



## 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        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> 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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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  $\geq 3$  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     |
| <b>Arm title</b>             | 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

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | 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

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | 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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1</b> | 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            | - | - | - |

| <b>Number of subjects in period 1</b> | 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:  |   |
| <ul style="list-style-type: none"><li>• ≥ 20% improvement in tender joint count;</li><li>• ≥ 20% improvement in swollen joint count; and</li><li>• ≥ 20% improvement in at least 3 of the 5 following parameters:<ul style="list-style-type: none"><li>◦ Physician global assessment of disease activity</li><li>◦ Patient global assessment of disease activity</li><li>◦ Patient assessment of pain</li><li>◦ Health Assessment Questionnaire – Disability Index (HAQ-DI)</li><li>◦ High sensitivity C-reactive protein (hsCRP).</li></ul></li></ul> |   |
| 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   |   |

| <b>End point values</b>           | 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              |

| <b>End point values</b>           | 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

| <b>Statistical analysis title</b>       | 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 <sup>[1]</sup>  |
| P-value                                 | = 0.153                     |
| Method                                  | Chi-squared                 |

Notes:

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

| <b>Statistical analysis title</b>       | 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 <sup>[2]</sup>  |
| P-value                                 | = 0.018                     |
| Method                                  | Chi-squared                 |

Notes:

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

| <b>Statistical analysis title</b>       | 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 <sup>[3]</sup>   |
| P-value                                 | = 0.001                      |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[4]</sup>   |
| P-value                                 | = 0.008                      |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[5]</sup>  |
| 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:

- $\geq 50\%$  improvement in tender joint count;
- $\geq 50\%$  improvement in swollen joint count; and
- $\geq 50\%$  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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[6]</sup>  |
| P-value                                 | = 0.034                     |
| Method                                  | Chi-squared                 |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[7]</sup>  |
| P-value                                 | = 0.003                     |
| Method                                  | Chi-squared                 |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[8]</sup>   |
| P-value                                 | = 0.002                      |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[9]</sup>   |
| P-value                                 | = 0.01                       |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[10]</sup> |
| 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:

- $\geq 70\%$  improvement in tender joint count;
- $\geq 70\%$  improvement in swollen joint count; and
- $\geq 70\%$  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

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[11]</sup> |
| P-value                                 | = 0.023                     |
| Method                                  | Chi-squared                 |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[12]</sup> |
| P-value                                 | = 0.003                     |
| Method                                  | Chi-squared                 |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[13]</sup>  |
| P-value                                 | = 0.145                      |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[14]</sup>  |
| P-value                                 | = 0.007                      |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[15]</sup> |
| 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 <sup>[16]</sup> |
| 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 <sup>[17]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Fisher exact                |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[18]</sup>  |
| P-value                                 | = 0.01                       |
| Method                                  | Fisher exact                 |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[19]</sup>  |
| P-value                                 | = 0.002                      |
| Method                                  | Fisher exact                 |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[20]</sup> |
| 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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[21]</sup> |
| P-value                                 | = 0.015                     |
| Method                                  | Chi-squared                 |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[22]</sup> |
| P-value                                 | = 0.008                     |
| Method                                  | Chi-squared                 |

Notes:

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

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[23]</sup> |
| P-value                                 | = 0.029                     |
| Method                                  | Chi-squared                 |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[24]</sup>  |
| P-value                                 | = 0.003                      |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[25]</sup> |
| 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  $\leq 10$ .

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

| <b>End point values</b>           | 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                |

| <b>End point values</b>           | 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

| <b>Statistical analysis title</b>       | 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 <sup>[26]</sup> |
| P-value                                 | = 0.039                     |
| Method                                  | Chi-squared                 |

Notes:

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

| <b>Statistical analysis title</b>       | 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 <sup>[27]</sup> |
| P-value                                 | = 0.039                     |
| Method                                  | Chi-squared                 |

Notes:

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

| <b>Statistical analysis title</b>       | 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 <sup>[28]</sup>  |
| P-value                                 | = 0.046                      |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[29]</sup>  |
| P-value                                 | = 0.005                      |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[30]</sup> |
| 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  $\leq$  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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[31]</sup> |
| P-value                                 | = 0.269                     |
| Method                                  | Chi-squared                 |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[32]</sup> |
| P-value                                 | = 0.16                      |
| Method                                  | Chi-squared                 |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[33]</sup>  |
| P-value                                 | = 1                          |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[34]</sup>  |
| P-value                                 | = 0.16                       |
| Method                                  | Chi-squared                  |

Notes:

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

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[35]</sup> |
| 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          |

| <b>Serious adverse events</b>                                       | 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 %

| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)  | 0 / 50 (0.00%)<br>0                            | 0 / 50 (0.00%)<br>0                            | 0 / 50 (0.00%)<br>0                            |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 50 (0.00%)<br>0                            | 0 / 50 (0.00%)<br>0                            | 1 / 50 (2.00%)<br>1                            |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 0 / 50 (0.00%)<br>0                            | 1 / 50 (2.00%)<br>1                            | 1 / 50 (2.00%)<br>1                            |
| Musculoskeletal and connective tissue disorders<br>Back Pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 50 (0.00%)<br>0                            | 1 / 50 (2.00%)<br>1                            | 3 / 50 (6.00%)<br>3                            |
| Infections and infestations<br>Influenza<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 50 (0.00%)<br>0<br><br>1 / 50 (2.00%)<br>1 | 0 / 50 (0.00%)<br>0<br><br>1 / 50 (2.00%)<br>1 | 0 / 50 (0.00%)<br>0<br><br>2 / 50 (4.00%)<br>2 |
| Metabolism and nutrition disorders<br>Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 50 (0.00%)<br>0                            | 1 / 50 (2.00%)<br>1                            | 0 / 50 (0.00%)<br>0                            |

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 20 November 2014 | <ul style="list-style-type: none"><li>• Updated throughout to reflect that subjects may have had the opportunity to enter the OLE Study M13-538.</li><li>• Clarified rescreening and lab retesting requirements.</li><li>• Updated the timeframe for PK trough blood draws and requirement for taking morning dose of study drug at the site on visit days.</li><li>• Clarified that folic acid and MTX were allowed to be taken on the same day.</li><li>• Updated prohibited and acceptable concomitant medications.</li><li>• 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.</li><li>• Updated Inclusion Criterion #8 to exclude meperidine 4 weeks prior to Baseline as a high potency opiate.</li><li>• 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.</li><li>• Updated Exclusion Criterion #19 for history of uncontrolled diabetes mellitus (as evidenced by HbA1c <math>\geq</math> 7.5%) to history of uncontrolled diabetes with the last 6 months prior to screening.</li><li>• Updated Exclusion Criterion #21 to add grapefruit juice as a known strong CYP3A inhibitor.</li><li>• Removed local requirements for the TB skin test in Czech Republic (due to local requirements not applicable to the study).</li><li>• Added clarification that cardiovascular system-related and central nervous system-related events were to be recorded on supplemental eCRF pages.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported