

## 2.0 Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> ABT-494	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> ABT-494	<b>Page:</b>	
<b>Title of Study:</b> 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		
<b>Investigator:</b> ████████████████████		
<b>Study Sites:</b> 59 sites in the United States (including Puerto Rico), Europe, Chile, Israel, Mexico, and South Africa		
<b>Publications:</b> None		
<b>Studied Period (Years):</b> First Subject First Visit: 26 March 2014 Last Subject Last Visit: 02 July 2015	<b>Phase of Development:</b> 2	
<b>Objective:</b> The primary objective of the study was to compare the safety and efficacy of multiple doses of ABT-494 versus placebo in subjects with moderately to severely active RA on stable background MTX therapy who had not shown an adequate response to MTX alone.		
<b>Methodology:</b> This was a Phase 2, randomized, double-blind, parallel-group, placebo-controlled multicenter study comparing the safety and efficacy of multiple doses of ABT-494 versus placebo administered for 12 weeks in subjects with moderately to severely active RA who had shown inadequate response to MTX and were naïve to biologic therapy. Included was a Screening period of up to 30 days and a 30-day follow-up visit. Subjects who met eligibility criteria were randomized in a 1:1:1:1:1:1 ratio to 1 of 6 treatment arms: placebo twice daily (BID) or ABT-494 3 mg BID, 6 mg BID, 12 mg BID, 18 mg BID, or 24 mg once daily (QD). Study site visits occurred at Week 0 (Baseline) and at Weeks 2, 4, 6, 8 and 12 (or premature discontinuation), and at 30-day follow-up. Study drug was to be taken orally for 12 weeks beginning on Day 1, with the last dose of study drug taken on the evening prior to the Week 12 visit. Subjects were to continue their weekly stable dose of MTX. Subjects who completed Week 12 had the opportunity to enter the open-label extension Study M13-538 to receive open-label ABT-494.		
<b>Number of Subjects (Planned and Analyzed):</b> Planned: 270 subjects (45 placebo; 225 ABT-494); Analyzed: 299 (50 placebo; 249 ABT-494)		

**Diagnosis and Main Criteria for Inclusion:**

Adult males and females who were at least 18 years of age; were diagnosed with RA based on either the 1987 American College of Rheumatology (ACR) classification criteria or the 2010 ACR/European League against Rheumatism criteria for  $\geq 3$  months; had active RA as defined by minimum disease activity criteria ( $\geq 6$  tender joints [based on 68 joint counts] at Screening and Baseline visits,  $\geq 6$  swollen joints [based on 66 joint counts] at Screening and Baseline visits, high-sensitivity C-reactive protein [hs-CRP]  $>$  upper limit of normal [ULN] or positive for both rheumatoid factor [RF] and anti-cyclic citrullinated peptide [CCP] at Screening); had been receiving oral or parenteral MTX therapy for  $\geq 3$  months and were on a stable prescription of 7.5 to 25 mg/week for at least 4 weeks prior to Baseline; had no prior exposure to biologic RA therapy; had no history of acute inflammatory joint disease of a different origin than RA and no history of malignancy (including lymphoma and leukemia); and had no Screening laboratory values in the excluded specified cutoff for serum alanine transaminase (ALT), aspartate transaminase (AST), estimated glomerular filtration rate, total white blood cell (WBC) count, absolute neutrophil count, platelet count, absolute lymphocyte count, and hemoglobin.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

ABT-494 3 mg immediate-release capsules for oral administration; Bulk lot number: 13-004590; 15-000327

ABT-494 12 mg immediate-release capsules for oral administration; Bulk lot number: 13-004770; 15-000395

**Duration of Treatment:** 12 weeks

**Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:**

Matching placebo, capsules for oral administration; Bulk lot number: 12-002434; 14-001960

**Criteria for Evaluation**

**Efficacy:**

The primary efficacy endpoint was the ACR20 response rate at Week 12. A subject was considered an ACR20 responder based on achievement of 20% or greater reduction (improvement) from Baseline in both tender joint count (TJC) and swollen joint count (SJC) and a 20% or greater reduction (improvement) from Baseline in 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 [PhGA], hs-CRP, and Health Assessment Questionnaire – Disability Index [HAQ – DI]).

Secondary efficacy endpoints were:

- ACR50 and ACR70 response rates at Week 12;
- proportion of subjects achieving low disease activity (LDA) or clinical remission based on disease activity score (DAS28 [CRP]) and clinical disease activity index (CDAI) criteria at Week 12;
- proportion of subjects achieving clinical remission based on DAS28 [CRP] and CDAI criteria at Week 12.

Note: DAS28 [CRP] score was determined on a continuous scale of combined measures of TJC (28 joints), SJC (28 joints), PtGA, and hs-CRP; CDAI, a composite index (without CRP), was based on the simple summation of the counts of TJC28 and SJC28 along with PtGA and PGA.

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**Criteria for Evaluation (Continued)****Efficacy (Continued):**

Additional efficacy endpoints included: ACR20/50/70 response rates at Weeks 2, 4, 6, and 8; change from Baseline in DAS [CRP] at Weeks 2, 4, 6, 8, and 12; change from Baseline in CDAI at Weeks 2, 4, 6, 8, and 12; ACRn at Week 12; change from Baseline in individual ACR components (TJC, SJC, patient's assessment of pain, PtGA, PGA, hs-CRP, HAQ – DI) at Weeks 2, 4, 6, 8, and 12; and change from Baseline in patient-reported health outcomes other than HAQ-DI (i.e., Functional Assessment of Chronic Illness Therapy – fatigue [FACIT-F], Work Instability Scale – Rheumatoid Arthritis [RA-WIS], European Quality of Life – 5 Dimensions questionnaire [EQ-5D], and Short Form-36 Health Status Survey questionnaire [SF-36™]) at Weeks 4, 8, and 12.

**Pharmacokinetics:**

For all subjects, blood samples for ABT-494 assay were collected prior to the morning dosing at each visit from Day 1 (Baseline) through Week 12 (total of 6 blood samples). For subjects who participated in the pharmacokinetic (PK) intensive cohort, additional samples were collected on Day 1 and at Week 8 at 1, 2, and 3 hours post-morning dose.

**Safety:**

Adverse events (AEs), physical examinations, vital signs, and clinical laboratory (hematology, chemistry, and urinalysis) data were assessed throughout the study.

**Statistical Methods**

Two statistical analysis plans (SAPs) were prepared for this study: a SAP (dated 04 March 2015) that described the analyses for the primary, secondary, and exploratory efficacy variables, and a SAP (dated 24 June 2015) that mainly included changes to the data presentation for the efficacy analyses. Database lock occurred on 25 September 2015; the last subject completed the 30-day follow-up visit (02 July 2015). The database was updated (unlocked/relocked) on 11 April 2016 to add PK sample times and update pharmacogenetic sample data.

The efficacy and safety analyses were conducted using all randomized subjects who received at least 1 dose of study drug, defined as the modified intent-to-treat (mITT) population and the safety analysis population. One subject was randomized to ABT-494 (24 mg QD) but did not receive a dose of study drug since the subject was receiving treatment for an ongoing infection (bronchitis) (exclusion criterion); the subject was excluded from all efficacy and safety analyses.

**Efficacy:**

In general, statistical tests were conducted at 2-sided significance level of 0.05. Descriptive statistics were provided (including standard deviation, median, minimum, and maximum for continuous variables; number and percentages for categorical or discrete variables). Last observation carried forward (LOCF) was the primary imputation method. Sensitivity analyses for ACR responses were conducted using 1 or more imputation methods for missing data (nonresponder imputation [NRI], mixed imputation) or no imputation method (observed cases), with conservative imputation rules used for joints that were not assessed or replaced for sensitivity analyses of the primary endpoint.

### **Statistical Methods (Continued)**

#### **Efficacy (Continued):**

The primary endpoint, ACR20 response rate at Week 12, was summarized for each treatment group using point estimate and 95% confidence interval (CI). The ACR20 response rate at Week 12 for each ABT-494 dose group was compared with the placebo group using a chi-square test or Fisher's exact test (if 25% of the cells had expected counts less than 5). Point estimate and 2-sided 95% CI were calculated for each response rate difference between the groups; unadjusted *P* values for each comparison were presented. Subjects who were discontinued prior to Week 2 were categorized according to LOCF imputation.

For secondary endpoints: For each treatment group, the number and percentage of ACR50/70 responders and of subjects achieving LDA or clinical remission, based on DAS28 [CRP] or CDAI criterion, were summarized at Week 12 using point estimate and 95% CI, and for each ABT-494 dose group, were compared with the placebo group using a chi-square test or Fischer's exact test (if 25% of the cells had expected counts less than 5).

For additional endpoints:

- for ACR20/50/70 response rates at other post-Baseline timepoints, the same statistical methodology as for the secondary endpoints was used.
- for individual core components of ACR (discrete variables) and for all patient-reported health outcomes, change from Baseline to post-Baseline timepoints was summarized by treatment group (point estimate, 95% CI) and the treatment difference between each of the ABT-494 dose groups and placebo examined using an analysis of covariance (ANCOVA) model with Baseline measure as the covariate (on LOCF imputed data; except for SF-36 on observed data).
- for continuous variables (i.e., DAS28 [CRP] disease activity score and CDAI), change from Baseline to post-Baseline timepoints was summarized by treatment group (point estimate, 95% CI) and the treatment difference between each of the ABT-494 dose groups and placebo examined using an ANCOVA model with Baseline measure as the covariate (on LOCF imputed data).

#### **Pharmacokinetics:**

ABT-494 plasma concentrations for each ABT-494 dose level were combined across all visits and summarized by dose group and time since the previous dose of ABT-494. PK parameters (time to maximum observed plasma concentration [ $T_{max}$ ] and maximum observed plasma concentration [ $C_{max}$ ]) were estimated from the intensive PK samples collected on Day 1 and at Week 8.

#### **Safety:**

Treatment emergent adverse events (TEAEs) were defined as AEs that began or worsened in severity after the first dose of study drug through 30 days after the last dose of study drug for subjects who did not enter the open-label extension study. TEAEs were tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) system (version 17.1) organ class (SOC) and preferred term (PT) for each treatment group. AEs starting more than 30 days following discontinuation of study drug were summarized separately as posttreatment AEs. All AEs discussed in this report are treatment-emergent.

### **Statistical Methods (Continued)**

#### **Safety (Continued):**

An overview of AEs, including AEs of special interest such as AEs leading to death and AEs leading to premature discontinuation, AEs by MedDRA SOC and PT, AEs by maximum relationship to study drug, and AEs by maximum severity were summarized by number and percentage of subjects. AE severity was summarized 2 different ways: 1) For maximum severity, an AE with unknown severity was counted as "unknown" unless the subject had another occurrence of the same event with the most extreme severity (severe), in which case the event was counted as severe; 2) For severity assessments, an AE with unknown severity was counted as severe. For causality assessments, an AE with unknown relationship or a relationship not assessable was counted as having a "reasonable possibility" of being related to study drug. A subject reporting more than 1 AE with the same PT was counted only once for that PT using the most extreme occurrence (i.e., most severe and most related). A subject reporting 2 or more different PTs within the same SOC was counted only once in the SOC total. A subject reporting 2 or more AEs in different SOCs was counted only once in the overall AE total.

The number and percent of subjects with AEs and AEs of special interest was provided for each treatment group; comparisons between each ABT-494 dose group and the placebo group were made using Fisher's exact test. AEs per 100 patient years of exposure were calculated for all TEAEs and for serious AEs (SAEs). All TEAEs (including by relationship and severity), AEs of special interest, SAEs, AEs leading to death, and AEs leading to discontinuation were also listed.

Changes from Baseline in laboratory data and vital signs were summarized using descriptive statistics; treatment group differences between the ABT-494 dose groups and the placebo group were analyzed using a 1-way analysis of variance. For laboratory parameters, the number and percent of subjects with laboratory parameter shifts from Baseline to minimum, maximum, and final values according to the normal range for each laboratory parameter were provided; listings were provided for abnormal values, whereby the normal range of the analyzing laboratory was used. For vital signs and select laboratory parameters, the number and percent of subjects meeting criteria for potentially clinically significant values (for labs: Rheumatology Common Toxicity Criteria version 2.0) was provided; a listing of all subjects with any vital sign variable or laboratory parameter determination meeting these criteria was provided, along with the entire course of the variable.

#### **Summary/Conclusions**

This report presents the efficacy and safety data of multiple doses of ABT-494 administered orally versus placebo in subjects with moderately to severely active RA who had had an inadequate response to MTX therapy and were naïve to biologic therapy through the end of the treatment period (Week 12), including through the 30-day follow-up visit for subjects who did not enter the open-label extension study. In the mITT population (N = 299), the majority of subjects were female, white, and non-users of nicotine and alcohol, with a body mass index of 25 or greater. In addition, the majority of subjects in the placebo and ABT-494 (total) groups were 45 to < 65 years of age (64.0% and 57.8%, respectively), while 18.0% and 23.3%, respectively, were ≥ 65 years of age. No statistically significant differences were observed between the treatment groups for any demographic characteristic.

**Summary/Conclusions (Continued)**

Subjects (54.0% placebo; 63.5% ABT-494 [total]) reported having RA for 3 years or more (mean of approximately 4 to 9 years) and had significantly active disease per protocol-defined inclusion criteria as indicated by (placebo, ABT-494 [total]) mean TJC68 (28.7, 27.6), SJC66 (18.8, 17.3), and hs-CRP (15.2 mg/L, 13.0 mg/L). In addition, the majority of subjects (> 75%) reported no use of disease-modifying antirheumatic drugs other than MTX prior to Baseline.

**Efficacy Results:**

The efficacy of treatment with the tested ABT-494 doses (3 mg BID, 6 mg BID, 12 mg BID, 18 mg BID, and 24 mg QD) in subjects with moderate to severe RA was demonstrated in this Phase 2, placebo-controlled study. The study met its primary endpoint and demonstrated that the proportion of subjects who achieved an ACR20 response with ABT-494 treatment (mITT population: 6 mg BID, 12 mg BID, 18 mg BID, and 24 mg QD) was statistically significantly higher ( $P \leq 0.05$ ; LOCF) at Week 12 compared with placebo. Sensitivity analyses (NRI, mixed imputation, and OC [no imputation]) also showed that a statistically significantly higher ( $P \leq 0.05$ ) proportion of subjects achieved an ACR20 response at Week 12 in the ABT-494 6 mg BID, 12 mg BID, and 24 mg QD dose groups compared with placebo, with the 18 mg BID missing statistical significance using NRI and mixed imputation. Similarly, compared with placebo, statistically significantly higher ( $P \leq 0.05$ ; LOCF) proportions of subjects achieved ACR50 and ACR70 responses at Week 12 with most of the tested ABT-494 doses (excluding 12 mg BID for ACR70 response), reached a state of LDA at Week 12 (LOCF) as measured by either DAS28 [CRP] or CDAI (excluding 24 mg QD for CDAI), and achieved clinical remission by DAS28 [CRP] (LOCF; excluding 24 mg QD). Sensitivity analyses for the secondary endpoints using other imputation methods provided similar results as LOCF imputation.

With ABT-494 treatment, efficacy endpoint results over time (Baseline to Week 12) compared with placebo generally showed: increased ACR20, ACR50, and ACR70 response rates; improvement in disease activity (by decreases in DAS28 [CRP] and CDAI, as well as assessments by patients and physicians); decreases in the number of tender and swollen joints; decreases in pain; and improvement in functioning and disease-related disability (i.e., ability to function in daily life due to illness). In addition, subjects in each ABT-494 dose group had statistically significantly greater ( $P \leq 0.05$ ) decreases in hs-CRP values compared with placebo. Among the ABT-494 doses, ABT-494 6 mg BID dosing consistently provided robust efficacy, with some possible further benefit provided with 12 mg BID dosing for some selected efficacy outcomes.

At Week 12, with ABT-494 treatment, subjects reported improvement in chronic illness fatigue and its effect on functioning and daily activities, in their RA-associated work instability (for subjects who were working), in their current health status in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and in their assessment of their overall health state, and in their view of their health and well-being, i.e., how they felt and how well they were able to do their usual activities. Overall, treatment with ABT-494 resulted in numerically better results than placebo for the patient-reported health outcomes studied (fatigue, work instability, and health state). Statistically significantly greater ( $P \leq 0.05$ ) mean increases from Baseline compared with placebo were consistently observed in physical health scores for subjects in the ABT-494 6 mg BID and 12 mg BID dose groups (physical function, bodily pain, general health, and physical component summary).

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**Summary/Conclusions (Continued)**

**Pharmacokinetic Results:**

Within 12 hours of dosing, ABT-494 mean plasma concentrations ranged from 5 ng/mL to 18.3 ng/mL for 3 mg BID, from 8.6 ng/mL to 33.7 ng/mL for 6 mg BID, from 18.6 ng/mL to 67.8 ng/mL for 12 mg BID, and from 23.5 ng/mL to 74.1 ng/mL for 18 mg BID. Within 24 hours of dosing, ABT-494 mean plasma concentrations ranged from 7.58 ng/mL to 99.4 ng/mL for 24 mg QD.

ABT-494 mean  $C_{max}$  in the intensive PK cohort was 30.6 ng/mL and 23.7 ng/mL for 3 mg BID, 46.6 ng/mL and 54.1 ng/mL for 6 mg BID, 112 ng/mL and 105 ng/mL for 12 mg BID, 139 ng/mL and 135 ng/mL for 18 mg BID, and 201 and 172 ng/mL for 24 mg QD on Day 1 and Week 8, respectively.

**Safety Results:**

The overall rates of AEs were higher for subjects who received ABT-494 (total) compared with placebo (45.8% versus 26.0%). The most frequently reported AE in the ABT-494 (total) group was nasopharyngitis (12 subjects [4.8%]). The SOC with the highest proportion of subjects with TEAEs was infections and infestations for subjects in both the ABT-494 (total) (19.3%) and placebo (12.0%) groups. The most frequently reported TEAEs considered by the investigator to have a reasonable possibility of being related to ABT-494 were (ABT-494 [total] group): headache (6 subjects [2.4%]) and blood creatine phosphokinase (CPK) increased (5 subjects [2.0%]).

No deaths were reported for any subject during the treatment period. One subject (ABT-494 6 mg BID dose group) was diagnosed with lung neoplasm malignant 11 days after the final scheduled visit in the study. The subject died 3 months later (14 weeks after study completion).

The overall rate of SAEs for subjects in the ABT-494 (total) group was 3.2% (8 subjects). Pneumonia in 1 subject (ABT-494 12 mg BID dose group) and pyrexia in 1 subject (18 mg BID dose group) led to discontinuation from the study. No subject treated with ABT-494 3 mg BID or placebo had an SAE. No individual SAE was reported by more than 1 subject. Overall, the number of subjects who had AEs leading to discontinuation of study drug was low: 1 subject in the placebo group and 1 subject in each ABT-494 dose group except 18 mg BID, in which 4 of 5 subjects discontinued for AEs related to laboratory changes (hyperbilirubinemia, hemoglobin decreased, neutrophil count decreased, and blood WBC count decreased [2 subjects]).

Of the AEs of special interest categories, no subject in any treatment group reported an opportunistic infection, non-melanoma skin cancer, or gastrointestinal perforation. A total of 49 (19.7%) subjects in the ABT-494 (total) group reported treatment-emergent infections, with nasopharyngitis (12 [4.8%] subjects) and urinary tract infection (8 [3.2%] subjects) being the most frequently reported infections. There were 3 subjects with herpes zoster (1 subject in the 3 mg BID and 2 subjects in the 24 mg QD dose groups). No herpes zoster event involved more than 1 dermatome, and none affected the eye or central nervous system; all events resolved with concomitant medication during the study, and no subject discontinued study drug due to herpes zoster.

**Summary/Conclusions (Continued)**

**Safety Results (Continued):**

There was 1 serious infection (community-acquired pneumonia, which resolved with antibiotic treatment [ABT-494 12 mg BID]), 1 malignancy (lung neoplasm malignant [ABT-494 6 mg BID]), 3 hepatic disorders (hepatic cyst [3 mg BID]; hyperbilirubinemia [18 mg BID]; ALT increased [18 mg BID]); 1 case of anemia (18 mg BID); and 1 cerebral infarction (12 mg BID), which was a prespecified cardiovascular event adjudicated as ischemic stroke by the independent Cardiovascular Event Adjudication Committee. An additional subject (18 mg BID) had a nonserious AE of hemoglobin decreased (term not included in the "anemia" search criteria), which led to discontinuation from the study. The lung neoplasm malignant and pneumonia were serious; the pneumonia and hyperbilirubinemia led to discontinuation from the study. During ABT-494 treatment, some changes in hemoglobin levels, neutrophil counts, and lymphocyte counts were observed that resulted in reported AEs of anemia (1 subject in the 18 mg BID dose group) and leukopenia (4 subjects: 3 in the 12 mg BID and 1 in the 18 mg BID dose groups). In addition, lymphocyte count decreased and neutrophil count decreased were reported in 1 subject each (24 mg QD and 18 mg BID dose group, respectively). At the Week 12 visit, there was no event of neutropenia in any ABT-494 dose group and 1 event of neutropenia in the placebo group.

ABT-494 treatment also resulted in modest increases in low density lipoprotein-cholesterol (LDL-C) and low density lipoprotein-cholesterol (HDL-C), and the effect appeared to plateau at exposures achieved with ABT-494 6 mg BID or higher, but the ratio of LDL-C/HDL-C remained unchanged through Week 12. In addition, there appeared to be a trend toward a dose-dependent increase in CPK; however, the mean values for each ABT-494 dose group were within the normal range during the study. Seven subjects (6 subjects in the ABT-494 [total] group and 1 subject in the placebo group) had CPK laboratory values  $> 4 \times$  ULN; for 1 of the subjects (ABT-494 group), increased blood CPK was reported as an AE. All subjects with elevated CPK values, including those for whom AEs were reported, were asymptomatic (i.e., no weakness or signs/symptoms of rhabdomyolysis, and elevated CPK not life-threatening). No subject discontinued the study due to an elevated CPK. Based on Rheumatology Common Toxicity Criteria severity grades, there were a few isolated changes in clinical chemistry variables ALT, AST, and total bilirubin in the ABT-494 [total] group: 4 subjects with Grade 3 and 1 subject with Grade 4 ALT elevations, 3 subjects with Grade 3 AST elevations, and 2 subjects with Grade 3 and 1 subject with Grade 4 total bilirubin elevations; however, there did not appear to be a dose-response relationship between ABT-494 and elevation of these variables, and no Hy's law case was identified.

**Conclusions:**

Phase 2 Study M13-537 met its primary endpoint; a statistically significantly greater ( $P \leq 0.05$ ) proportion of subjects treated with ABT-494 achieved an ACR20 response at Week 12 compared with placebo. Similarly, at Week 12 compared with placebo, significantly higher ( $P \leq 0.05$ ) proportions of subjects achieved ACR50 and ACR70 responses, reached a state of LDA as measured by either DAS28 [CRP] or CDAI, and achieved clinical remission as measured by DAS28 [CRP] with most of the tested ABT-494 doses. Overall, the efficacy and patient-reported health outcomes data demonstrated a positive treatment effect for ABT-494 in subjects with moderately to severely active RA who had an inadequate response to MTX therapy. ABT-494 6 mg BID dosing consistently provided robust efficacy and patient-reported results, with some further benefit provided with 12 mg BID dosing. The AEs observed, as well as the changes in vital signs and clinical laboratory results, did not indicate any safety concerns for further evaluation of ABT-494 in subjects with RA.