcutaneous Injection	Oral
Dosing Instructions	Take one tablet by mouth BID	Take one tablet by mouth BID	Per Package Insert, consistent with stable dose	Per Package Insert, consistent with stable dose
Packaging and Labeling			Marketed product	Marketed product
Manufacturer			Site to source/script	Sites to source/script

Abbreviation: BID = twice daily.

6.2 Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

ATI-450 and placebo will be stored under controlled conditions according to the storage requirements described on the label(s).

The Investigator (or designee) will instruct patients to store the study drug in accordance to the instructions on the label(s).

Only patients enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drug using the Drug Accountability Form. These forms must be available for inspection at any time.

Additional instructions regarding study drug preparation and handling can be found in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

All patients will be centrally assigned to randomized study treatment using an Interactive Voice/Web Response System (IxRS). Before the study is initiated, access instructions and directions for the IxRS will be provided to each study center.

Study treatment will be dispensed at the study visits summarized in the SoA ([Table 1](#)). Refer to the study Pharmacy Manual for specific guidelines concerning dispensing and accountability procedures for study treatment.

Patients will be randomized to study treatment via stratified randomization using 2 separate stratification factors:

- positive for RF and/or anti-CCP at screening; and
- prior biologic or JAK RA treatment.

This is a double-blind study with limited access to the randomization code. The ATI-450 and placebo tablets will be identical in physical appearance. The treatment each patient will receive will not be disclosed to the Investigator, study center staff, patient, or Sponsor. The treatment codes will be available to a limited number of third party vendor personnel (IxRS administrative

personnel, Clinical Supplies Management personnel, and unblinded Biostatistician) and Data Safety Monitoring Board (DSMB) members, as necessary, for them to support their functions on the study.

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

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departure from the intended regimen must be recorded in the eCRF.

At each visit, prior to dispensing study treatment, previously dispensed study treatment will be retrieved by the Investigator and compliance assessed both through tablet counting and review of a dosing diary completed by the patient. Patients exhibiting poor compliance as assessed by tablet counts and diary completion should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking < 80% or > 120% of study treatment during any evaluation period (visit to visit). See Section 8.4 regarding treatment of ATI-450 overdose.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment (within 14 days before the time of enrollment) or receives during the study must be recorded on the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates and times (if available); and
- Dosage information including dose and frequency.

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

To be eligible to participate in the study, patients must have received a minimum of 12 weeks of treatment with MTX with a stable MTX dose (defined as 15 to 25 mg/week or 10 mg/week for

patients with documented intolerance) for at least 4 weeks prior to the Screening Visit. Patients must have also received stable dose of folic or folinic acid (defined as ≥ 5 mg/week) for at least 4 weeks prior to the Screening Visit.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.5.1 Rescue Medicine

Rescue therapy for RA is not permitted except for the addition of or increased dose of acetaminophen/paracetamol (dosed no more than 4.0 grams per day) to address breakthrough pain. If a patient is already taking stable background doses of acetaminophen/paracetamol, s/he may increase the dose up to 4.0 grams per day for rescue purposes, following dosage as per label.

Neither the study center nor the Sponsor will supply rescue medication for breakthrough pain, as outlined above.

6.6 Dose Modification

No dose modifications are permitted in this study.

6.7 Treatment After the End of the Study

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The Sponsor will not provide any additional care to patients after they leave the study because such care should not differ from what is normally expected for patients with RA.

7.0 DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

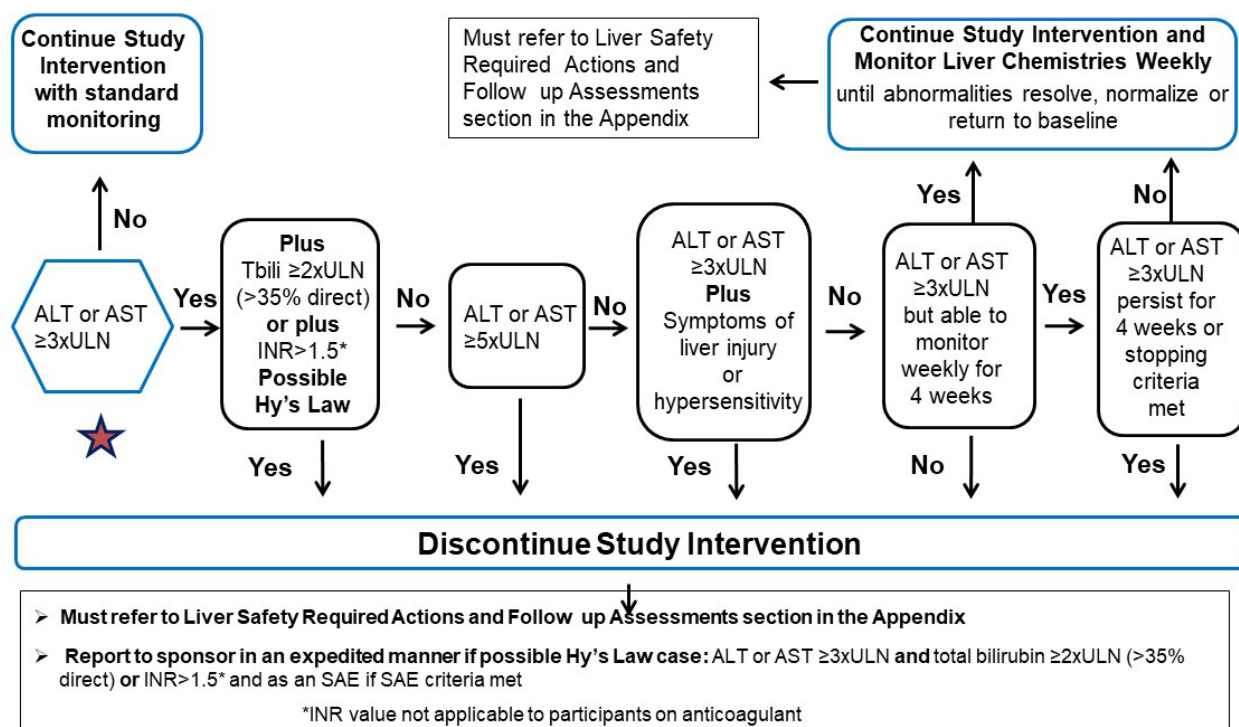
7.1 Discontinuation of Study Drug

Criteria for discontinuation due to abnormal liver function, neutrophil laboratory values, CK laboratory values, and skin toxicity are outlined below. In the event that a patient discontinues treatment with study drug prematurely, it is preferred (so as to minimize missing data) that the patient be given the opportunity to complete the remainder of his/her expected study visits per the SoA ([Table 1](#)) rather than being discharged from the study in full.

LIVER FUNCTION

Study intervention will be discontinued for a patient if liver chemistry stopping criteria are met and confirmed upon repeat testing. Samples for confirmation testing should be collected as soon as possible after receipt of initial laboratory results indicative of the need to monitor for stopping criteria. If ALT or AST is $\geq 5 \times \text{ULN}$, then study drug should be held while confirming.

Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase, INR = international normalized ratio; SAE = serious adverse event; Tbili = total bilirubin, ULN = upper limit of normal.

Note: The red star indicates the starting point.

Liver Safety: Suggested Actions and Follow-up Assessments can be found in [Appendix 6](#).

NEUTROPHIL LAB VALES

Withdraw study drug if absolute neutrophil count drops below 500 cells/mm³ and is maintained below 500 cells/mm³ on a confirmatory sample.

CK LAB VALUES

Withdraw study drug if an elevation of CK $> 5 \times$ ULN is observed on repeat testing without benign explanation (eg, recent exercise) occurs.

SKIN TOXICITY

Withdraw study drug in the case of any severe skin reaction which is considered to be related to the study drug.

If drug is stopped for reasons as described above, restarting the study drug is not allowed.

7.1.1 Potential Temporary Discontinuation due to Unrelated Adverse Events or COVID-19 Diagnosis

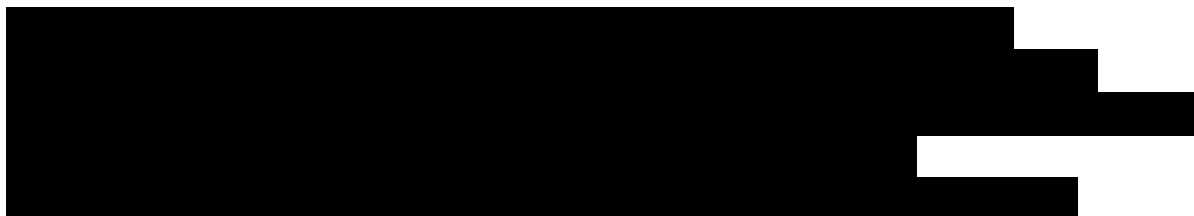
If a drug is stopped temporarily due to a clearly unrelated adverse event, for example, treatment of a fracture caused by a motor vehicle accident or COVID-19 infection, dosing may be reinitiated, after discussion with the Medical Monitor, if the temporary discontinuation was shorter than a maximum of 14 days in the total 12-week treatment period. In exceptional circumstances, medical monitor may allow dosing to be resumed with a gap of up to 21 days. In all cases, if the dosing gap is in excess of 21 days, dosing should be discontinued permanently.

In case of a COVID 19 infection, consult study Medical Monitor to discuss risk/benefit considerations of patient continuing or discontinuing study medication treatment.

7.1.2 ECG Criterion for Drug Discontinuation

In the event that a study ECG assessment demonstrates either of the bulleted criteria below (upon local review by the Investigator), a PK and lab sample (serum potassium and magnesium levels) should be drawn. The ECG should be repeated within 30 minutes. Patient study drug dosing should be interrupted until the results of the centrally read cardiologist report are received and the study Medical Monitor should be notified:

- QTcF (average of triplicate set) > 500 msec
- Change from baseline QTcF (average of triplicate set) > 60 msec



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.1.3 **Rechallenge**

Rechallenge is allowed in only limited circumstances when the drug is temporarily stopped, as noted in [Section 7.1.1](#). Once the drug is permanently stopped, no rechallenge is allowed.

7.2 **Patient Discontinuation/Withdrawal from the Study**

All patients will be advised that they are free to withdraw from participation in the study at any time, for any reason, and without prejudice. The Investigator also has the right to withdraw patients from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the patient, for intolerable or unacceptable AEs, intercurrent illness, noncompliance, with study procedures, administrative reasons, or in the Investigator's opinion, to protect the patient's best interest. The Sponsor reserves the right to request the withdrawal of a patient due to protocol violations or other reasons.

- 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.
- If the patient withdraws consent, the Investigator must clearly determine and document if the patient is making a full and immediate revocation of consent (eg, no additional data collection may occur) or if the patient is willing to proceed with additional study procedures to ensure a safe and orderly discharge from the study (eg, completion of Early Termination and EoS Visits).
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- If there is a medical reason for withdrawal, the patient should remain under the supervision of the Investigator until satisfactory health has returned.
- See the SoA ([Table 1](#)) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-up

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

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

- The study center must attempt to contact the patient and reschedule the missed visit as soon as possible and 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, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's source documents.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA ([Table 1](#)).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening and baseline evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Patient Reported Outcomes (PRO) questionnaires should be completed by patients before any other assessment at a clinic visit.
- An evaluation made by the independent joint assessor (see [Section 8.1.7](#)) must be made before any assessments completed by the treating physician (Investigator).
- The maximum amount of blood collected from each patient over the duration of the study, not including any extra assessments that may be required, will be specified in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Patient's Global Assessment of Disease Activity

When the Patient's Global Assessment of Disease Activity is required in the SoA ([Table 1](#)), it should be completed prior to administration of the in-clinic morning dose of study drug.

The patient's global assessment of their arthritis disease activity will be assessed by completion of a visual analog scale (VAS). The VAS will have anchors of 0 (no activity at all, very well) to 100 (worst activity imaginable, very poor).

This questionnaire will be administered by electronic means and should take approximately 1 minute to complete.

8.1.2 Patient's Assessment of Arthritis Pain

The severity of the participant's joint pain will be assessed by completion of a Patient's Assessment of Arthritis Pain VAS. The VAS will have anchors of 0 (no pain at all, no pain) to 100 (worst pain imaginable, the worst possible pain).

This questionnaire will be administered by electronic means and should take approximately 1 minute to complete.

8.1.3 Health Assessment Questionnaire Disability Index (HAQ-DI)

The HAQ-DI (standard disability method calculation) will be utilized to assess the patient's physical function or disability according to the patient. The HAQ-DI is a 20-item, validated questionnaire used to assess the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities [errands and chores]) ([Fries et al., 1983](#)). Responses in each functional area are scored from 0 (no difficulty) to 3 (inability to perform a task in that area). The study staff should not clarify any of the questions for the patient.

There are 41 total items on the HAQ-DI: 20 4-point Likert-scale questions assessing specific activities of daily living, 13 additional questions assessing use of assistive devices, and 8 additional questions assessing help received from another.

There are 3 steps to scoring the HAQ-DI: 1) identify the highest subcategory score from each of the 8 categories. Adjust for use of aids/help by increasing the category score from 0 or 1 to a 2 if use of aids/help for that category (utilize table of companion aids/help for HAQ categories). If the category score is already a 2 or 3, no adjustment is made; 2) sum the category scores; and 3) divide the final sum by the number of categories answered to obtain the final HAQ score rounded to the nearest value evenly divisible by 0.125. The HAQ-DI requires a minimum of 6 categories to be answered. If less than 6 categories are answered, a score will not be generated for the assessment time point in question.

This questionnaire will be administered by electronic means and should take approximately 5 minutes to complete.

8.1.4 Short Form-36 Health Status Survey Questionnaire Version 2 (SF-36v2)

The SF-36v2 will be used to assess health-related quality of life according to an acute (1 week) timeframe recall format. The SF-36v2 is a well-known, generic health survey consisting of 8 health-related domains: physical functioning, role-physical, bodily pain, general health, vitality, social function, role-emotional and mental health. Summary measures for a physical component and a mental component are derived from the 8 applicable health domains ([Ware et al., 1992](#)).

This questionnaire will be administered by electronic means and should take approximately 5 to 10 minutes to complete.

8.1.5 Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue)

The FACIT-Fatigue is a 13-item questionnaire that measures an individual's level of fatigue during their usual daily activities over the past week. The scale was originally developed to assess fatigue in cancer patients but has been validated for use in other chronic conditions, including RA ([Cella et al., 2005](#)).

This questionnaire will be administered by electronic means and should take approximately 2 minutes to complete.

8.1.6 High Sensitivity C-reactive Protein (hsCRP)

Levels of hsCRP will be measured from blood samples drawn for routine clinical laboratory assessment at the times specified in the SoA ([Table 1](#)). Samples will be analyzed by a central laboratory. Specific instructions for collection, processing, storage, and shipment of blood samples will be provided in the Laboratory Manual.

8.1.7 Swollen (66) and Tender (68) Joint Count Assessments

For assessment of swollen joints, a total of 66 joints will be scored for the presence or absence of swelling. For assessment of tender joints, a total of 68 joints will be scored for presence or absence of tenderness. All swollen and tender joint assessments will occur per the time points outlined in the SoA ([Table 1](#)).

All joint assessments will be performed by an experienced independent and blinded joint evaluator who has been certified as trained by the Sponsor or designee and must be identified on the delegation of authority for this responsibility. Every effort should be made to ensure that joint assessments for 1 particular patient are performed by the same evaluator throughout the study to minimize inter-observer variation. At each time point, the score for each joint (and assessor identification) will be recorded directly into an electronic Clinical Outcomes Assessment (eCOA) application, which will serve as the source documentation. Joints that have been replaced or injected with intra-articular steroids during the study are considered unevaluable. Eligibility for the screening and baseline assessments is based on the 66/68 joint count.

8.1.8 Physician's Global Assessment of Disease Activity

When the Physician's Global Assessment of Disease Activity is required in the SoA ([Table 1](#)), it should be completed prior to administration of the in-clinic morning dose of study drug and without the knowledge of PRO measures.

The Physician's Global Assessment of Disease Activity VAS is a measure to be completed by the Investigator or designee. The VAS will have anchors of 0 (no activity at all, no arthritis activity) to 100 (worst activity imaginable, extremely active arthritis).

This assessment will be administered electronically and should take approximately 1 minute to complete.

8.1.9 Clinical Disease Activity Index (CDAI)

The CDAI is the sum of 4 outcome parameters:

- Tender joint count out of 28 joint count (TJC28);
- Swollen joint count out of 28 joint count (SJC28);
- Patient's Global Assessment of Disease Activity (see Section 8.1.1); and
- Physician's Global Assessment of Disease Activity (see Section 8.1.8).

Interpretation of the CDAI disease activity measure is on a scale of 0 to 76, where ≤ 2.8 is considered remission, > 2.8 to ≤ 10 is considered low/minimal disease activity, > 10 to ≤ 22 is considered moderate disease activity, and > 22.0 is considered high/severe disease activity (7.1.1 et al., 2012).

8.1.10 American College of Rheumatology 20/50/70 (ACR20/50/70)

The ACR20 (50/70) response criteria is an endpoint that indicates the proportion of patients with $\geq 20\%$ (50%/70%) improvement in the number of swollen and tender joints (66/68 joint counts) and $\geq 20\%$ (50%/70%) improvement in ≥ 3 of the following ACR core measures:

To meet the ACR20 criteria, the patient must have $\geq 20\%$ improvement in the following ACR Core Set:

Both

- Swollen joint count (66 joint count)
- Tender joint count (68 joint count)

And an improvement of $\geq 20\%$ in ≥ 3 of the following 5 measures:

- Patient's Global Assessment of Disease Activity (VAS)
- Patient's Assessment of Arthritis Pain (VAS)
- HAQ-DI
- Physician's Global Assessment of Disease Activity (VAS)
- Acute phase reactant as measured by hsCRP

ACR50 = 50% improvement in the swollen and tender joint count and $\geq 50\%$ improvement in ≥ 3 of the 5 measures.

ACR70 = 70% improvement in the swollen and tender joint count and $\geq 70\%$ improvement in ≥ 3 of the 5 measures.

8.1.11 Disease Activity Score using 28-Joint Count-C-reactive Protein (DAS28-CRP) and DAS Remission

Assessments of RA by the DAS, modified to include the 28 joint counts according to [Smolen et al., 1995](#), will be conducted at the time points in the SoA ([Table 1](#)). The DAS28-CRP consists of a composite score of the following variables: TJC28, SJC28, CRP (hsCRP to be used for the purposes of this study), and Patient's Global Assessment of Disease Activity (see [Section 8.1.1](#)).

The following equation will be used to calculate the DAS28-CRP:

$$\text{DAS28 (CRP)} = 0.56\sqrt{\text{TJC28}} + 0.28\sqrt{\text{SJC28}} + 0.36\ln(\text{CRP} + 1) + 0.014 \times (\text{Patient's Global Assessment of Disease Activity}) + 0.96.$$

Interpretation of the DAS28-CRP disease activity measure is on a scale of 0 to 9.4, where < 2.6 is considered remission, ≥ 2.6 to < 3.2 is considered low/minimal disease activity, ≥ 3.2 to ≤ 5.1 is considered moderate disease activity, and > 5.1 is considered high/severe disease activity ([7.1.1 et al., 2012](#)).

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA ([Table 1](#)).

8.2.1 Physical Examinations

A complete PE will include, at a minimum, 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.

A targeted PE will include, at a minimum, signs of RA.

Body weight and height (height at screening only) will also be measured and recorded. Body mass index (BMI) will be calculated electronically in the eCRF. The patient should be dressed in lightweight clothing, without shoes.

Investigators should pay attention to clinical signs related to previous illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as AEs, as appropriate (see [Section 8.3](#)).

See [Section 7.0](#) for discontinuation criteria based on skin toxicity.

8.2.2 Vital Signs

Vital signs will be measured prior to dosing and immediately following dosing in a semi-supine position after ≥ 5 minutes' rest without distractions (eg, television, cell phones). Vital signs (to be taken before blood collection for laboratory tests, when applicable) will consist of 1 body

temperature measurement, 1 pulse rate measurement, 1 respiratory rate measurement, and 3 systolic and diastolic BP measurements (3 consecutive BP readings will be recorded at intervals of ≥ 1 minute). Each of the 3 BP readings will be recorded in the eCRF with an average value derived by the system. Abnormal, clinically significant vital sign results will be recorded as AEs (see Section 8.3). If known, the underlying etiology for the abnormal clinically significant vital sign will be recorded as an AE rather than the vital sign itself.

BP and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (Table 1) using an ECG machine supplied by the Central ECG Laboratory that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.1 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

Three individual ECG tracings should be obtained as closely as possible in succession and completed in less than 4 minutes.

The ECG tracing should clearly identify the patient, include the date and time of the assessment, and include the signature and date of the person who made the local interpretation; the tracing will be archived at the study site and electronic files sent to the Central ECG Laboratory. Abnormal, clinically significant ECG results will be recorded as AEs (see Section 8.3). If there is noise or other artifacts, they will be repeated. The QTcF intervals should be reviewed based on the automatic read from the ECG machine in real time.

ECGs will be transferred and read centrally by a qualified vendor. ECGs collected at the Baseline Visit (prior to randomization) should be assessed locally by the Investigator for confirmation of eligibility, but the final centrally read report will serve as the document of record in the patient's source chart and form the primary ECG database (EXPERT) for the study.

Triplicate 12-lead ECGs will be performed at least 30 seconds apart, in a supine position, resting for at least 10 minutes without external stimulation (e.g., talking, TV, noise) and submitted for central reading. Screening ECGs will be collected prior vital signs and blood samples. On Day 1 and 8, ECGs will be taken predose and 2 hours postdose. Patients not fasting on Day 1 and 8 will have an additional 4 hr postdose ECG. On Days 15, 29, 43, 57, and 85 ECGs will be performed as the last assessment in the clinic.

8.2.4 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and the SoA (Table 1) for the timing and frequency.

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. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

See Section 7.0 for discontinuation criteria based on abnormal liver function tests, neutrophil values, CK values, or positive SARS-CoV-2 test.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days (+ 7 days) after the last dose of study treatment 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, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the SoA (Table 1).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the eCRF.
- Serum potassium levels < 3.8 mmol/L will be treated and repeated as will serum magnesium levels < LLN.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue study treatment or the study (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected at the time points specified in the SoA (Table 1). SAE reporting will start at the time of consent. Any AE that occurs between the time of consent and prior to dosing on Day 1 will be recorded as medical history. TEAEs will be collected following

the first dose of study drug on Day 1 through the Follow-up Visit (30 days after the last administration of study drug).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in [Appendix 4](#). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in [Appendix 4](#).

8.3.2 Method of Detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (AESIs) (as defined in Section [8.3.6](#)), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section [7.3](#)). Further information on follow-up procedures is given in [Appendix 4](#).

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of patients and the safety of a study treatment under clinical investigation are met.

The Sponsor and/or designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor and/or designee will review and then file it along with the IB, and will also notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

All patients are required to meet the requirements relating to pregnancy and use of contraception described in the inclusion and exclusion criteria (see Sections [5.1](#) and [5.2](#), respectively).

Serum pregnancy testing will be performed only for women of childbearing potential (WOCBP) at screening (Day -28 to Day -1); the result must be negative for the patient to be eligible. A urine pregnancy test will be performed only for WOCBP on Day 1 (prior to dosing) and at every subsequent study visit through the Follow-up Visit (Visit 9). The serum pregnancy tests will be analyzed by the central laboratory, and the urine pregnancy tests will be analyzed locally.

- Details of all pregnancies in female patients and, if indicated, female partners of male patients will be collected after the start of study treatment and until 30 days (ie, 1 menstrual cycle) after the last dose of study drug.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in [Appendix 7](#).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

The following AEs will be classified as AESI in this study:



8.3.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable. Further information on general AE/SAE considerations is given in [Appendix 4](#).

8.4 Treatment of Overdose

For this study, any dose of > 3 tablets of ATI450/placebo per day OR > 2 tablets of ATI-450/placebo taken at any single dosing time point (eg, morning dose, evening dose) will be

considered an overdose. The dose of ATI-450 used in this study is based on doses previously studied in Phase 1, and plasma exposure is unlikely to exceed previously studied levels if patients adhere to dosing instructions. Given the blinded nature of the study, the above recommendations make the assumption that each blinded tablet contains 50 mg of ATI-450.

The Sponsor does not recommend specific treatment for an overdose.

In the event of suspected or confirmed overdose, the Investigator should:

1. Undertake any supportive measures, as per Investigator judgment.
2. Contact the Medical Monitor immediately.
3. Closely monitor the patient for any AE/SAE and/or laboratory abnormalities until the risk is considered to be resolved as agreed with the Medical Monitor.
4. Obtain a plasma sample for PK analysis and any other relevant interventions or assessments, if requested by the Medical Monitor (determined on a case-by-case basis).
5. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.
6. Communicate the event to the Sponsor or designee within 24 hours of its occurrence.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient. Treatment of confirmed or suspected overdose with ATI-450 should consist of clinically appropriate supportive measures.

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 8.3.4.

8.5 Pharmacokinetics

Up to twelve (12) venous blood samples of approximately 2 mLs each will be collected for measurement of plasma concentrations of ATI-450 and its primary circulating metabolite, CDD-2164, as specified in the SoA (Table 1). Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. The date and time of study treatment administration will also be recorded.

A PK sample will be collected if ECG withdrawal criteria are met, see section 7.1.1.

Samples will be used to evaluate the PK of ATI-450. Each plasma sample will be divided into 2 aliquots (1 each for primary analysis and back-up). Samples collected for analyses of ATI-450, CDD-2164, and other metabolite/enantiomer plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

At visits during which blood samples for the determination of PK of ATI-450 will be taken, 1 sample of sufficient volume can be used. Every effort will be taken to collect the blood samples as close as possible to the scheduled time points, but a window of $\pm 10\%$ is permitted for each blood draw. In instances where different assessments are due at the same time point, they will be performed such that the blood samples for PK analyses will be drawn at the correct time (as long as patient safety is not compromised).

Drug concentration information that may unblind the study will not be reported to study centers or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and study center study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

If a patient refuses blood collection for PK analysis, this will not be considered a protocol violation as the PK analysis is a secondary objective.

Details regarding the processing and shipment of all blood samples can be found in the Laboratory Manual.

8.6

8.7 Genetics

Genetics will not be evaluated in this study.

8.8 Biomarkers

Biomarkers, other than the pharmacodynamic markers, will not be evaluated in this study.

8.9 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters will not be evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary statistical hypothesis to be tested in this study is the hypothesis that at least one of the ATI-450 treatment groups is superior to placebo for the treatment of RA based upon the 12-week ACR20 assessment versus the null hypothesis of no difference in any of the treatment groups. Note that each ATI-450 treatment group will be compared to placebo separately (ATI-450 treatment groups will not be pooled) requiring 2 separate hypothesis tests. These hypotheses will be conducted using a two-sided testing procedure with an alpha level of 0.05. No adjustment for multiplicity will be made.

Secondary superiority hypotheses will be tested on the secondary efficacy endpoints to gather supportive evidence for the primary hypothesis. These secondary assessments will have the same null and alternatives hypotheses as the primary and will be tested using a two-sided procedure with an alpha level of 0.05.

The secondary dose response modeling objectives do not have an associated statistical or theoretical hypothesis since they are by nature estimation objectives.

9.2 Estimands

The primary objective of this study is to assess the efficacy of multiple doses of ATI 450 plus MTX versus placebo plus MTX in patients with moderate to severe active RA. This efficacy assessment is intended to provide a rank order and relative magnitude of the reduction in RA signs and symptoms for the different ATI-450 treatment groups to aid in the selection of an optimal dose to progress in future clinical development. At a minimum the optimal dose of ATI-450 will be superior to the control group (placebo plus MTX) in the reduction of signs and symptoms of RA. The following estimands (International Council for Harmonisation [ICH] E9-R1) are defined to adequately achieve the intended primary objective for this study.

9.2.1 Treatment

The treatment condition of interest for this study is the fixed 12-week BID dosing of 20 mg or 50 mg of ATI-450 plus MTX versus placebo plus MTX. The administration of Protocol Excluded Mediations/Treatments listed in Appendix 5 for the purpose of rescue or as standard care following the discontinuation of study medication is strictly outside the treatment condition of interest for this study since they could confound or prohibit the determination of an optimal dose for ATI-450. Treatment durations less than 12-weeks, while providing supportive information, are, for the purpose of the primary estimand, outside the treatment condition of interest.

9.2.2 Population

The population of patients targeted by the clinical question of interest for this study includes patients with moderate to severe active RA as defined by the inclusion and exclusion criteria who are randomized in the study.

9.2.3 Variable

ACR20 was chosen as the variable (or endpoint) of our primary estimand because it is a well-established, validated, and sensitive measure of the improvement in the signs and symptoms of RA. ACR20 is a threshold responder endpoint based upon a composite of different measures. If the ACR20 cannot be computed due to missing component measures or the occurrence of intercurrent events that could confound the observed ACR20 value, a non-response will be imputed for the ACR20 variable in the primary estimand.

9.2.4 Intercurrent Event Strategy

A composite variable strategy will be employed for the primary estimand of this study because some intercurrent events provide information about the patient's outcome. Patients who discontinue due to lack of efficacy indicate the inadequacy of a treatment to improve RA signs and symptoms. Patients who discontinue for toxicity prior to week 12 will also not be considered to have been treated successfully and that information should be included in the estimand to select the optimal dose. Therefore, all missing data for ACR20 and all data following confounding intercurrent events will be imputed with a non-response.

Discontinuation of study medication prior to week-12 ACR20 observation for any reason and the administration of any of the protocol prohibited medications listed in Appendix 5 for any reason prior to the week-12 ACR20 observation are two confounding intercurrent events that are likely to occur in some patients during conduct of the trial.

9.2.5 Population-Level Summary

The population-level summary for this study will be the model-based treatment differences and corresponding p-values for the proportions of patients meeting the ACR20 criteria. The statistical model will be a logistic regression that includes fixed factors for treatment group and the stratum used in the randomization (positive for RF and/or anti-CCP at screening and prior biologic or JAK RA treatment). Each ATI-450 treatment group will be compared with placebo; model-based point estimates for the difference in proportions, 95% CIs, and p-values will be calculated.

9.2.6 Sensitivity

If more than 10% of the Week-12 ACR20 values require imputation due to missing values or intercurrent events, then a tipping point sensitivity analysis may be conducted for the primary ITT analysis. Details of the tipping point analysis will be provided in the SAP.

9.3 Sample Size Determination

Approximately 240 participants will be enrolled to achieve 80 randomized patients per treatment arm.

Data from 80 randomized patients in each arm provides 90.1% power to demonstrate the superiority of ATI-450 versus placebo for ACR20 response rates in the Intent-to-treat (ITT) Population. This power computation was based on a Fisher's exact test of the differences in proportions and assumes a response rate for ATI-450 of 62% and a response rate for placebo of 35%. These response rate assumption for ATI-450 was based upon the observed rate in the ATI-450-RA-201 study, accounting for differences in biologic experienced versus biologic naive patients. The assumed placebo response rate was based upon studies [NCT00413660](#) and [NCT01960855](#).

9.4 Populations for Analyses

For purposes of analysis, the analysis sets in [Table 4](#) are defined.

Table 4 Analysis Sets

Analysis Set	Description
Intent-to-treat (ITT) Population	All randomized patients, analyzed according to the treatment to which the patient was randomized. The ITT population will be used for the primary analysis.
Per-protocol (PP) Population	All randomized patients who remain on study drug and complete their assessments for the Day 85 visit and no major protocol deviations, analyzed according to the treatment that the patient actually received.
Safety Population	All patients randomly assigned to study treatment and who take at least 1 dose of study treatment. Patients will be analyzed according to the treatment they actually received.
Pharmacokinetic (PK) Population	All patients randomly assigned to study treatment and who take at least 1 dose of study treatment and have at least 1 evaluable PK measurement.
Pharmacodynamic (PD) Population	All patients randomly assigned to study treatment and who take at least 1 dose of study treatment and have at least 1 evaluable PD measurement.

9.5 Statistical Analyses

All analyses, summaries, and listings will be performed using SAS® software (Version 9.4 or higher) 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. The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: number of observations, mean, standard deviation, median, minimum, and maximum.
- Categorical variables: counts and percentages.

Individual patient data will be presented in listings.

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

9.5.1 Efficacy Analyses

All efficacy summaries will be conducted per [Table 5](#) on both the ITT and PP Populations; analyses per the PP Population will be considered supportive. Efficacy parameters may be summarized by important subgroups, but no formal statistical treatment comparison will be conducted on subgroups.

Table 5 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary efficacy endpoint (proportion of patients achieving ACR20 at Week 12) will be analyzed using logistic regression on the ITT population. The statistical model will include fixed factors for treatment group and the stratum used in the randomization (positive for RF and/or anti-CCP at screening and prior biologic or JAK RA treatment). Patients with missing ACR20 values at Week 12 will be considered non-responders as will patients with confounding intercurrent events. Each ATI-450 treatment group will be compared with placebo; model-based point estimates, 95% CIs, and p-values will be calculated.
Secondary	The proportion of patients achieving ACR50/70 at Week 12, the proportion of patients achieving ACR20/50/70 at each scheduled collection time, the proportion of patients achieving DAS28-CRP remission (score < 2.6) at each scheduled collection time, the proportion of patients achieving DAS28-CRP low disease activity (score ≤ 3.2) at each scheduled collection time, and the proportion of patients achieving CDAI remission (score ≤ 2.8) at each scheduled collection time will be assessed using the same analysis method as used for the primary efficacy endpoint. Continuous secondary efficacy endpoints (mean change from baseline over time in DAS28-CRP, CDAI, HAQ-DI score, SF-36v2 score, and FACIT-Fatigue score) will be analyzed using a mixed model repeated measures. This model will include fixed factors for treatment group, time, treatment-by-time interaction, and the stratum used in the randomization, as well as a random effect for patient. Patients with missing continuous efficacy measures or measures following confounding intercurrent events will be imputed in the ITT analysis using a model-based multiple imputation procedure, where applicable. Model-based point estimates and 95% CIs will be provided for treatment effects at each scheduled collection time, separately. Point estimates, 95% CIs, and p-values will be provided for treatment differences versus placebo at each time point. Statistical hypothesis tests will not be conducted on hsCRP but the standard summary statistics for continuous variables will be provided for the value, the change from baseline, and the percent change from baseline at each scheduled collection time. Dose response modeling will be conducted for ACR20/50/70 responder rates, the change from baseline in DAS28-CRP, and other efficacy parameters as deemed appropriate.
Exploratory	Will be described in the SAP finalized before database lock.

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%/50%/70% improvement criteria; anti-CCP = anti-cyclic citrullinated protein; CDAI = Clinical Disease Activity Index; CI = confidence interval; DAS28-CRP = Disease Activity Score using 28 joint count-C-reactive protein; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; HAQ-DI = Health Assessment Questionnaire Disability Index; hsCRP = high sensitivity C-reactive protein; ITT = Intent-to-treat; JAK = Janus kinase; PP = Per-protocol; RA = rheumatoid arthritis; RF = rheumatoid factor; SAP = statistical analysis plan; SF-36v2 = Short Form-36 Health Status Survey Questionnaire Version 2.

9.5.2 Safety Analyses

The Safety Analysis Population will be used for the analysis of safety data (AEs, exposure to study drug, clinical laboratory values, vital signs, PE, and ECG parameters).

TEAEs are defined as AEs with an onset date on or after the date of first administration of study drug and before the date of last administration of study drug + 30 days.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be presented by system organ class (SOC) and preferred term (PT) in frequency tables. Patients with multiple AEs will be counted only once within each SOC and PT. 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 drug will be listed.

TEAEs by maximum severity (see [Appendix 4](#)), TEAEs by relationship to study treatment, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study drug will be tabulated for each treatment group. Commonly occurring TEAEs will be summarized using descriptive statistics.

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

9.5.3 Other Analyses

9.5.3.1 Pharmacokinetic Analyses

All PK analyses will be performed using the PK Population. Plasma concentrations of ATI-450 and its primary circulating metabolite, CDD-2164, will be summarized by day and sample time. Concentration versus time since dose (Days 1, 8, 15, 29, 43, 57, and 85) will be displayed by linear scale. Population PK modeling and related exposure response modeling may be explored, as appropriate.

9.5.3.2

9.5.4 Missing Data

Missing data will not be imputed for the efficacy analyses or summaries conducted on the PP Population or on the safety summaries conducted on the Safety Population. For binary efficacy analyses (ie, ACR20/50/70 and DAS28-CRP < 2.6) conducted on the ITT Population, patients with missing values will be considered non--responders. For analyses of continuous endpoints conducted on the ITT Population, a model--based multiple imputation procedure will be used to impute missing data, where appropriate. If more than 10% of patients are missing their efficacy evaluation at Day 85, then a tipping point sensitivity analysis may be conducted for the primary ITT analysis. Details of the tipping point analysis will be provided in the SAP.

9.6 Interim Analyses

No interim efficacy analysis is planned.

9.7 Data Safety Monitoring Board

An independent DSMB will convene to monitor interim safety data. The DSMB is responsible for reviewing and evaluating unblinded safety data at regularly scheduled meetings. The Committee may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study. Details regarding DSMB membership, responsibilities, and meeting frequency are outlined in the DSMB Charter.

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