Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Investigate the Safety and Efficacy of ABT-494 with Background Methotrexate (MTX) in Subjects with Active Rheumatoid Arthritis (RA) Who Have Had an Inadequate Response to MTX Alone.

Summary

EudraCT number	2013-003984-72
Trial protocol	LV HU CZ SK ES
Global end of trial date	02 July 2015

Results information

Result version number	v2 (current)
This version publication date	10 October 2019
First version publication date	15 July 2016
Version creation reason	• Correction of full data set Correction needed

Trial information

Trial identification

Sponsor protocol code	M13-537

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02066389
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbvie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110,
Scientific contact	Aileen L. Pangan, AbbVie , aileen.pangan@abbvie.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	02 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the safety and efficacy of multiple doses of ABT-494 versus placebo in subjects with moderately to severely active rheumatoid arthritis on stable background MTX therapy who have not shown an adequate response to MTX alone.

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy:

Subjects were to have received oral or parenteral MTX therapy for at least 3 months, and been on a stable prescription (titration completed) of 7.5 to 25 mg/week MTX for at least 4 weeks prior to initiating study drug. Subjects were to continue on their stable dose of MTX throughout the study. In addition, all subjects were to take a dietary supplement of oral folic acid (or equivalent) from 4 weeks prior to Day 1 (Baseline) throughout the study. Folic acid dosing and timing of the regimen was to be followed according to PI instructions.

Evidence for comparator: -

Actual start date of recruitment	26 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Bulgaria: 59
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Latvia: 14
Country: Number of subjects enrolled	Chile: 31
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Mexico: 22
Country: Number of subjects enrolled	Puerto Rico: 3
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	United States: 30

Worldwide total number of subjects	300
EEA total number of subjects	185

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)	232
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 300 subjects were enrolled at 59 study sites located in 16 countries.

Pre-assignment

Screening details:

This study recruited adult females and males who were at least 18 years of age with a diagnosis of RA, as defined by either the 1987-revised ACR classification criteria or the ACR/European League Against Rheumatism (EULAR) 2010 Criteria, for ≥ 3 months and who had an inadequate response or intolerance to MTX therapy alone.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo capsules twice daily for 12 weeks.

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

Dosage and administration details:

Administered orally twice daily

Arm title	ABT-494 3 mg BID

Arm description:

Participants received 3 mg ABT-494 twice daily (BID) for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	ABT-494
Investigational medicinal product code	ABT-494
Other name	Upadacitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered orally twice daily

Arm title	ABT-494 6 mg BID

Arm description:

Participants received 6 mg ABT-494 twice daily for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	ABT-494
Investigational medicinal product code	ABT-494
Other name	Upadacitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Administered orally twice daily

Arm title	ABT-494 12 mg BID

Arm description:
Participants received 12 mg ABT-494 twice daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	ABT-494
Investigational medicinal product code	ABT-494
Other name	Upadacitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Administered orally twice daily

Arm title	ABT-494 18 mg BID

Arm description:
Participants received 18 mg ABT-494 twice daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	ABT-494
Investigational medicinal product code	ABT-494
Other name	Upadacitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Administered orally twice daily

Arm title	ABT-494 24 mg QD

Arm description:
Participants received 24 mg ABT-494 once daily (QD) for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	ABT-494
Investigational medicinal product code	ABT-494
Other name	Upadacitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Administered orally once daily

Number of subjects in period 1	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID
Started	50	50	50
Received Treatment	50	50	50
Completed	45	49	44
Not completed	5	1	6

Randomized in error	-	-	-
Consent withdrawn by subject	4	-	5
Adverse event	1	1	1
Lost to follow-up	-	-	-

Number of subjects in period 1	ABT-494 12 mg BID	ABT-494 18 mg BID	ABT-494 24 mg QD
Started	50	50	50
Received Treatment	50	50	49
Completed	47	43	45
Not completed	3	7	5
Randomized in error	-	-	1
Consent withdrawn by subject	1	1	2
Adverse event	1	5	1
Lost to follow-up	1	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo capsules twice daily for 12 weeks.	
Reporting group title	ABT-494 3 mg BID
Reporting group description:	
Participants received 3 mg ABT-494 twice daily (BID) for 12 weeks.	
Reporting group title	ABT-494 6 mg BID
Reporting group description:	
Participants received 6 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 12 mg BID
Reporting group description:	
Participants received 12 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 18 mg BID
Reporting group description:	
Participants received 18 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 24 mg QD
Reporting group description:	
Participants received 24 mg ABT-494 once daily (QD) for 12 weeks.	

Reporting group values	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID
Number of subjects	50	50	50
Age categorical Units: Subjects			
18 to < 45 years	9	11	9
45 to < 65 years	32	30	30
≥ 65 years	9	9	11
Gender categorical Units: Subjects			
Female	38	40	34
Male	12	10	16

Reporting group values	ABT-494 12 mg BID	ABT-494 18 mg BID	ABT-494 24 mg QD
Number of subjects	50	50	50
Age categorical Units: Subjects			
18 to < 45 years	7	13	7
45 to < 65 years	32	25	27
≥ 65 years	11	12	16
Gender categorical Units: Subjects			
Female	41	42	43
Male	9	8	7

Reporting group values	Total		
Number of subjects	300		

Age categorical Units: Subjects			
18 to < 45 years	56		
45 to < 65 years	176		
≥ 65 years	68		
Gender categorical Units: Subjects			
Female	238		
Male	62		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo capsules twice daily for 12 weeks.	
Reporting group title	ABT-494 3 mg BID
Reporting group description:	
Participants received 3 mg ABT-494 twice daily (BID) for 12 weeks.	
Reporting group title	ABT-494 6 mg BID
Reporting group description:	
Participants received 6 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 12 mg BID
Reporting group description:	
Participants received 12 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 18 mg BID
Reporting group description:	
Participants received 18 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 24 mg QD
Reporting group description:	
Participants received 24 mg ABT-494 once daily (QD) for 12 weeks.	

Primary: Percentage of Participants with an American College of Rheumatology 20% (ACR20) Response at Week 12

End point title	Percentage of Participants with an American College of Rheumatology 20% (ACR20) Response at Week 12

End point description:

A participant was a responder if the following 3 criteria for improvement from baseline were met:
- ≥ 20% improvement in tender joint count;
- ≥ 20% improvement in swollen joint count; and
- ≥ 20% improvement in at least 3 of the 5 following parameters:
  - Physician global assessment of disease activity
  - Patient global assessment of disease activity
  - Patient assessment of pain
  - Health Assessment Questionnaire – Disability Index (HAQ-DI)
  - High sensitivity C-reactive protein (hsCRP).

The analysis was performed in all randomized and treated participants; last observation carried forward (LOCF) imputation was used for participants who discontinued prior to Week 12.

End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	48	49	49
Units: percentage of participants				
number (not applicable)	50	64.6	73.5	81.6

End point values	ABT-494 18 mg BID	ABT-494 24 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: percentage of participants				
number (not applicable)	76.6	81.6		

Statistical analyses

Statistical analysis title	ABT-494 3 mg BID vs Placebo
Comparison groups	Placebo v ABT-494 3 mg BID
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.153
Method	Chi-squared

Notes:

[1] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 6 mg BID vs Placebo
Comparison groups	ABT-494 6 mg BID v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.018
Method	Chi-squared

Notes:

[2] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 12 mg BID vs Placebo
Comparison groups	ABT-494 12 mg BID v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.001
Method	Chi-squared

Notes:

[3] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 18 mg BID vs Placebo
Comparison groups	ABT-494 18 mg BID v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.008
Method	Chi-squared

Notes:

[4] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 24 mg QD vs Placebo
Comparison groups	ABT-494 24 mg QD v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.001
Method	Chi-squared

Notes:

[5] - Statistical tests were 1-sided at a significance level of 0.05.

Secondary: Percentage of Participants with an ACR50 Response at Week 12

End point title	Percentage of Participants with an ACR50 Response at Week 12

End point description:

A participant was a responder if the following 3 criteria for improvement from baseline were met:
- ≥ 50% improvement in tender joint count;
- ≥ 50% improvement in swollen joint count; and
- ≥ 50% improvement in at least 3 of the 5 following parameters:
  - Physician global assessment of disease activity
  - Patient global assessment of disease activity
  - Patient assessment of pain
  - Health Assessment Questionnaire – Disability Index (HAQ-DI)
  - High sensitivity C-reactive protein (hsCRP).

The analysis was performed in all randomized and treated participants; last observation carried forward (LOCF) imputation was used for participants who discontinued prior to Week 12.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	48	49	50
Units: percentage of participants				
number (not applicable)	19.6	39.6	49	50

End point values	ABT-494 18 mg BID	ABT-494 24 mg QD		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: percentage of participants				
number (not applicable)	44.7	43.8		

Statistical analyses

Statistical analysis title	ABT-494 3 mg BID vs Placebo
Comparison groups	ABT-494 3 mg BID v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.034
Method	Chi-squared

Notes:

[6] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 6 mg BID vs Placebo
Comparison groups	ABT-494 6 mg BID v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.003
Method	Chi-squared

Notes:

[7] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 12 mg BID vs Placebo
Comparison groups	ABT-494 12 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.002
Method	Chi-squared

Notes:

[8] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 18 mg BID vs Placebo
Comparison groups	ABT-494 18 mg BID v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.01
Method	Chi-squared

Notes:

[9] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 24 mg QD vs Placebo
Comparison groups	ABT-494 24 mg QD v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.012
Method	Chi-squared

Notes:

[10] - Statistical tests were 1-sided at a significance level of 0.05.

Secondary: Percentage of Participants with an ACR70 Response at Week 12

End point title	Percentage of Participants with an ACR70 Response at Week 12

End point description:

A participant was a responder if the following 3 criteria for improvement from baseline were met:
- ≥ 70% improvement in tender joint count;
- ≥ 70% improvement in swollen joint count; and
- ≥ 70% improvement in at least 3 of the 5 following parameters:
  - Physician global assessment of disease activity
  - Patient global assessment of disease activity
  - Patient assessment of pain
  - Health Assessment Questionnaire – Disability Index (HAQ-DI)
  - High sensitivity C-reactive protein (hsCRP).

The analysis was performed in all randomized and treated participants; last observation carried forward (LOCF) imputation was used for participants who discontinued prior to Week 12.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	47	49	50
Units: percentage of participants				
number (not applicable)	6.5	23.4	30.6	16

End point values	ABT-494 18 mg BID	ABT-494 24 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: percentage of participants				
number (not applicable)	27.7	25		

Statistical analyses

Statistical analysis title	ABT-494 3 mg BID vs Placebo
Comparison groups	ABT-494 3 mg BID v Placebo

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.023
Method	Chi-squared

Notes:

[11] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 6 mg BID vs Placebo
Comparison groups	ABT-494 6 mg BID v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.003
Method	Chi-squared

Notes:

[12] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 12 mg BID vs Placebo
Comparison groups	ABT-494 12 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.145
Method	Chi-squared

Notes:

[13] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 18 mg BID vs Placebo
Comparison groups	ABT-494 18 mg BID v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.007
Method	Chi-squared

Notes:

[14] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 24 mg QD vs Placebo
Comparison groups	ABT-494 24 mg QD v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.014
Method	Chi-squared

Notes:

[15] - Statistical tests were 1-sided at a significance level of 0.05.

Secondary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28(CRP) at Week 12

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28(CRP) at Week 12

End point description:

The disease activity score-28-CRP (DAS28 [CRP]) assesses RA disease activity based on a continuous scale of combined measures of 28 tender joint counts (TJC28), 28 swollen joint counts (SJC28), C-reactive protein (CRP), and the patient global assessment of disease activity (measured on a visual analogue scale from 0 to 100 mm). DAS28(CRP) scores range from 0 to 10 where higher scores indicate more disease activity.
LDA is defined as a DAS28(CRP) score < 3.2.
The analysis was performed in all randomized and treated participants; last observation carried forward (LOCF) imputation was used for participants who discontinued prior to Week 12.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	49	49	50
Units: percentage of participants				
number (not applicable)	21.3	49	57.1	46

End point values	ABT-494 18 mg BID	ABT-494 24 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: percentage of participants				
number (not applicable)	51	42.9		

Statistical analyses

Statistical analysis title	ABT-494 3 mg BID vs Placebo
Comparison groups	ABT-494 3 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.005
Method	Fisher exact

Notes:

[16] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 6 mg BID vs Placebo
Comparison groups	ABT-494 6 mg BID v Placebo

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.001
Method	Fisher exact

Notes:

[17] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 12 mg BID vs Placebo
Comparison groups	ABT-494 12 mg BID v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.01
Method	Fisher exact

Notes:

[18] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 18 mg BID vs Placebo
Comparison groups	ABT-494 18 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.002
Method	Fisher exact

Notes:

[19] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 24 mg QD vs Placebo
Comparison groups	ABT-494 24 mg QD v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.024
Method	Fisher exact

Notes:

[20] - Statistical tests were 1-sided at a significance level of 0.05.

Secondary: Percentage of Participants Achieving Clinical Remission (CR) Based on DAS28(CRP) at Week 12

End point title	Percentage of Participants Achieving Clinical Remission (CR) Based on DAS28(CRP) at Week 12

End point description:

The disease activity score-28-CRP (DAS28 [CRP]) assesses RA disease activity based on a continuous scale of combined measures of 28 tender joint counts (TJC28), 28 swollen joint counts (SJC28), C-reactive protein (CRP), and the patient global assessment of disease activity (measured on a visual analogue scale from 0 to 100 mm). DAS28(CRP) scores range from 0 to 10 where higher scores indicate more disease activity.
CR is defined as a DAS28(CRP) score < 2.6.
The analysis was performed in all randomized and treated participants; last observation carried forward (LOCF) imputation was used for participants who discontinued prior to Week 12.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	49	49	50
Units: percentage of participants				
number (not applicable)	14.9	36.7	38.8	34

End point values	ABT-494 18 mg BID	ABT-494 24 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: percentage of participants				
number (not applicable)	42.9	22.4		

Statistical analyses

Statistical analysis title	ABT-494 3 mg BID vs Placebo
Comparison groups	ABT-494 3 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.015
Method	Chi-squared

Notes:

[21] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 6 mg BID vs Placebo
Comparison groups	ABT-494 6 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.008
Method	Chi-squared

Notes:

[22] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 12 mg BID vs Placebo
Comparison groups	ABT-494 12 mg BID v Placebo

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.029
Method	Chi-squared

Notes:

[23] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 18 mg BID vs Placebo
Comparison groups	ABT-494 18 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.003
Method	Chi-squared

Notes:

[24] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 24 mg QD vs Placebo
Comparison groups	ABT-494 24 mg QD v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.343
Method	Chi-squared

Notes:

[25] - Statistical tests were 1-sided at a significance level of 0.05.

Secondary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on CDAI at Week 12

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on CDAI at Week 12

End point description:

The clinical disease activity index (CDAI) is a composite index for assessing disease activity based on the summation of the counts of TJC28 and SJC28, patient global assessment of disease activity measured on a VAS from 0 to 10 cm, and physician global assessment of disease activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity. LDA is defined as a CDAI score ≤ 10.
The analysis was performed in all randomized and treated participants; last observation carried forward (LOCF) imputation was used for participants who discontinued prior to Week 12.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	49	49	50
Units: percentage of participants				
number (not applicable)	21.3	40.8	40.8	40

End point values	ABT-494 18 mg BID	ABT-494 24 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: percentage of participants				
number (not applicable)	49	36.7		

Statistical analyses

Statistical analysis title	ABT-494 3 mg BID vs Placebo
Comparison groups	ABT-494 3 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.039
Method	Chi-squared

Notes:

[26] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 6 mg BID vs Placebo
Comparison groups	ABT-494 6 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.039
Method	Chi-squared

Notes:

[27] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 12 mg BID vs Placebo
Comparison groups	ABT-494 12 mg BID v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.046
Method	Chi-squared

Notes:

[28] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 18 mg BID vs Placebo
Comparison groups	ABT-494 18 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.005
Method	Chi-squared

Notes:

[29] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 24 mg QD vs Placebo
Comparison groups	ABT-494 24 mg QD v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.096
Method	Chi-squared

Notes:

[30] - Statistical tests were 1-sided at a significance level of 0.05.

Secondary: Percentage of Participants Achieving Clinical Remission Based on CDAI at Week 12

End point title	Percentage of Participants Achieving Clinical Remission Based on CDAI at Week 12

End point description:

The clinical disease activity index (CDAI) is a composite index for assessing disease activity based on the summation of the counts of TJC28 and SJC28, patient global assessment of disease activity measured on a VAS from 0 to 10 cm, and physician global assessment of disease activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity. LDA or CR is defined as a CDAI score ≤ 2.8.
The analysis was performed in all randomized and treated participants; last observation carried forward (LOCF) imputation was used for participants who discontinued prior to Week 12.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	49	49	50
Units: percentage of participants				
number (not applicable)	4.3	12.2	14.3	6

End point values	ABT-494 18 mg BID	ABT-494 24 mg QD		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: percentage of participants				
number (not applicable)	14.3	6.1		

Statistical analyses

Statistical analysis title	ABT-494 3 mg BID vs Placebo
Comparison groups	ABT-494 3 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.269
Method	Chi-squared

Notes:

[31] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 6 mg BID vs Placebo
Comparison groups	ABT-494 6 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.16
Method	Chi-squared

Notes:

[32] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 12 mg BID vs Placebo
Comparison groups	ABT-494 12 mg BID v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 1
Method	Chi-squared

Notes:

[33] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 18 mg BID vs Placebo
Comparison groups	ABT-494 18 mg BID v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.16
Method	Chi-squared

Notes:

[34] - Statistical tests were 1-sided at a significance level of 0.05.

Statistical analysis title	ABT-494 24 mg QD vs Placebo
Comparison groups	ABT-494 24 mg QD v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 1
Method	Chi-squared

Notes:

[35] - Statistical tests were 1-sided at a significance level of 0.05.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first dose of study drug until 30 days after last dose.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: Participants received placebo capsules twice daily for 12 weeks.	
Reporting group title	ABT-494 3 mg BID
Reporting group description: Participants received 3 mg ABT-494 twice daily (BID) for 12 weeks.	
Reporting group title	ABT-494 6 mg BID
Reporting group description: Participants received 6 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 12 mg BID
Reporting group description: Participants received 12 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 18 mg BID
Reporting group description: Participants received 18 mg ABT-494 twice daily for 12 weeks.	
Reporting group title	ABT-494 24 mg QD
Reporting group description: Participants received 24 mg ABT-494 once daily (QD) for 12 weeks.	

Serious adverse events	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	2 / 50 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Neoplasm Malignant			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Forearm Fracture			

subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head Injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian Cyst			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ABT-494 12 mg BID	ABT-494 18 mg BID	ABT-494 24 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 50 (2.00%)	3 / 50 (6.00%)	2 / 49 (4.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Neoplasm Malignant			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head Injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	0 / 49 (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
Syncope			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	0 / 49 (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
Reproductive system and breast disorders			
Ovarian Cyst			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	0 / 49 (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			
Osteonecrosis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 50 (4.00%)	5 / 50 (10.00%)	7 / 50 (14.00%)
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 50 (2.00%)	2 / 50 (4.00%)	1 / 50 (2.00%)
occurrences (all)	1	2	1
Blood and lymphatic system disorders			

Leukopenia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	3 / 50 (6.00%)
occurrences (all)	0	1	3
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	2 / 50 (4.00%)
occurrences (all)	1	1	2
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	ABT-494 12 mg BID	ABT-494 18 mg BID	ABT-494 24 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 50 (34.00%)	6 / 50 (12.00%)	6 / 49 (12.24%)
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	3 / 50 (6.00%)	2 / 50 (4.00%)	1 / 49 (2.04%)
occurrences (all)	3	2	1
Nervous system disorders			
Headache			

subjects affected / exposed	3 / 50 (6.00%)	0 / 50 (0.00%)	1 / 49 (2.04%)
occurrences (all)	4	0	2
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	3 / 50 (6.00%)	1 / 50 (2.00%)	0 / 49 (0.00%)
occurrences (all)	3	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)	1 / 50 (2.00%)	1 / 49 (2.04%)
occurrences (all)	3	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 50 (6.00%)	1 / 50 (2.00%)	0 / 49 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 50 (8.00%)	1 / 50 (2.00%)	0 / 49 (0.00%)
occurrences (all)	4	1	0
Nasopharyngitis			
subjects affected / exposed	4 / 50 (8.00%)	2 / 50 (4.00%)	3 / 49 (6.12%)
occurrences (all)	4	2	3
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 50 (0.00%)	0 / 49 (0.00%)
occurrences (all)	3	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2014	• Updated throughout to reflect that subjects may have had the opportunity to enter the OLE Study M13-538. • Clarified rescreening and lab retesting requirements. • Updated the timeframe for PK trough blood draws and requirement for taking morning dose of study drug at the site on visit days. • Clarified that folic acid and MTX were allowed to be taken on the same day. • Updated prohibited and acceptable concomitant medications. • Updated Inclusion Criterion #7 to clarify that tramadol, codeine, hydrocodone, and propoxyphene taken PRN were allowed, but could not be taken 24 hours prior to any study visit. • Updated Inclusion Criterion #8 to exclude meperidine 4 weeks prior to Baseline as a high potency opiate. • Updated Exclusion Criterion #6 to clarify that subjects with intra-articular, intramuscular, IV, intra-bursa, or intra-tendon sheath administration of corticosteroids in the preceding 8 weeks prior to the Baseline visit would not be eligible for the study. • Updated Exclusion Criterion #19 for history of uncontrolled diabetes mellitus (as evidenced by HbA1c ≥ 7.5%) to history of uncontrolled diabetes with the last 6 months prior to screening. • Updated Exclusion Criterion #21 to add grapefruit juice as a known strong CYP3A inhibitor. • Removed local requirements for the TB skin test in Czech Republic (due to local requirements not applicable to the study). • Added clarification that cardiovascular system-related and central nervous system-related events were to be recorded on supplemental eCRF pages.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported