# Clinical trial results:
# A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to investigate the Safety and Efficacy of ABT-494 Given with Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis (RA) Who Have Had an Inadequate Response or Intolerance to Anti-TNF Biologic Therapy

## Summary

| | |
|---|---|
| EudraCT number | 2013-002358-57 |
| Trial protocol | ES CZ HU NL BE |
| Global end of trial date | 27 July 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 06 August 2016 |
| First version publication date | 06 August 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | M13-550 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01960855 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | AbbVie Deutschland GmbH & Co. KG |
| Sponsor organisation address | Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4XE |
| Public contact | Global Medical Information, AbbVie, 001 800-633-9110, |
| Scientific contact | Steven Jungerwirth, MD, AbbVie, steven.jungerwirth@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 | 27 July 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 July 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to compare the safety and efficacy of multiple doses of ABT-494 versus placebo in moderately to severely active RA subjects on stable background MTX therapy with inadequate response or intolerance to anti-TNF biologic therapy.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 31 October 2013 |
| 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 | Poland: 33 |
| Country: Number of subjects enrolled | Spain: 16 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Country: Number of subjects enrolled | Hungary: 20 |
| Country: Number of subjects enrolled | Australia: 2 |
| Country: Number of subjects enrolled | New Zealand: 4 |
| Country: Number of subjects enrolled | Puerto Rico: 11 |
| Country: Number of subjects enrolled | United States: 176 |
| Worldwide total number of subjects | 276 |
| EEA total number of subjects | 83 |

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) | 196 |
| From 65 to 84 years | 78 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study included a screening period of 30 days.

### 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, Monitor, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo BID |

Arm description:

Placebo twice daily (BID) 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:

Placebo for ABT-494 capsule administered orally twice daily (BID).

| | |
|---|---|
| **Arm title** | ABT-494 3 mg BID |

Arm description:

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

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

Dosage and administration details:

ABT-494 capsule administered orally twice daily (BID).

| | |
|---|---|
| **Arm title** | ABT-494 6 mg BID |

Arm description:

ABT-494 6 mg twice daily (BID) for 12 weeks.

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

Dosage and administration details:

ABT-494 capsule administered orally twice daily (BID).

| **Arm title** | ABT-494 12 mg BID |
|---|---|

Arm description:

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

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

Dosage and administration details:

ABT-494 capsule administered orally twice daily (BID).

| **Arm title** | ABT-494 18 mg BID |
|---|---|

Arm description:

ABT-494 18 mg  twice daily (BID) for 12 weeks.

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

Dosage and administration details:

ABT-494 capsule administered orally twice daily (BID).

| **Number of subjects in period 1** | Placebo BID | ABT-494 3 mg BID | ABT-494 6 mg BID |
|---|---|---|---|
| Started | 56 | 55 | 55 |
| Completed | 45 | 51 | 46 |
| Not completed | 11 | 4 | 9 |
| Consent withdrawn by subject | 3 | 1 | 2 |
| Not specified | 2 | 1 | 1 |
| Adverse event | 2 | - | 6 |
| Lost to follow-up | 2 | 1 | - |
| Subject noncompliant | 1 | - | - |
| Lack of efficacy | 1 | 1 | - |

| **Number of subjects in period 1** | ABT-494 12 mg BID | ABT-494 18 mg BID |
|---|---|---|
| Started | 55 | 55 |
| Completed | 51 | 50 |
| Not completed | 4 | 5 |
| Consent withdrawn by subject | 1 | 1 |
| Not specified | 1 | - |
| Adverse event | 2 | 2 |
| Lost to follow-up | - | 2 |
| Subject noncompliant | - | - |

| | | |
|---|---|---|
| Lack of efficacy | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo BID |
| Reporting group description: | |
| Placebo twice daily (BID) for 12 weeks. | |
| Reporting group title | ABT-494 3 mg BID |
| Reporting group description: | |
| ABT-494 3 mg twice daily (BID) for 12 weeks. | |
| Reporting group title | ABT-494 6 mg BID |
| Reporting group description: | |
| ABT-494 6 mg twice daily (BID) for 12 weeks. | |
| Reporting group title | ABT-494 12 mg BID |
| Reporting group description: | |
| ABT-494 12 mg twice daily (BID) for 12 weeks. | |
| Reporting group title | ABT-494 18 mg BID |
| Reporting group description: | |
| ABT-494 18 mg twice daily (BID) for 12 weeks. | |

| Reporting group values | Placebo BID | ABT-494 3 mg BID | ABT-494 6 mg BID |
|---|---|---|---|
| Number of subjects | 56 | 55 | 55 |
| Age categorical<br>Units: Subjects | | | |

| Age continuous | | | |
|---|---|---|---|
| Modified intent-to-treat (mITT) population, defined as all randomized subjects who received at least 1 dose of study drug. | | | |
| Units: years | | | |
| arithmetic mean | 57.5 | 57 | 56.3 |
| standard deviation | ± 12.04 | ± 13.06 | ± 11.71 |
| Gender categorical | | | |
| mITT population. | | | |
| Units: Subjects | | | |
| Female | 48 | 43 | 43 |
| Male | 8 | 12 | 12 |

| Reporting group values | ABT-494 12 mg BID | ABT-494 18 mg BID | Total |
|---|---|---|---|
| Number of subjects | 55 | 55 | 276 |
| Age categorical<br>Units: Subjects | | | |

| Age continuous | | | |
|---|---|---|---|
| Modified intent-to-treat (mITT) population, defined as all randomized subjects who received at least 1 dose of study drug. | | | |
| Units: years | | | |
| arithmetic mean | 59.1 | 56.7 | |
| standard deviation | ± 11.4 | ± 12.39 | - |

| Gender categorical | | | |
|---|---|---|---|
| mITT population. | | | |
| Units: Subjects | | | |
| Female | 45 | 42 | 221 |
| Male | 10 | 13 | 55 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo BID |
| Reporting group description: | |
| Placebo twice daily (BID) for 12 weeks. | |
| Reporting group title | ABT-494 3 mg BID |
| Reporting group description: | |
| ABT-494 3 mg twice daily (BID) for 12 weeks. | |
| Reporting group title | ABT-494 6 mg BID |
| Reporting group description: | |
| ABT-494 6 mg twice daily (BID) for 12 weeks. | |
| Reporting group title | ABT-494 12 mg BID |
| Reporting group description: | |
| ABT-494 12 mg twice daily (BID) for 12 weeks. | |
| Reporting group title | ABT-494 18 mg BID |
| Reporting group description: | |
| ABT-494 18 mg twice daily (BID) for 12 weeks. | |

### Primary: Number of Subjects Achieving American College of Rheumatology 20% (ACR20) Response at Week 12

| | |
|---|---|
| End point title | Number of Subjects Achieving American College of Rheumatology 20% (ACR20) Response at Week 12 |
| End point description: | |
| Response defined as at least 20% reduction (improvement) compared with baseline in tender joint count (TJC68), swollen joint count (SJC66), and at least 3 of the 5 remaining ACR core set measures: patient's assessment of pain, patient's global assessment of disease activity (PtGA); physician's global assessment of disease activity (PGA), Health Assessment Questionnaire – Disability Index (HAQ-DI), and high-sensitivity C-reactive protein (hs CRP). Last observation carried forward (LOCF) was used for missing data. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline (Week 0) and Week 12 | |

| End point values | Placebo BID | 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 | 54[1] | 54[2] | 52[3] | 55[4] |
| Units: subjects | 19 | 30 | 33 | 40 |

Notes:

[1] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[2] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[3] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[4] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

| End point values | ABT-494 18 mg BID | | | |
|---|---|---|---|---|

| Subject group type | Reporting group | | | |
|---|---|---|---|---|
| Number of subjects analysed | 55[5] | | | |
| Units: subjects | 39 | | | |

Notes:

[5] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

### Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 3 mg BID |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.033 |
| Method | Chi-squared |

| Statistical analysis title | Statistical analysis 2 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 6 mg BID |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.004 |
| Method | Chi-squared |

| Statistical analysis title | Statistical analysis 3 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 12 mg BID |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Chi-squared |

| Statistical analysis title | Statistical analysis 4 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 18 mg BID |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Chi-squared |

## Secondary: Number of Subjects Achieving American College of Rheumatology 50%

## (ACR50) Response at Week 12

| End point title | Number of Subjects Achieving American College of Rheumatology 50% (ACR50) Response at Week 12 |
|---|---|

End point description:

Response defined as at least 50% reduction (improvement) compared with baseline in tender joint count (TJC68), swollen joint count (SJC66), and at least 3 of the 5 remaining ACR core set measures: patient's assessment of pain, PtGA; PGA, HAQ-DI, and hs CRP. LOCF was used.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Week 0) and Week 12

| End point values | Placebo BID | 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 | 53[6] | 54[7] | 52[8] | 55[9] |
| Units: subjects | 9 | 13 | 20 | 24 |

Notes:

[6] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[7] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[8] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[9] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

| End point values | ABT-494 18 mg BID | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 55[10] | | | |
| Units: subjects | 22 | | | |

Notes:

[10] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

### Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 3 mg BID |
| Number of subjects included in analysis | 107 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.364 |
| Method | Chi-squared |

| Statistical analysis title | Statistical analysis 2 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 6 mg BID |

| | |
|---|---|
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.014 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 3 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 12 mg BID |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.003 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 4 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 18 mg BID |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.008 |
| Method | Chi-squared |

**Secondary: Number of Subjects Achieving American College of Rheumatology 70% (ACR70) Response at Week 12**

| End point title | Number of Subjects Achieving American College of Rheumatology 70% (ACR70) Response at Week 12 |
|---|---|

End point description:

Response defined as at least 70% reduction (improvement) compared with baseline in tender joint count (TJC68), swollen joint count (SJC66), and at least 3 of the 5 remaining ACR core set measures: patient's assessment of pain, PtGA; PGA, HAQ-DI, and hs CRP. LOCF was used.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Week 0) and Week 12

| **End point values** | Placebo BID | 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 | 55[11] | 54[12] | 52[13] | 55[14] |
| Units: subjects | 2 | 7 | 14 | 12 |

Notes:

[11] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[12] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value
[13] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value
[14] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

| **End point values** | ABT-494 18 mg BID | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 55[15] | | | |
| Units: subjects | 12 | | | |

Notes:
[15] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

**Statistical analyses**

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 3 mg BID |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.093 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|
| Comparison groups | ABT-494 6 mg BID v Placebo BID |
| Number of subjects included in analysis | 107 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 3 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 12 mg BID |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.004 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 4 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 18 mg BID |

| | |
|---|---|
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.004 |
| Method | Chi-squared |

## Secondary: Number of Subjects Achieving Low Disease Activity (LDA) Based on Disease Activity Score (DAS28) or Clinical Remission (CR) based on (DAS28) at Week 12

| | |
|---|---|
| End point title | Number of Subjects Achieving Low Disease Activity (LDA) Based on Disease Activity Score (DAS28) or Clinical Remission (CR) based on (DAS28) at Week 12 |

End point description:

LDA is defined as DAS28 from 2.6 to < 3.2 at Week 12. CR is defined as DAS28 (CRP) < 2.6 at Week 12. The DAS28 is a validated index of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, hs CRP, and general health are included in the DAS28 score. Scores on the DAS28 range from 0 to 10. A DAS28 score >5.1 indicates high disease activity, a DAS28 score <3.2 indicates low disease activity, and a DAS28 score <2.6 indicates clinical remission. LOCF was used.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Week 12

| End point values | Placebo BID | 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 | 55[16] | 54[17] | 53[18] | 55[19] |
| Units: subjects | 14 | 18 | 20 | 29 |

Notes:

[16] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[17] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[18] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[19] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

| End point values | ABT-494 18 mg BID | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 55[20] | | | |
| Units: subjects | 25 | | | |

Notes:

[20] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

### Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 3 mg BID |

| | |
|---|---|
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.366 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 6 mg BID |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.17 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 3 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 12 mg BID |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.003 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 4 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 18 mg BID |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.028 |
| Method | Chi-squared |

**Secondary: Number of Subjects Achieving CR based on DAS28 at Week 12**

| End point title | Number of Subjects Achieving CR based on DAS28 at Week 12 |
|---|---|

End point description:

The DAS28 is a validated index of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, hs CRP, and general health are included in the DAS28 score. Scores on the DAS28 range from 0 to 10. A DAS28 score >5.1 indicates high disease activity, a DAS28 score <3.2 indicates low disease activity, and a DAS28 score <2.6 indicates clinical remission. LOCF was used.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 12

| End point values | Placebo BID | 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 | 55[21] | 54[22] | 53[23] | 55[24] |
| Units: subjects | 7 | 13 | 14 | 18 |

Notes:

[21] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[22] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[23] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

[24] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

| End point values | ABT-494 18 mg BID | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 55[25] | | | |
| Units: subjects | 17 | | | |

Notes:

[25] - Subjects in the mITT population with a baseline value and at least 1 post-baseline value

**Statistical analyses**

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 3 mg BID |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.126 |
| Method | Chi-squared |

| Statistical analysis title | Statistical analysis 2 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 6 mg BID |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.072 |
| Method | Chi-squared |

| Statistical analysis title | Statistical analysis 3 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 12 mg BID |

| | |
|---|---|
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.012 |
| Method | Chi-squared |

| **Statistical analysis title** | Statistical analysis 4 |
|---|---|
| Comparison groups | Placebo BID v ABT-494 18 mg BID |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.021 |
| Method | Chi-squared |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs (TEAEs) were collected from first dose of study drug until up to 30 days after discontinuation of study drug (up to 16 weeks); SAEs were collected from the time informed consent was obtained (20 weeks).

Adverse event reporting additional description:

A treatment-emergent AE (TEAE) is defined as any AE with onset or worsening reported by a participant from the time that the first dose of study drug is administered 30 days have elapsed following discontinuation of study drug administration.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo BID |

Reporting group description:

Placebo twice daily (BID) for 12 weeks.

| | |
|---|---|
| Reporting group title | ABT-494 3 mg BID |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | ABT-494 6 mg BID |

Reporting group description:

ABT-494 6 mg twice daily (BID) for 12 weeks.

| | |
|---|---|
| Reporting group title | ABT-494 12 mg BID |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | ABT-494 18 mg BID |

Reporting group description:

ABT-494 18 mg twice daily (BID) for 12 weeks.

| Serious adverse events | Placebo BID | ABT-494 3 mg BID | ABT-494 6 mg BID |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 55 (3.64%) | 2 / 55 (3.64%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 55 (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 | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 0 / 55 (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 |
| Bronchiectasis | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 55 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| 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 | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 55 (1.82%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 55 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 55 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 55 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 55 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 55 (1.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 55 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 55 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo BID | ABT-494 3 mg BID | ABT-494 6 mg BID |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 56 (16.07%) | 13 / 55 (23.64%) | 13 / 55 (23.64%) |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 55 (5.45%) | 3 / 55 (5.45%) |
| occurrences (all) | 2 | 3 | 4 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 1 / 55 (1.82%) |
| occurrences (all) | 0 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 4 / 55 (7.27%) | 1 / 55 (1.82%) |
| occurrences (all) | 1 | 4 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 55 (5.45%) | 0 / 55 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 55 (5.45%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 3 / 55 (5.45%) | 0 / 55 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 55 (3.64%) | 1 / 55 (1.82%) |
| occurrences (all) | 1 | 2 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 2 / 55 (3.64%) | 1 / 55 (1.82%) |
| occurrences (all) | 2 | 2 | 1 |
| Metabolism and nutrition disorders | | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 2 / 55 (3.64%) |
| occurrences (all) | 1 | 0 | 2 |

| **Non-serious adverse events** | ABT-494 12 mg BID | ABT-494 18 mg BID | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 55 (25.45%) | 27 / 55 (49.09%) | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 5 / 55 (9.09%) | |
| occurrences (all) | 0 | 5 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 3 / 55 (5.45%) | |
| occurrences (all) | 4 | 6 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 1 / 55 (1.82%) | |
| occurrences (all) | 3 | 1 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 4 / 55 (7.27%) | |
| occurrences (all) | 0 | 5 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Constipation | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 4 / 55 (7.27%) | |
| occurrences (all) | 0 | 7 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 4 / 55 (7.27%) | |
| occurrences (all) | 3 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 55 (1.82%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 55 (1.82%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 3 / 55 (5.45%) | |
| occurrences (all) | 0 | 4 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 55 (1.82%) | |
| occurrences (all) | 1 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 4 / 55 (7.27%) | |
| occurrences (all) | 5 | 4 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 7 / 55 (12.73%) | |
| occurrences (all) | 2 | 9 | |
| Metabolism and nutrition disorders | | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 3 / 55 (5.45%) | |
| occurrences (all) | 1 | 3 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 December 2013 | The purpose of this amendment is to update inclusion (including RA diagnosis criteria, prior biologic use, hsCRP <ULN criteria, and permitted medications) and exclusion criteria (including live vaccinations, laboratory values, and prohibited medications and therapies), and update study procedures (including chest x-ray permitted at any time per investigator decision, TB tests, and clinical lab tests). |
| 18 November 2014 | The purpose of this amendment was to increase the number of sites expected to participate in the study, add and internal independent safety data review committee, add an interim analysis of efficacy, and clarify inclusion (including prior treatment, prohibited and acceptable concomitant medications), clarify study procedures (including blood samples for pharmacokinetics), and clarify patient rollover into open label extension. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported