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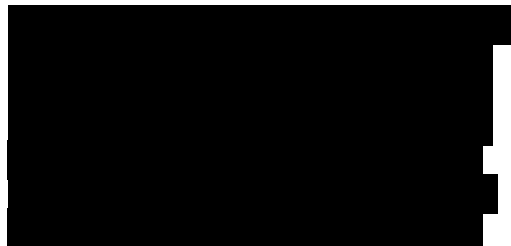
STATISTICAL ANALYSIS PLAN

Study Title: 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

Phase: 2b

Protocol No.: ATI-450-RA-202

Protocol Date(s):



Analysis Plan Version and Date: Version 2.0 Final, 17OCT2023

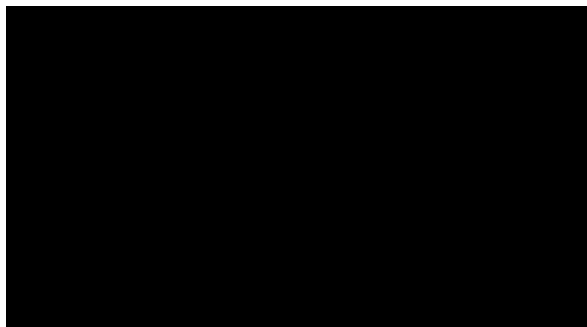
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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

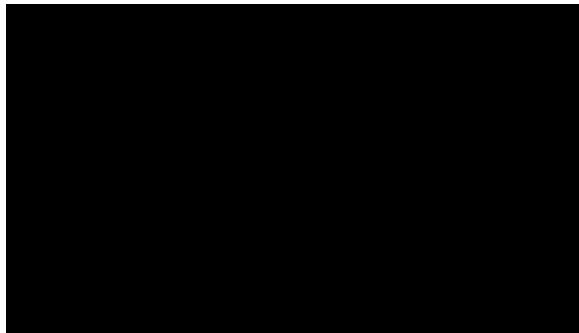
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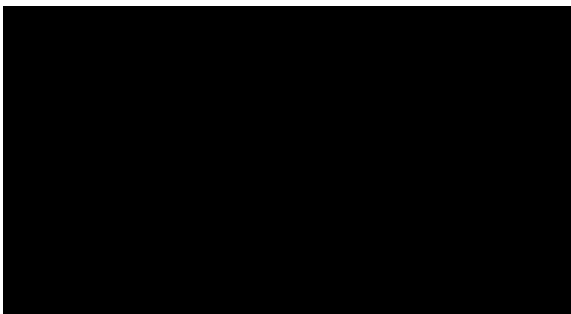
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Oct-17-2023 | 22:41 EDT

Date

Aclaris Therapeutics, Inc.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ACR	American College of Rheumatology
ACR20/50/70	American College of Rheumatology 20%/50%/70% improvement criteria
AE	Adverse Event
ALT	Alanine aminotransferase
Anti-CCP	Anti-cyclic citrullinated protein
AST	Aspartate aminotransferase
ATC	Anatomical therapeutical chemical
BID	Twice daily
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood Pressure
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
C _{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Event
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score using 28 Joint Count-C-reactive Protein
DBP	Diastolic blood pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ED ₅₀	Median effective dose; dose that produces 50% of the maximal effect
ED ₉₀	Dose that produces 90% of the maximal effect
E _{max}	Dose that produces the maximum effect
EOS	End of Study
EoT	End of treatment
ET	Early termination
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HIV	Human immunodeficiency virus
hsCRP	High sensitivity C-reactive protein
ICH	International Council for Harmonisation
IL	Interleukin

ITT	Intent-to-treat
IxRS	Interactive Voice/Web Response System
JAK	Janus kinase
LS	Least square
MCS	Mental component summary
MMRM	Mixed model repeated measures
MNAR	Missing not at random
MTX	Methotrexate
QTcF	Fredericia-corrected QT interval
PCS	Physical component summary
PD	Pharmacodynamics
PE	Physical examination
PK	Pharmacokinetics
PP	Per-protocol
PT	Preferred term
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SBP	Systolic blood pressure
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE	Standard error
SF-36v2	Short Form-36 Health Status Survey Questionnaire Version 2
SJC28	Swollen joint count out of 28 joint count
SOC	System organ class
TB	tuberculosis
TEAE	Treatment-emergent adverse event
TJC28	Tender joint count out of 28 joint count
ULN	Upper limit of normal
VAS	Visual analog scale
WOCBP	Women of childbearing potential

1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol ATI-450-RA-202. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (eCRFs) for details of study conduct and data collection.

The scope of this document excludes the analysis of genetics data, biomarker data, medical resource utilization and health economics parameters being collected at specific sites.

1.1. STUDY OVERVIEW

This is a Phase 2b, randomized, multicenter, double-blind, parallel group, placebo controlled, dose ranging study to investigate the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (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, trough 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. Safety and tolerability will be evaluated at each study visit by assessment of adverse events and vital signs, and at select visits, ECGs and clinical laboratory tests will be completed.

Approximately 51 investigators and study centers are expected to participate in this study. Approximately 240 participants will be enrolled to achieve 80 randomized patients per treatment arm.

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.

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.

1.2. 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/EW)	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	

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/EW)	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

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

1

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. **OBJECTIVES**

Primary Objective:

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

Secondary Objective:

The secondary objectives are as follow:

- To assess the efficacy and safety of ATI-450 plus MTX in patients with moderate to severe active RA
- To assess the PK of ATI-450 in patients with moderate to severe active RA who are receiving concomitant MTX
- To conduct dose response modeling of ATI-450 in patients with moderate to severe RA who are receiving concomitant MTX

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

3. **GENERAL STATISTICAL CONSIDERATIONS**

3.1. SAMPLE SIZE AND POWER

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%. The 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.

3.2. RANDOMIZATION AND MASKING

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 schedule of assessments. 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.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

One strata used in the randomization (prior biologic or JAK RA treatment at screening) will be used in the primary and secondary efficacy models, unless otherwise specified.

3.3.2. Examination of Patient Subsets

There is no examination of patient subsets.

3.3.3. Multiple Testing and Comparisons

There are no planned adjustments for multiple comparisons.

3.3.4. Missing Data and Outliers

Missing data will not be imputed for the safety summaries conducted on the Safety Population, unless otherwise specified. For binary efficacy analyses (i.e., ACR20/50/70, DAS28-CRP Remission, and CDAI Remission) conducted on the ITT Population, patients with missing values will be considered non-responders. For analyses of continuous endpoints, 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. The details of the tipping point analysis are given in Section 5.4.4.

If an AE has missing relationship to the study drug or severity, then that AE will be considered as 'related' to the study drug and the severity will be considered as 'Severe' in the table summaries, but the AE will be displayed as having a missing relationship or severity in the listings.

3.3.5. Imputation of Incomplete Dates

A missing date is one in which the day, month or year are all unknown. For adverse events, if a date is missing entirely then the date will be set to equal Day 1.

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a patient. For many of the analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

To minimize bias, the project statistician will impute dates in a systematic, but reasonable manner. If the month/year is the same as the Day 1 month/year, then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. For nonexistent dates occurring at the end of a month created by this imputation method, the first date of the next month will be used (e.g. Day 1 = 31JAN2017, incomplete date = XXFEB2017 -> imputed date = 01MAR2017).

3.3.6. Imputation of Alphanumeric Data

Should there be instances where a clinical laboratory parameter is reported with imbedded non-numeric characters, as for example, "<0.1" or ">10", the data will be imputed for the purpose of quantitative summaries. The actual values as reported in the database will be presented in data listings.

For incorporation in quantitative summaries, the following imputation rules will be employed:

The lower limit of quantification will be replaced with $\frac{1}{2}$ the value of the lower limit. For example, "< 0.1" will be imputed as "0.05".

The upper limit of quantitation will be increased by one level of precision that precedes the value. For example, ">0.1" will be imputed as "0.11", and ">10" will be imputed as "10.1".

Results reported as " $\geq X$ " and " $\leq X$ " will be imputed as "X".

3.3.7. Definitions and Terminology

Duration of RA (years)

$(\text{Date of informed consent minus the start date of the RA} + 1) / 365.25$

The start date of the RA is collected as part of Medical History and based on the Medical Dictionary for Regulatory Activities (MedDRA) coded preferred term of 'Rheumatoid arthritis'.

Baseline Value

For purpose of analysis, the baseline value is defined as the last non-missing value obtained on or prior to initiation of study drug. The randomization date will be used for patients who were randomized but not dosed.

Study Day

Study Day is defined relative to Day 1, where Day 1 is the day of date of first dose as reported on the Dosing Diary eCRF. Thus, the study day of an event is calculated as:

Study Day = ((event date – date of Day 1) + 1) for dates on or after Day 1

Study Day = (event date – date of Day 1) for dates prior to Day 1

Last Dose of Study Drug

Last Dose of Study Drug is defined as the date of last dose as recorded on Dosing Diary CRF. If the date of last dose is missing on the Dosing Diary CRF, then the last available dosing date will be used.

Study Drug Exposure (days)

Study drug exposure is defined as the number of days from Day 1 to the last dose of study drug.

Dose Interruptions

Dose interruption is defined as ≥ 2 consecutive days where the patient missed both doses of the study drug as determined by the date missed and number of tablets missed field on the Dosing Diary CRF.

Study drug compliance (%) based on number of doses

$\text{Compliance (\%)} = (\text{number of doses taken} / \text{number of doses that should have been taken}) \times 100$.

- The number of doses taken is calculated as: $[(2 * \text{study drug exposure days}) - \text{sum of number of tablets missed field on the Dosing Diary CRF}]$.
- The number of doses that should have been taken is calculated as follows:
 - $(2 * \text{study drug exposure days})$ for patients who discontinued study medication
 - $(2 * 84 + 1)$ for patients who completed study medication.

If the number of tablets missed is unknown, it will be imputed as 2.

Prior Medications

Prior medications are those medications taken prior to the initiation of study medication, regardless of whether it continues into the blinded treatment period.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study medication through the end of treatment date minus 1. This definition includes medications started prior to the initiation of study medication but continuing concomitantly with the study medication.

Change from Baseline

Change from Baseline for a given endpoint is defined as the value at the analysis visit minus the baseline value.

Percent Change from Baseline

Percent Change from Baseline for a given endpoint is defined as the value at the analysis visit minus the baseline value, quantity divided by the baseline value.

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.

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

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

Clinical Disease Activity Index (CDAI)

The CDAI is the sum of 4 outcome parameters:

- Tender joint count out of 28 joints (TJC28);
- Swollen joint count out of 28 joints (SJC28);
- Patient's Global Assessment of Disease Activity / 10; and
- Physician's Global Assessment of Disease Activity / 10.

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

Treatment-Emergent Adverse Event (TEAE)

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.

Treatment-emergent Laboratory Abnormalities

A treatment-emergent laboratory abnormality is defined as a result in which the baseline value is within normal laboratory limits and the post-baseline value is outside normal laboratory limits. If the relevant baseline assessment is missing, then any post-baseline value outside normal laboratory limits will be considered a treatment-emergent value.

Treatment-emergent Laboratory Toxicity

A treatment-emergent laboratory toxicity is defined as an increase of at least one toxicity grade from the baseline assessment at any post baseline visit. If the relevant baseline assessment is missing, then any graded abnormality (i.e., at least Grade 1) is considered to be treatment-emergent.

3.3.8. Presentations by Study Visit

Scheduled and unscheduled assessments collected from Visit 1 through Visit 8 for all efficacy assessments and safety assessments (labs, vital signs, and ECG) will be assigned to an analysis visit window using the study day ranges described in Table 1. All study days up to and including Day 1 are in the baseline-eligible analysis visit window. The last non-missing assessment in the baseline-eligible analysis visit window will be used in any summaries that present the baseline results with the exception of ECG interpretation if all triplicate interpretation values are not the same. In this case, the best result from the triplicate values will be chosen, where normal is better than abnormal and abnormal not clinically significant is better than abnormal clinically significant. Day 1 post-dose ECG and PK assessments will be analyzed as collected. Day 8 ECG assessments will be windowed per Table 1, then each timepoint will be analyzed as collected. For all other assessments,

for post-baseline analysis windows, if multiple assessments occur within a given analysis visit window, the result closest to the target study day, regardless of whether scheduled or unscheduled, will be used for summary presentations. If two measurements have the same distance to the target study day, the first assessment will be used in the summary presentations with the exception of ECG interpretation if all triplicate values are not the same. In this case, the worst result from the triplicate values for the given visit will be chosen, where abnormal is worse than normal and abnormal clinically significant is worse than abnormal not clinically significant. All assessments will be presented in the listings. In addition to the analysis visits indicated in Table 1, for patients who prematurely discontinue the study, data collected during the withdrawal visit will be used as an EOS assessment for these patients. The EOS assessment will be included in safety analyses.

Efficacy assessments and safety assessments that are collected less frequently than demonstrated in Tables 1 and 2 will be summarized based on the windows collected.

Table 1: Visit Windows for FACIT, SF-36, HAQ-DI, and Patient Assessment of Arthritis Pain

<i>CRF Visit</i>	<i>Target Study Day</i>	<i>Analysis Visit</i>	<i>Study Day Range</i>
Visit 1	-28 to -1	Baseline	<1 or Day 1 pre-dose
Visit 2	1		
Visit 5	29	Week 4	[2 – 42]
Visit 7	57	Week 8	[43 – 70]
Visit 8(EoT/ET)	85	Week 12	[71 – 98]

Table 2: Visit Windows for Other Efficacy and Safety Assessments

<i>CRF Visit</i>	<i>Target Study Day</i>	<i>Analysis Visit</i>	<i>Study Day Range</i>
Visit 1	-28 to -1	Baseline	<1 or Day 1 pre-dose
Visit 2	1		
Visit 3	8	Week 1	[2 – 11]
Visit 4	15	Week 2	[12 – 21]
Visit 5	29	Week 4	[22 – 35]
Visit 6	43	Week 6	[36 – 49]
Visit 7	57	Week 8	[50 – 70]
Visit 8(EoT/ET)	85	Week 12	[71 – 98]
Visit 9(EoS)	30 days after last dose	EOS	Latest assessment after the EoT/ET

3.4. TIMING OF ANALYSES

When all patients have completed study ATI-450-RA-202 or terminated early from the study and the database has been locked, the analyses will be performed according to this SAP. No interim analysis is planned for this study.

4. ANALYSIS POPULATIONS

The populations for analysis will include the intent-to-treat population (ITT), the per-protocol (PP) population, the safety population, and the Pharmacokinetic (PK) Population.

4.1. 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.

4.2. PER PROTOCOL (PP) POPULATION

All randomized patients who remain on study drug and complete their assessments for the Day 85 visit and do not have major protocol deviations that could substantially impact efficacy. Patients are considered to have completed their Day 85 assessments if the count of swollen and tender joints are recorded in the Week 12 analysis visit window, along with at least 3 of the efficacy assessments required to evaluate the primary efficacy endpoint. Protocol deviations and violations will be tracked as part of clinical monitoring and clinically evaluated by the sponsor as major or minor. Determination of protocol deviations that could impact efficacy will be conducted in a blinded manner by the sponsor prior to database lock.

4.3. 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 received. Patients who receive multiple dose levels will be analyzed according to the maximum dose received at any time.

4.4. PHARMACOKINETIC (PK) POPULATION

All patients randomly assigned to study treatment, take at least 1 dose of study treatment and have at least 1 evaluable PK assay will be included in the PK population, even if the results are below the limit of quantification (BLQ).

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the primary and key secondary efficacy endpoints. Unless stated otherwise, the term “descriptive statistics” refers to number of patients, mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data.

For categorical variables, the denominator of percentages will be the number of patients with a non-missing value at the visit and/or the scheduled timepoint. If a different denominator is used, this will be identified in the summary table.

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number. Assessments indicated as 'Not Done' will not be included in the listings.

The term 'treatment group' refers to all patients on the same dosing regimen. There will be three treatment groups in this study: Placebo BID plus MTX, ATI-450 20mg BID plus MTX, and ATI-450 50mg BID plus MTX.

All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05 unless otherwise stated. P-values will be presented to three decimal places. For the efficacy endpoints, the ATI-450 plus MTX treatment groups will be tested versus Placebo plus MTX via statistical inference.

The statistical analyses will be conducted with the SAS® software package version 9.4 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be independently verified by a second programmer or statistician prior to issuance of the draft statistical report. All documents will be reviewed by the lead statistician to ensure accuracy and consistency.

5.1. PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patient disposition will be presented for all patients in the ITT. The number of patients who completed the study or discontinued the study early will be provided. The reasons for early discontinuation from the study will be presented by treatment group. Similarly, descriptive statistics for end of treatment status (completed or discontinued) and the reasons for early discontinuation of study treatment will be presented.

Demographic and baseline characteristics will be summarized using the ITT population.

Demographic data reported by treatment group will include age, sex (at birth), race, ethnicity, and baseline weight (kg), baseline height (cm) and baseline body mass index (BMI) (kg/m²). This information will be reviewed for baseline differences, but no statistical testing will be performed. Missing race and ethnicity for patients from the Czech Republic will be summarized as 'Not Reported.'

To allow evaluation of baseline RA disease characteristics, descriptive statistics for the duration of RA disease (years) and continuous measures of baseline tender joint count, baseline swollen joint count, baseline hsCRP, and baseline DAS28-CRP will be summarized by treatment group. Baseline DAS28-CRP will also be analysed as categorical. For the categorical analysis, the number and percentage of patients in each of the following DAS28-CRP categories will be provided: ≥ 3.2 to $\leq$

5.1 (moderate disease activity) and > 5.1 (high/severe disease activity). Additionally, the number (%) of patients within the randomization strata based on the stratification factors of positive for RF and/or anti-CCP at screening and prior biologic or JAK RA treatment will be reported by treatment group.

Medical conditions/events will be summarized using the system organ class and preferred terms coded with MedDRA version 24.0.

Findings from the screening physical examination (PE) will be summarized using the pre-specified body system categories and include reporting of abnormal not clinically significant and abnormal clinically significant.

The results of special labs collected at screening only (TB, Anti-CCP antibody, hepatitis B core antibody, hepatitis C antibody, HIV-12 AB, and SARS-CoV-2 virus) will be presented in listings.

5.2. PRIOR, CONCOMITANT AND RA MEDICATIONS

All medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken from 30 days before start of screening until the end of the follow-up period will be recorded in the appropriate section of the eCRF.

Prior and concomitant medications will be coded using the WHO Drug Dictionary (version March 2021 B3 Global) for the entire period of the study.

A summary by treatment for prior medications and a summary by treatment of concomitant medication will be provided for the ITT population. Each summary table will report the number (%) of patients by anatomical therapeutic chemical (ATC) classification using ATC level 2 and medication preferred term. Patients will be counted only once within each ATC and preferred term.

All prior and concomitant medications will be included in a data listing. Listings will distinguish medications as prior and/or concomitant.

5.3. STUDY DRUG EXPOSURE

Study drug exposure and compliance will be summarized by treatment and overall for the Safety population. The study drug treatment duration along with summaries of dose interruptions and treatment compliance will be reported.

The study drug dosing data collected in the patient diary will be provided in a data listing. Likewise, full accounting of the study drug dispensing, collection, and tablet counts will be provided in a data listing.

5.4. EFFICACY ANALYSIS

All efficacy summaries will be conducted per SAP on both the ITT and PP Populations; analyses per the PP Population will be considered supportive.

5.4.1. Primary Efficacy Endpoint

The primary efficacy variable will be the proportion of patients achieving ACR20 at Week 12 in the ITT population.

5.4.1.1. Statement of Estimand

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 Harmonization [ICH] E9- R1) are defined to adequately achieve the intended primary objective for this study.

5.4.1.2. 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 Medications/Treatments listed in the Protocol 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.

5.4.1.3. 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.

5.4.1.4. 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.

5.4.1.5. 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 of the Protocol that could substantially impact efficacy 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. Prohibited medications that could have substantial impact on efficacy will be determined in a blind manner prior to database lock.

5.4.1.6. 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 one of the strata used in the randomization (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.

5.4.2. Primary Efficacy Analysis

In all presentations of the primary efficacy endpoint (proportion of patients achieving ACR20 at Week 12), the endpoint will be presented in percentages (e.g., (number responders/population N)*100). The denominator will always be the ITT population N for the applicable analysis.

Patients missing the ACR20 endpoint in the Week 12 analysis visit window will be considered non-responders. Additionally, regardless of having an assessment in the week 12 analysis window, patients with any of the following confounding intercurrent events will count as a non-responder:

- Early discontinuation from the study due to lack of efficacy
- Early discontinuation from the study due to an adverse event
- Early discontinuation from study drug prior to the start of Week 12 analysis visit window (e.g., study day 71)
- Use of prohibited medications as listed in the Appendix 5 of the protocol that could substantially impact efficacy prior to the start of Week 12 analysis visit window (e.g., study day 71). Patients who used prohibited medications will be identified via the protocol deviation tracking process.

For each treatment group, the observed responder rate for ACR20, after applying non-responder rules, will be reported along with the 95% CI for the response rate using the normal approximation. The difference in observed response rates (vs placebo) will also be presented.

Inferential results will include model-based responder estimates and associated 95% CIs, differences in estimates and associated 95% CIs for each active group versus placebo, and p-values testing for significance in the difference. The model will be a Firth's penalized likelihood logistic regression model with fixed effects for treatment, and use of prior biologic or JAK RA treatment (Yes/No). Inferences for the model-based treatment effect will be computed using asymptotic normality with approximate standard errors obtained from the delta method (Billingsley 1986). The error degrees of freedom will be set to the number of observations entering the logistic regression. Model-based treatment group estimates and differences will be made at levels of the prior biologic or JAK RA treatment covariate that correspond to the ITT patient population by multiplying the covariate parameter estimate by the actual proportion of patients in the prior biologic or JAK RA treatment within each treatment group. This is analogous to estimating LSMeans at the mean value for a covariate.

The model results performed at analysis visit Week 12 are the primary efficacy analysis.

5.4.3. Supportive Analysis of Primary Efficacy Endpoint

Using the ITT population, the following analysis are planned to aid in interpretation and confirmation of the results of the primary efficacy analysis:

- Distribution of reasons for non-response with respect to composite ACR20. Categories for reasons for non-responder will be: ACR20 criteria not met, use of prohibited medications that could substantially impact efficacy and withdrew from study or withdrew from study medication with reasons for discontinuation
- LS mean change from baseline in the ACR Components at Week 12 will be summarized and based on a linear regression model adjusted for treatment, baseline value, and one of the strata used in the randomization (prior biologic or JAK RA treatment). The components to be presented will include swollen joint count (68), tender joint count (66), HAQ-DI score, Patient Pain, Patient Global Assessment, Physician Global Assessment, and hsCRP.

5.4.4. Tipping Point Sensitivity Analysis for the Primary Efficacy Endpoint

For the primary end point ACR, imputation of patients to be non-responders is planned for confounding intercurrent events. To evaluate the extent to which the imputed non-responders are impacting the treatment difference, starting with the responder rates for the non-imputed values, the proportion attributable to the non-completers will be varied independently for each treatment group to get new estimates. Bernoulli sampling in SAS will be used to generate 15 imputations of the data to generate 15 complete datasets. The logistic regression specified in the primary efficacy analysis will be performed on each of the 15 complete sets of data and then results from the 15 analyses will be pooled for inference using PROC MIANALYZE to obtain inferential results. The difference in response rates (p-values) for each of the pairwise comparisons of active dose to placebo will be presented and clinically reviewed for the occurrence of any plausible number of responders that tip the primary results to a different finding. This analysis will only be conducted if more than 10% of the data from the primary analysis are imputed.

5.4.5. Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Proportion of patients achieving ACR50/70 at Week 12
- Proportion of patients achieving ACR20/50/70 at each scheduled timepoint
- Mean change from baseline in DAS28-CRP at each scheduled timepoint
- Proportion of patients achieving DAS28-CRP remission (score < 2.6) at each scheduled timepoint
- Proportion of patients achieving DAS28-CRP low disease activity (score ≤ 3.2) at each scheduled timepoint
- Mean change from baseline in CDAI at each scheduled timepoint
- Proportion of patients achieving CDAI remission (score ≤ 2.8) at each scheduled timepoint
- Percent change from baseline in hsCRP level at each scheduled timepoint
- HAQ-DI score at each scheduled timepoint
- SF-36v2 score at each scheduled timepoint
- FACIT-Fatigue score at each scheduled timepoint

The ACR20/ACR50/ACR70, DAS28-CRP, and CDAI will all be derived per the algorithms indicated in Section 3.3.6, as part of the statistical analysis. In contrast, for the HAQ-DI, SF-36v2, and the FACIT-Fatigue, the scale scores and any sub-scale scores, as applicable, will be used as computed and transferred from the clinical database. For the SF-36v2, the specific endpoint will be the Physical Component Summary (PCS), composed of four scales assessing physical function, role limitations caused by physical problems, bodily pain, and general health. All analyses will be based on the analysis visit windows defined in Section 3.3.7. Endpoints will only be presented for those analysis visit windows at which the endpoint was scheduled for collection.

5.4.6. Secondary Efficacy Analysis

The proportion of patients achieving ACR50/70 at Week 12, the proportion of patients achieving ACR20/50/70 at scheduled timepoints, the proportion of patients achieving DAS28-CRP remission (score < 2.6) at scheduled timepoints, the proportion of patients achieving DAS28-CRP low disease activity (score ≤ 3.2) at scheduled timepoints, and the proportion of patients achieving CDAI remission (score ≤ 2.8) at scheduled timepoints will be assessed using the same Firth's penalized likelihood logistic regression analysis method as used for the primary efficacy endpoint.

For continuous efficacy measures DAS28-CRP score, CDAI, HAQ-DI score, SF-36v2 Physical Component Summary (PCS) score, and FACIT-Fatigue score, the descriptive statistics for the observed scores, change from baseline, and percent change will be reported for each analysis visit at which the assessment was planned for collection.

For the SF-36v2, the analyses will specifically focus on the Physical Component Summary (PCS). PCS is composed of four scales assessing physical function, role limitations caused by physical problems, bodily pain, and general health. Higher scores represent better physical health.

For these continuous measures, the ATI-450 treatment groups will be assessed for differences to placebo treatment in the change from baseline using a mixed model repeated measures (MMRM). The MMRM will include fixed factors for treatment group, time, treatment-by-time interaction, and the one of the randomization strata (prior biologic or JAK RA treatment at screening), as well as a random effect for patient. At each applicable post-baseline analysis visit window in the treatment period, model-estimated least square (LS) means and SE, along with the 95% CI for the LS mean and difference in LS Means (vs placebo) will be presented for each treatment group. The p-value for testing hypothesis of no difference in the LS means between the ATI-450 treatment groups versus placebo will be presented.

For the analysis in the ITT population, for patients who discontinue treatment early and have missing assessments for all visits after discontinuation, the missing values for the expected scheduled visits will be imputed using the method of multiple imputation. The variables contributing to the MI model include treatment, baseline value for the applicable measure, one randomization strata (prior biologic or JAK RA treatment), and analysis week. For the MI approach, missing not at random (MNAR) is assumed. The procedure PROC MI in SAS will be used to generate 15 imputations of the data to generate 15 complete datasets. The MMRM will be performed on each of the 15 complete sets of data and then results from the 15 MMRM analyses will be pooled for inference using PROC MIANALYZE to obtain inferential results. For each analysis visit window, the pooled results will include the difference (95% CI) in LS Mean (vs Placebo), SE for the difference, and p-value associated with test of no difference in LS means between the active dose and placebo.

For the analysis in the PP population, the analysis specified above for the ITT population will be repeated for the PP population.

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 post-baseline timepoint.

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. All dose response modeling will be done at analysis visit Week 12. The treatment groups will be the independent variables and treated as continuous with values 0 for placebo and 20 and 50 for the ATI-450 20mg and 50 mg groups. An attempt will be made to fit a logistic regression to the responder endpoints (ACR20/50/70) and an Emax model will be attempted for the continuous endpoint DAS28-CRP. If these models can be fit to the data, then model-based estimates for the median effective dose (ED50) and ED90 (dose that produces the effect in 90% of the population) along with 95% CIs for these parameters will be provided. If the model for the continuous endpoint cannot be fit to the data, a linear regression model will be developed, and prediction responses will be plotted overlaid with the observed data.

All efficacy data will be presented in data listings.

5.4.7. Graphical Displays

For the binary efficacy endpoint of proportion of patients achieving ACR20, the responder rate (percentage) and 95% CI will be plotted over time by treatment group. For SJC, TJC, HAQ-DI, Patient Assessment of Pain, Patient Global Assessment, and Physician's Global Assessment, the mean change from baseline and 95% CI will be plotted by analysis visit. For hsCRP, the mean percent change from baseline and 95% CI will be plotted by analysis visit. For DAS-CRP, the LS mean change from baseline and 95% CI will be plotted by analysis visit.

5.5. SAFETY

All safety analyses will be performed on the Safety Population. Values for all safety variables will be listed by subject number and visit (as applicable).

5.5.1. Adverse Events

Adverse events (AE) will be mapped to a PT and system organ classification by Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.

An overall summary will be presented which includes the number of TEAEs and the number and percentage of patients who experienced at least one TEAE. This summary will also include:

- Any TEAE
- Any TEAE included in Events of Special Interest
- Any Serious TEAE
- Any Mild TEAEs
- Any Moderate TEAEs
- Any Severe TEAEs
- Any Related TEAEs
- Any TEAEs leading to discontinuation
- Any Related TEAEs leading to discontinuation

[REDACTED]

An additional summary of TEAEs will be provided showing the number and percentage of patients who experienced at least one TEAE. These summaries will be presented by system organ class (SOC) and PT. If a participant reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC for that participant. As with the PT, if a participant reports multiple conditions within the same SOC, that SOC will only be counted once for that participant. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all participants within each SOC.

The occurrence of TEAEs related to study medication, TEAEs leading to discontinuation, study drug related TEAEs leading to discontinuation, SAEs, and SAEs related to study medication will

also be tabulated by SOC and PT. An additional summary of TEAEs will be provided by SOC, PT and greatest severity. Most frequent TEAEs, defined as AEs occurring in 10% of all ATI-450 patients, will be summarized by PT.

All AEs reported will be listed by individual patient, showing both verbatim and PT. All AEs reported with a start date prior to the initiation of study medication will be excluded from the TEAE tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 3.3.5 as required to determine TEAEs.

5.5.2. Clinical Laboratory Assessments, Vital Signs, and Physical Examination Findings

Laboratory data (hematology, serum chemistry, coagulation, lipids and urinalysis) will be converted to Système International (SI) units for reporting and processing purposes. Descriptive summaries of absolute values of quantitative clinical laboratory results and their change from baseline values will be presented by analysis visit and by treatment group and overall. Observed values of categorical urinalysis data will be displayed with frequencies and percentages. All laboratory data will be listed for individual patients.

Treatment-emergent abnormal laboratory assessments will be based on the lab provided normal ranges. If the baseline laboratory assessment is normal and shifts to Low or High post-baseline, then the laboratory value is considered a TE abnormal laboratory value. For each protocol specified lab test, the number and percent of patients reporting a TE abnormal lab will be reported.

For CPK, Absolute Neutrophils, ALT, AST, and Bilirubin, laboratory abnormalities will be graded via the Common Terminology Criteria for Adverse Event (CTCAE) version 5.0. A summary of treatment-emergent laboratory toxicities for the indicated laboratory results by maximum CTCAE toxicity grades will be reported. A separate summary of CPK and ALT or AST treatment-emergent toxicities will be provided. The number of patients by maximum toxicity grade as well as every occurrence/event will be summarized separately for CPK and ALT or AST as well as the combination.

All laboratory summaries will be limited to the tests specified in the protocol.

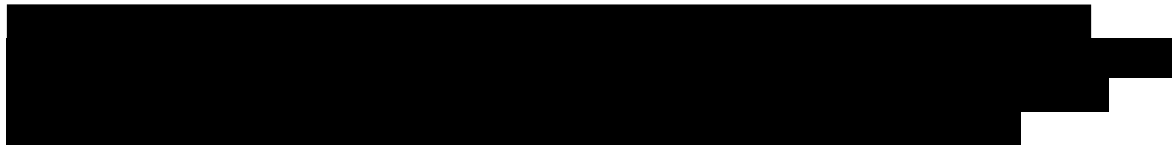
Vital signs include height, weight, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, respiratory rate, and pulse. Summary tables will present the average for BMI, temperature, respiratory rate and pulse and the average of the triplicate results for SBP and DBP. Change from baseline will be summarized descriptively by treatment group at each scheduled evaluation and all vital sign data will be listed.

5.5.3. Other Safety Analyses

ECG measurements will include heart rate, QT interval, Fredericia-corrected QT interval (QTcF), PR interval, and QRS interval. Triplicate ECG values will be obtained at each timepoint. Summary tables will present the average of the triplicate ECG results. Change from baseline will be summarized descriptively by treatment group at each scheduled evaluation and all ECG data will be listed. The proportion of patients with abnormal ECG interpretations will be summarized at each study visit and by treatment group and overall for both investigator and central interpretation. Proportion of patients who meet each of the following criteria from International Conference on Harmonization Guideline E14 “Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs” (October 2005) for QT and corrected QT intervals will be summarized across treatment groups:

- QTcF >450 msec
- QTcF >480 msec
- QTcF >500 msec
- QTcF increases from baseline by >30 msec
- QTcF increases from baseline by >60 msec

The above summaries will be repeated with QT instead of QTcF.



5.5.4. Safety Graphs

Plots of QTcF and laboratory values over time will be prepared for tests as specified by the DSMB. The laboratory tests include: CPK, Absolute Neutrophils, ALT, AST, and Bilirubin.

5.6. PHARMAKOKINETICS

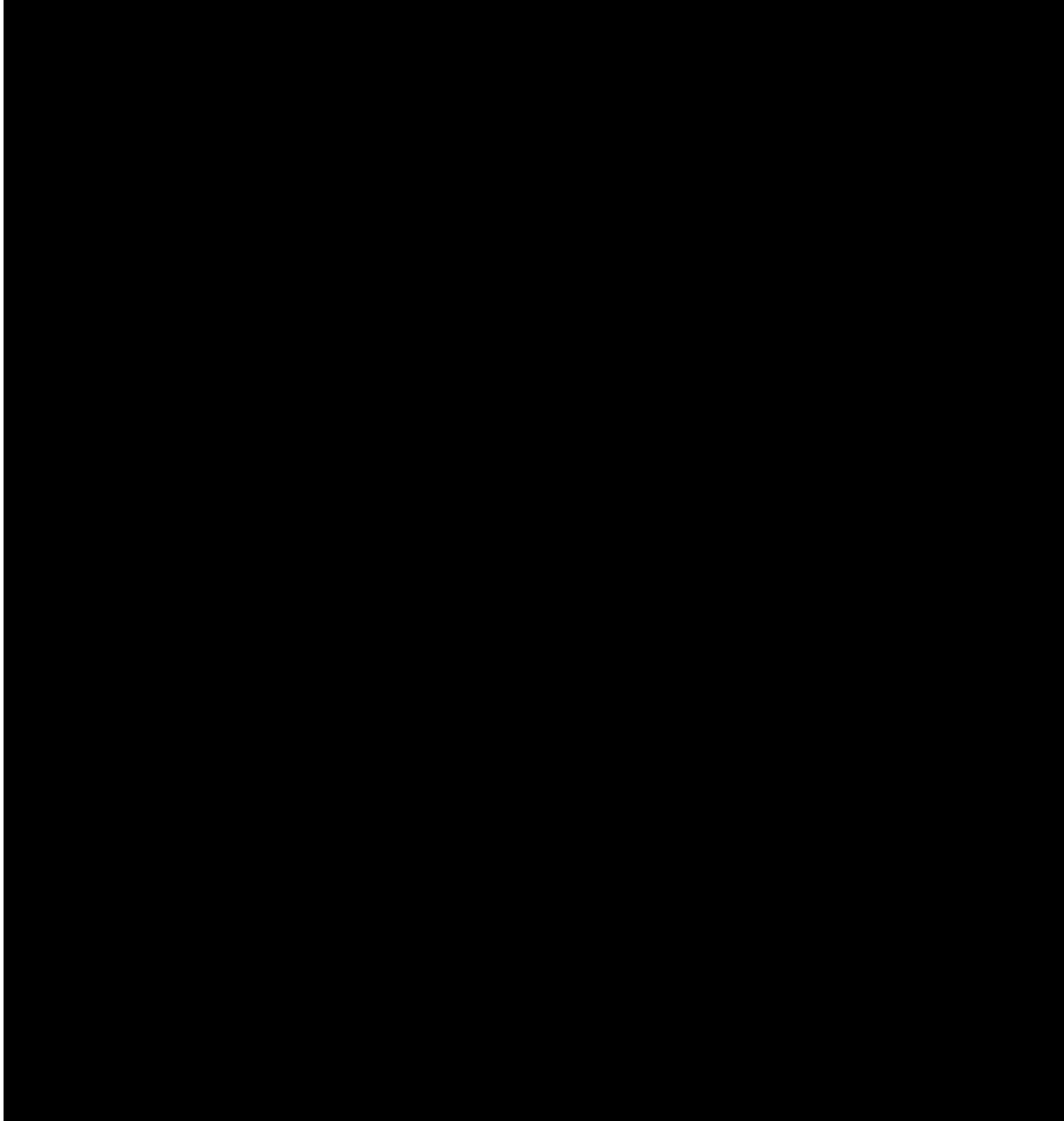
All PK analyses will be performed using the PK Population. Plasma concentrations of ATI-450 and its primary circulating metabolite, CDD-2164, will be summarized by day. Concentration versus time since dose (Days 1, 8, 15, 29, 43, 57, and 85) will be displayed by linear scale.

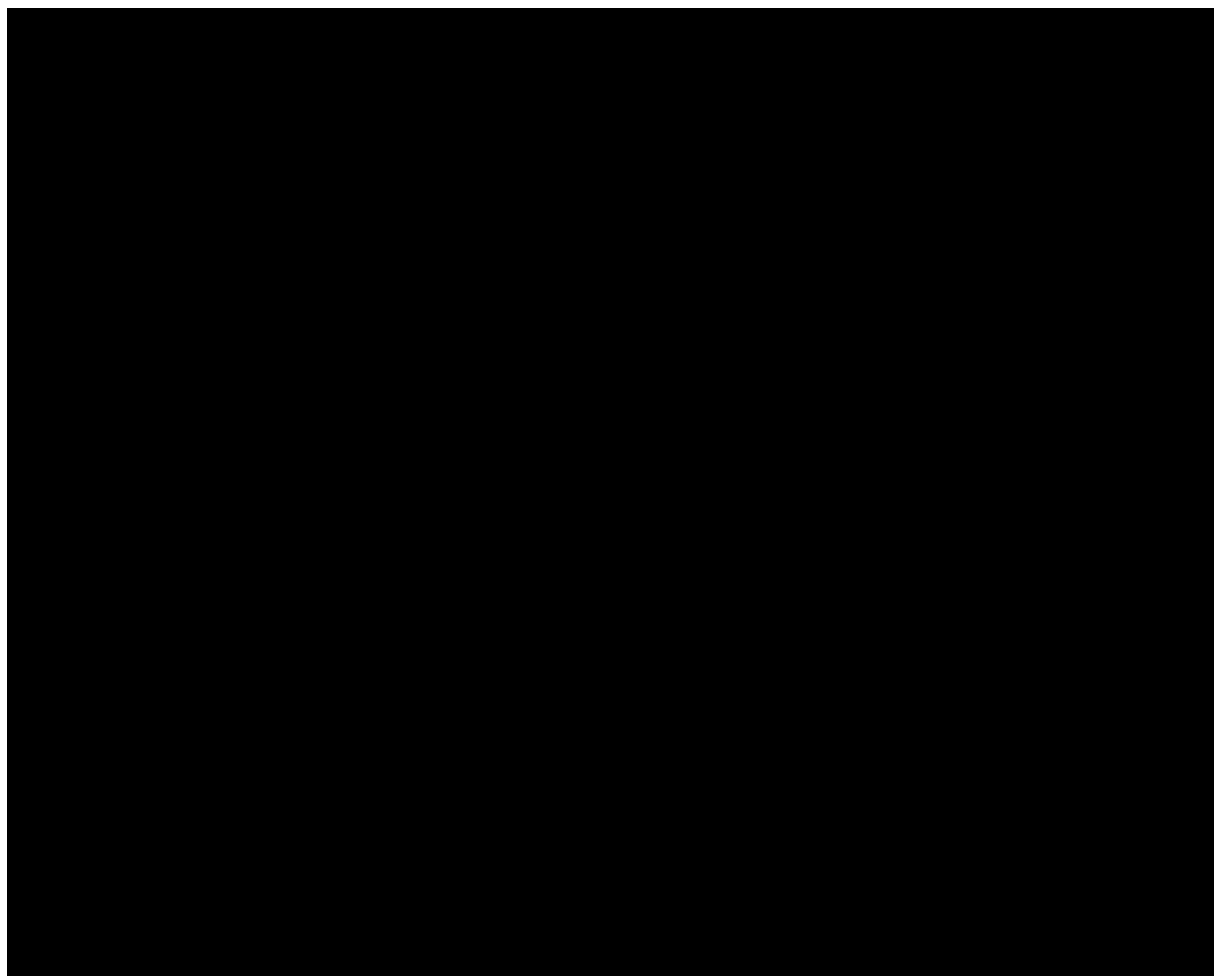
The PK blood sample collection dates and times for each nominal day and timepoint will be reported in a data listing. The listing will also include the actual elapsed time calculated relative to the time of dosing for each nominal timepoint and the ATI-450 plasma concentration value.

6. CHANGES IN THE PROTOCOL-SPECIFIED ANALYSES

All analyses specified in the SAP are consistent with those specified in the protocol. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

7. REVISION HISTORY





8. **REFERENCES**

Billingsley, P. (1986). Probability and Measure. 2nd ed. New York: John Wiley and Sons.

9. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8.
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all patients.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of patients contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of patients in the analysis population due to missing data.
 - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations.
 - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by treatment group, subject number and date, if applicable. Lab listings may be sorted by subject, parameter, and date.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- Numerical Values: The presentation of numerical values will adhere to the following guidelines:
 - Raw measurements will be reported to the number of significant digits as captured electronically or on the eCRFs.
 - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented.
 - Means will be reported to one decimal place beyond the number of significant digits as the parameter.

- Calculated percentages will be reported to one decimal place.
- Dates will be formatted as DDMMYYYY. Partial dates will be presented on data listings as recorded on eCRFs.
- Time will be presented according to the 24-hour clock (HH:MM).

10. PROPOSED TABLES, LISTINGS, AND FIGURES

Tables

Section 14.1 Accountability and Baseline Characteristics

Table 14.1.1.1 Study Disposition and Reasons for Early Termination from the Study, ITT Population

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