Clinical trial results:
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

Summary

EudraCT number	2021-002860-31
Trial protocol	CZ BG
Global end of trial date	11 October 2023

Results information

Result version number	v1 (current)
This version publication date	10 October 2024
First version publication date	10 October 2024

Trial information

Trial identification

Sponsor protocol code	ATI-450-RA-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aclaris Therapeutics, Inc.
Sponsor organisation address	701 Lee Road, Suite 103, Wayne/PA, United States, 19087
Public contact	Clinical Operations, Aclaris Therapeutics, Inc., 1 4843247933, clinicaloperations@aclaristx.com
Scientific contact	Clinical Operations, Aclaris Therapeutics, Inc., 1 4843247933, clinicaloperations@aclaristx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2022
Global end of trial reached?	Yes
Global end of trial date	11 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluates ATI-450 plus MTX versus placebo plus MTX in participants with moderate to severe active RA who have had an inadequate response to MTX alone.

Protection of trial subjects:

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCP), including the archiving of essential documents as well as the ethical principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 39
Country: Number of subjects enrolled	Czechia: 17
Country: Number of subjects enrolled	Poland: 131
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	251
EEA total number of subjects	187

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	187
From 65 to 84 years	64

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One participant randomized to the placebo group was identified as not meeting inclusion criteria and therefore, was not dosed in the study. The participant was included in the Intent-to-Treat (ITT) Population but excluded from the Safety Population.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ATI-450 20 mg plus MTX

Arm description:

Participants randomized to receive ATI-450 20 milligrams (mg) oral tablet twice daily (BID) with a stable weekly dose of methotrexate (MTX) (15 mg to 25 mg weekly).

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Stable weekly dose of methotrexate (15 mg to 25 mg) for 12 weeks

Investigational medicinal product name	ATI-450 20 mg
Investigational medicinal product code	
Other name	zunsemetinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ATI-450 20 mg oral tablet twice daily (BID) for 12 weeks

Arm title	ATI-450 50 mg plus MTX

Arm description:

Participants randomized to receive ATI-450 50 mg oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly)

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Stable weekly dose of methotrexate (15 mg to 25 mg) for 12 weeks

Investigational medicinal product name	ATI-450 50 mg
Investigational medicinal product code	
Other name	zunsemetinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ATI-450 50 mg oral tablet twice daily (BID) for 12 weeks

Arm title	Placebo plus MTX

Arm description:

Participants randomized to receive placebo oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly).

Arm type	Placebo
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Stable weekly dose of methotrexate (15 mg to 25 mg) for 12 weeks

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for 12 weeks

Number of subjects in period 1	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX
Started	83	84	84
ITT Population (Randomized)	83	84	84
Completed	66	63	73
Not completed	17	21	11
Consent withdrawn by subject	9	11	4
Adverse event, non-fatal	3	8	-
Lost to follow-up	3	2	1
Discontinued prior to dosing	-	-	1
Lack of efficacy	1	-	5
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	ATI-450 20 mg plus MTX
Reporting group description:	
Participants randomized to receive ATI-450 20 milligrams (mg) oral tablet twice daily (BID) with a stable weekly dose of methotrexate (MTX) (15 mg to 25 mg weekly).	
Reporting group title	ATI-450 50 mg plus MTX
Reporting group description:	
Participants randomized to receive ATI-450 50 mg oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly)	
Reporting group title	Placebo plus MTX
Reporting group description:	
Participants randomized to receive placebo oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly).	

Reporting group values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX
Number of subjects	83	84	84
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	55.9	55.8	55.5
standard deviation	± 10.28	± 10.79	± 11.86
Sex: Female, Male Units: participants			
Female	62	64	72
Male	21	20	12
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	14	12
Not Hispanic or Latino	72	61	67
Unknown or Not Reported	4	9	5
Race/Ethnicity, Customized Units: Subjects			
Black or African American	3	2	3
White	76	73	75
Asian	0	1	0
Not reported	4	8	6

DAS28-CRP (Categorical) Units: Subjects			
≥ 3.2 to ≤ 5.1 (Moderate Disease Activity)	27	30	27
> 5.1 (High/Severe Disease Activity)	56	54	56
Not Assessed	0	0	1
Disease Activity Score using 28 Joint Count-C-reactive Protein (DAS28-CRP)			
The DAS28-CRP consists of a composite score of the following variables: tender joint count out of 28 joint count (TJC28), swollen joint count out of 28 joint count (SJC28), C-reactive protein (CRP) (hsCRP is used for the purposes of this study), and Patient's Global Assessment of Disease Activity. Interpretation of the DAS28-CRP 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.			
Units: units on a scale			
arithmetic mean	5.43	5.47	5.45
standard deviation	± 0.769	± 0.866	± 0.806
High-sensitivity C-reactive protein (hsCRP) Units: mg/L			
median	5.58	6.22	4.40
full range (min-max)	0.17 to 74.63	0.15 to 127.53	0.46 to 74.58

Reporting group values	Total		
Number of subjects	251		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: participants			
Female	198		
Male	53		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	33		
Not Hispanic or Latino	200		
Unknown or Not Reported	18		
Race/Ethnicity, Customized Units: Subjects			
Black or African American	8		

White	224		
Asian	1		
Not reported	18		
DAS28-CRP (Categorical) Units: Subjects			
≥ 3.2 to ≤ 5.1 (Moderate Disease Activity)	84		
> 5.1 (High/Severe Disease Activity)	166		
Not Assessed	1		
Disease Activity Score using 28 Joint Count-C-reactive Protein (DAS28-CRP)			
The DAS28-CRP consists of a composite score of the following variables: tender joint count out of 28 joint count (TJC28), swollen joint count out of 28 joint count (SJC28), C-reactive protein (CRP) (hsCRP is used for the purposes of this study), and Patient's Global Assessment of Disease Activity. Interpretation of the DAS28-CRP 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.			
Units: units on a scale arithmetic mean standard deviation	- -		
High-sensitivity C-reactive protein (hsCRP) Units: mg/L median full range (min-max)	- -		

End points

End points reporting groups

Reporting group title	ATI-450 20 mg plus MTX
Reporting group description:	
Participants randomized to receive ATI-450 20 milligrams (mg) oral tablet twice daily (BID) with a stable weekly dose of methotrexate (MTX) (15 mg to 25 mg weekly).	
Reporting group title	ATI-450 50 mg plus MTX
Reporting group description:	
Participants randomized to receive ATI-450 50 mg oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly)	
Reporting group title	Placebo plus MTX
Reporting group description:	
Participants randomized to receive placebo oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly).	

Primary: Percentage of Participants Achieving ACR20 at Week 12

End point title	Percentage of Participants Achieving ACR20 at Week 12
End point description:	
Participants achieving American College of Rheumatology (ACR) 20 (responders) were defined as having ≥20% improvement in both the number of swollen and tender joints (66/68 joint counts) and ≥20% improvement in ≥3 of the following 5 measures: Patient's Global Assessment of Disease Activity (VAS), Patient's Assessment of Arthritis Pain (VAS), Health Assessment Questionnaire-Disability Index (HAQ-DI), Physician's Global Assessment of Disease Activity (VAS), and acute phase reactant as measured by hsCRP. Model-based estimates and 95% confidence intervals (CIs) were produced.	
End point type	Primary
End point timeframe:	
Week 12	

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	84	
Units: percentage of participants				
number (confidence interval 95%)	42.2 (31.5 to 52.9)	34.7 (24.2 to 44.9)	46.5 (35.7 to 57.2)	

Statistical analyses

Statistical analysis title	Participants Achieving ACR20
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX

Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12 [1]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-11.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.63
upper limit	3.07

Notes:

[1] - Significance level = 0.05.

Statistical analysis title	Participants Achieving ACR20
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.585 [2]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-4.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.38
upper limit	10.95

Notes:

[2] - Significance level = 0.05.

Secondary: Percentage of Participants Achieving ACR50 at Week 12

End point title	Percentage of Participants Achieving ACR50 at Week 12

End point description:

Participant achieving ACR50 (responders) were defined as having ≥50% improvement in both the number of swollen and tender joints (66/68 joint counts) and ≥50% improvement 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. Model-based estimates and 95% CIs were produced.

End point type	Secondary

End point timeframe:

Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	84	
Units: percentage of participants				
number (confidence interval 95%)	20.9 (12.1 to 29.7)	20.7 (12.0 to 29.4)	27.7 (18.1 to 37.3)	

Statistical analyses

Statistical analysis title	Participants Achieving ACR50
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.305 [3]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.84
upper limit	6.23

Notes:

[3] - Significance level = 0.05.

Statistical analysis title	Participants Achieving ACR50
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.286 [4]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-7.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.02
upper limit	5.93

Notes:

[4] - Significance level = 0.05.

Secondary: Percentage of Participants Achieving ACR70 at Week 12

End point title	Percentage of Participants Achieving ACR70 at Week 12

End point description:

Participants achieving ACR70 (responders) were defined as having ≥70% improvement in both the number of swollen and tender joints (66/68 joint counts) and ≥70% improvement 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. Model-based estimates and 95% CIs were produced.

End point type	Secondary

End point timeframe:

Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	84	
Units: percentage of participants				
number (confidence interval 95%)	8.9 (2.8 to 15.1)	7.6 (1.9 to 13.3)	14.7 (7.1 to 22.3)	

Statistical analyses

Statistical analysis title	Participants Achieving ACR70
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.144 [5]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-7.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.53
upper limit	2.43

Notes:

[5] - Significance level = 0.05.

Statistical analysis title	Participants Achieving ACR70
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.246 [6]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-5.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.53
upper limit	3.99

Notes:

[6] - Significance level = 0.05.

Secondary: Change from baseline in DAS28-CRP at Week 12

End point title	Change from baseline in DAS28-CRP at Week 12

End point description:

The DAS28-CRP consists of a composite score of the following variables: TJC28, SJC28, CRP (hsCRP was used for the purposes of this study), and Patient's Global Assessment of Disease Activity. Interpretation of the DAS28-CRP 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. The least square (LS) mean change from baseline in DAS28-CRP at Week 12 was estimated from the Mixed Model Repeated Measures (MMRM) model.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	84	
Units: units on a scale				
least squares mean (standard error)	-1.66 (± 0.170)	-1.64 (± 0.167)	-1.60 (± 0.162)	

Statistical analyses

Statistical analysis title	Change from baseline in DAS28-CRP
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87 [7]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.41

Notes:

[7] - Significance level = 0.05.

Statistical analysis title	Change from baseline in DAS28-CRP
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.797 [8]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.4

Notes:

[8] - Significance level = 0.05.

Secondary: Percentage of Participants Achieving DAS28-CRP Low Disease Activity (Score ≤ 3.2) at Week 12

End point title	Percentage of Participants Achieving DAS28-CRP Low Disease Activity (Score ≤ 3.2) at Week 12

End point description:

The DAS28-CRP consists of a composite score of the following variables: TJC28, SJC28, CRP (hsCRP is used for the purposes of this study), and Patient's Global Assessment of Disease Activity. Interpretation of the DAS28-CRP 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. Model-based estimates and 95% CIs were produced.

End point type	Secondary

End point timeframe:

Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	84	
Units: percentage of participants				
number (confidence interval 95%)	24.1 (14.8 to 33.4)	19.1 (10.7 to 27.6)	29.8 (19.9 to 39.7)	

Statistical analyses

Statistical analysis title	Achieving DAS28-CRP Low Disease Activity
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX

Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108 [9]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-10.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.65
upper limit	2.37

Notes:

[9] - Significance level = 0.05.

Statistical analysis title	Achieving DAS28-CRP Low Disease Activity
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.414 [10]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-5.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.19
upper limit	7.93

Notes:

[10] - Significance level = 0.05.

Secondary: Percentage of Participants Achieving DAS28-CRP Remission (Score <2.6) at Week 12

End point title	Percentage of Participants Achieving DAS28-CRP Remission (Score <2.6) at Week 12

End point description:

The Disease Activity Score using 28 Joint Count-C-reactive protein (DAS28-CRP) consists of a composite score of the following variables: TJC28, SJC28, CRP (hsCRP is used for the purposes of this study), and Patient's Global Assessment of Disease Activity. Interpretation of the DAS28-CRP 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. Model-based estimates and 95% CIs were produced.

End point type	Secondary

End point timeframe:

Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	84	
Units: percentage of participants				
number (confidence interval 95%)	19.8 (11.1 to 28.4)	14.8 (7.2 to 22.4)	21.9 (13.0 to 30.8)	

Statistical analyses

Statistical analysis title	Participants Achieving DAS28-CRP Remission
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.236 [11]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-7.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.77
upper limit	4.65

Notes:

[11] - Significance level = 0.05.

Statistical analysis title	Participants Achieving DAS28-CRP Remission
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.736 [12]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.49
upper limit	10.25

Notes:

[12] - Significance level = 0.05.

Secondary: Change from Baseline in CDAI Score at Week 12

End point title	Change from Baseline in CDAI Score at Week 12

End point description:

The Clinical Disease Activity Index (CDAI) was 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; and • Physician’s Global Assessment of Disease Activity. Interpretation of the CDAI disease activity was measured on a scale of 0 to 76, where ≤2.8 was considered remission, >2.8 to ≤10 was considered low/minimal disease activity, >10 to ≤22 was considered moderate disease activity, and >22.0 was considered high/severe disease activity. LS mean change from baseline in CDAI score at Week 12 was estimated from the MMRM model.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	83	
Units: units on a scale				
least squares mean (standard error)	-18.39 (± 1.595)	-17.79 (± 1.669)	-17.89 (± 1.524)	

Statistical analyses

Statistical analysis title	Change from Baseline in CDAI Score
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.963 [13]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	4.3

Notes:

[13] - Significance level = 0.05.

Statistical analysis title	Change from Baseline in CDAI Score
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.812 [14]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.66
upper limit	3.65

Notes:

[14] - Significance level = 0.05.

Secondary: Change from Baseline in HAQ-DI Score at Week12

End point title	Change from Baseline in HAQ-DI Score at Week12

End point description:

The HAQ-DI (standard disability method calculation) was utilized to assess the participant's physical function or disability according to the participant. 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]). Responses in each functional area are scored from 0 (no difficulty) to 3 (inability to perform a ask in that area). Overall score was computed as the sum of category scores and divided by the number of categories answered, ranging from 0 to 3. A lower score demonstrated less disability. LS mean change from baseline in HAQ-DI score at Week 12 was estimated from the MMRM model.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	79	81	
Units: units on a scale				
least squares mean (standard error)	-0.24 (± 0.072)	-0.33 (± 0.067)	-0.37 (± 0.063)	

Statistical analyses

Statistical analysis title	Change from Baseline in HAQ-DI Score
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.622 [15]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.21

Notes:
[15] - Significance level = 0.05.

Statistical analysis title	Change from Baseline in HAQ-DI Score
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.31

Secondary: Percentage of Participants Achieving CDAI Remission (score ≤ 2.8)

End point title	Percentage of Participants Achieving CDAI Remission (score ≤ 2.8)

End point description:

The CDAI was 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; and • Physician's Global Assessment of Disease Activity. Interpretation of the CDAI disease activity was measured on a scale of 0 to 76, where ≤2.8 was considered remission, >2.8 to ≤10 was considered low/minimal disease activity, >10 to ≤22 was considered moderate disease activity, and >22.0 was considered high/severe disease activity. Model-based estimates and 95% CIs were produced.

End point type	Secondary

End point timeframe:

Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	84	
Units: percentage of participants				
number (confidence interval 95%)	6.6 (1.3 to 12.0)	6.6 (1.2 to 11.9)	7.7 (2.0 to 13.5)	

Statistical analyses

Statistical analysis title	Participants Achieving CDAI Remission
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX

Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.765
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.97
upper limit	6.6

Statistical analysis title	Participants Achieving CDAI Remission
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78 [16]
Method	Regression, Logistic
Parameter estimate	Difference in Model Estimate
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.94
upper limit	6.72

Notes:

[16] - Significance level = 0.05.

Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) Score at Week 12

End point title	Change from Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) Score at Week 12

End point description:

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 level of fatigue is measured on a 4 point Likert scale (4 = not at all fatigued to 0 = very much fatigued). The total score range is from 0 to 52. The higher the score, the lower the fatigue level. LS mean change from baseline in FACIT-Fatigue score at Week 12 was estimated from the MMRM model.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	78	81	
Units: units on a scale				
least squares mean (standard error)	4.21 (± 1.296)	6.93 (± 1.313)	6.53 (± 1.168)	

Statistical analyses

Statistical analysis title	Change from Baseline in FACIT-Fatigue Score
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.816 [17]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.01
upper limit	3.81

Notes:

[17] - Significance level = 0.05.

Statistical analysis title	Change from Baseline in FACIT-Fatigue Score
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174 [18]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.66
upper limit	1.03

Notes:

[18] - Significance level = 0.05.

Secondary: Percent Change from Baseline in hsCRP Level at Week 12

End point title	Percent Change from Baseline in hsCRP Level at Week 12

End point description:

Blood samples were evaluated to measure levels of hsCRP.

End point type	Secondary

End point timeframe: Baseline, Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	59	76	
Units: percent change				
median (full range (min-max))	-28.274 (-89.766 to 1121.0533)	-22.779 (-86.392 to 528.571)	1.546 (-93.280 to 838.047)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Short Form Health Survey SF-36 Physical Component Summary (PCS) Score at Week 12

End point title	Change from Baseline in Short Form Health Survey SF-36 Physical Component Summary (PCS) Score at Week 12

End point description:

The PCS is composed of 4 scales of the Short Form-36 Health Status Survey Questionnaire (SF-36) version 2 assessing physical function, role limitations caused by physical problems, bodily pain, and general health. The range of the SF-36 PCS is between 0 and 100, where higher scores represent better physical functioning. A 2.5 to 5-point change from baseline is established as the minimum clinically-important difference for the PCS in RA participants. LS mean change from baseline in SF-36 PCS score at Week 12 was estimated from the MMRM model.

End point type	Secondary

End point timeframe: Baseline, Week 12

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo plus MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	80	81	
Units: units on a scale				
least squares mean (standard error)	6.48 (± 1.025)	7.08 (± 1.057)	7.01 (± 0.935)	

Statistical analyses

Statistical analysis title	Change from Baseline in SF-36 PCS Score
Comparison groups	ATI-450 50 mg plus MTX v Placebo plus MTX

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.958 [19]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	2.66

Notes:

[19] - Significance level = 0.05.

Statistical analysis title	Change from Baseline in SF-36 PCS Score
Comparison groups	ATI-450 20 mg plus MTX v Placebo plus MTX
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.687 [20]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	2.07

Notes:

[20] - Significance level = 0.05.

Secondary: ATI-450 and Metabolite (CDD-2164) Concentrations

End point title	ATI-450 and Metabolite (CDD-2164) Concentrations[21]

End point description:

End point type	Secondary

End point timeframe:

2 hours postdose on Days 1, 8, and 85

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified by the protocol and SAP, pharmacokinetic data are presented for ATI-450 and Metabolite (CDD-2164) only.

End point values	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	84		
Units: ng/milliliters (mL)				
arithmetic mean (standard deviation)				
ATI-450 Day 1	79.289 (± 46.0493)	177.627 (± 120.9491)		
ATI-450 Day 8	104.032 (± 41.8903)	245.377 (± 113.5619)		
ATI-450 Day 85	94.615 (± 58.6913)	244.670 (± 127.9654)		
CDD-2164 Day 1	30.609 (± 18.8977)	66.602 (± 47.0467)		
CDD-2164 Day 8	36.375 (± 15.6280)	89.692 (± 48.0216)		
CDD-2164 Day 85	33.219 (± 21.5870)	89.196 (± 50.6267)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (after dosing) through Week 16

Adverse event reporting additional description:

Serious adverse events (AEs) and non-serious AEs were assessed using Safety Population (dosed) and analyzed by treatment received. 1 participant in ATI-450 20 mg received 50 mg and was included in ATI-450 50 mg Plus MTX arm. 1 participant in placebo was not dosed and excluded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	ATI-450 20 mg plus MTX

Reporting group description:

Participants received ATI-450 20 mg oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly).

Reporting group title	ATI-450 50 mg plus MTX

Reporting group description:

Participants received ATI-450 50 mg oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly)

Reporting group title	Placebo Plus MTX

Reporting group description:

Participants received placebo oral tablet BID with a stable weekly dose of MTX (15 mg to 25 mg weekly).

Serious adverse events	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo Plus MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 82 (0.00%)	3 / 85 (3.53%)	1 / 83 (1.20%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Ultrasound ovary abnormal			
subjects affected / exposed	0 / 82 (0.00%)	1 / 85 (1.18%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 85 (1.18%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 85 (1.18%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 82 (0.00%)	1 / 85 (1.18%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 85 (1.18%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	ATI-450 20 mg plus MTX	ATI-450 50 mg plus MTX	Placebo Plus MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 82 (24.39%)	31 / 85 (36.47%)	12 / 83 (14.46%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	1 / 83 (1.20%)
occurrences (all)	0	2	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	1 / 83 (1.20%)
occurrences (all)	0	2	1
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 82 (2.44%)	3 / 85 (3.53%)	1 / 83 (1.20%)
occurrences (all)	2	3	1
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 82 (2.44%)	1 / 85 (1.18%)	0 / 83 (0.00%)
occurrences (all)	2	1	0
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Ventricular extrasystoles			
subjects affected / exposed	2 / 82 (2.44%)	0 / 85 (0.00%)	0 / 83 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 82 (2.44%)	1 / 85 (1.18%)	1 / 83 (1.20%)
occurrences (all)	2	1	1
Tremor			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Pregnancy, puerperium and perinatal conditions			
Headache			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	1 / 83 (1.20%)
occurrences (all)	0	2	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 85 (0.00%)	0 / 83 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 82 (2.44%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	2	2	0
Aphthous ulcer			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	1 / 82 (1.22%)	3 / 85 (3.53%)	1 / 83 (1.20%)
occurrences (all)	1	3	1
Nausea			

subjects affected / exposed	2 / 82 (2.44%)	4 / 85 (4.71%)	1 / 83 (1.20%)
occurrences (all)	2	4	1
Vomiting			
subjects affected / exposed	1 / 82 (1.22%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	1	2	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	1 / 82 (1.22%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 82 (1.22%)	2 / 85 (2.35%)	1 / 83 (1.20%)
occurrences (all)	1	2	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 82 (0.00%)	2 / 85 (2.35%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	2 / 82 (2.44%)	3 / 85 (3.53%)	3 / 83 (3.61%)
occurrences (all)	2	3	3
Upper respiratory tract infection			
subjects affected / exposed	5 / 82 (6.10%)	2 / 85 (2.35%)	1 / 83 (1.20%)
occurrences (all)	5	2	1
Urinary tract infection			
subjects affected / exposed	2 / 82 (2.44%)	2 / 85 (2.35%)	1 / 83 (1.20%)
occurrences (all)	2	2	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 85 (1.18%)	2 / 83 (2.41%)
occurrences (all)	1	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2001	- Additional ECGs and PKs to allow for cardiac safety monitoring. - Added Exclusion Criteria for cardiac safety.
12 August 2021	- Safety guidelines for SARS-CoV-2 pandemic.
22 November 2021	- One ATI-450 dose arm removed.
04 February 2022	- Updated concomitant medication allowed - Oral contraceptives allowed. - For Inclusion, Prior Hepatitis B, C, latent tuberculosis exposures, and marijuana use clarified.
13 May 2022	- Details added regarding rescreening guidelines. - COVID-19 treatment guidance added. Guidance added for temporary discontinuation due to COVID-19 or unrelated AEs. Maximum allowed number of days of a temporary discontinuation updated. - Sample size calculations updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: