2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-494	**Volume:**	
Name of Active Ingredient: ABT-494	**Page:**	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Investigate the Safety and Efficacy of ABT-494 Given with Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis (RA) Who Have Had an Inadequate Response or Intolerance to Anti-TNF Biologic Therapy		
Investigator: [redacted]		
Study Sites: 82 sites in the United States (including Puerto Rico), Australia, Czech Republic, Hungary, Spain, UK, Poland, Belgium, New Zealand		
Publications: 1 manuscript (in press)		
Studied Period (Years): First Subject First Visit: 31 October 2013 Last Subject Last Visit: 27 July 2015	**Phase of Development:** 2	
Objective: 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 RA on stable background MTX therapy who had shown an inadequate response or intolerance to anti-tumor necrosis factor (TNF) biologic therapy.		
Methodology: 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 an inadequate response or intolerance to anti-TNF 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 ratio to 1 of 5 treatment arms: placebo twice daily (BID) or ABT-494 3 mg BID, 6 mg BID, 12 mg BID, or 18 mg BID. 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.		
Number of Subjects (Planned and Analyzed): Planned: 250 subjects (50 placebo; 200 ABT-494); Analyzed: 276 (56 placebo; 220 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 (EULAR) criteria for ≥ 3 months; had active RA as defined by minimum disease activity criteria (≥ 6 tender joints [based on 68 joint counts] at Screening and Baseline visits, ≥ 6 swollen joints [based on 66 joint counts] at Screening and Baseline visits, high-sensitivity C-reactive protein [hsCRP] > 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 ≥ 3 months and were on a stable prescription of 7.5 to 25 mg/week for at least 4 weeks prior to Baseline; had been treated with 1 or more anti-TNF biologics for ≥ 3 months but had failed either due to lack of efficacy or intolerability; 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: 13-003339; 13-004590.

ABT-494 12 mg immediate-release capsules for oral administration; Bulk lot number: 13-003488; 13-004770.

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; 12-004542.

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], Health Assessment Questionnaire – Disability Index [HAQ – DI]), and hs-CRP.

Secondary efficacy endpoints were:

- ACR50/70 response rates at Week 12.
- Proportion of subjects achieving low disease activity (LDA) 2.6 ≤ DAS28 [CRP] < 3.2 or clinical remission based on DAS28 [CRP] < 2.6 at Week 12.
- Proportion of subjects achieving clinical remission based on DAS28 [CRP] < 2.6 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; clinical disease activity index (CDAI), a composite index (without CRP), was based on the simple summation of the counts of TJC28 and SJC28 along with PtGA and PGA.

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 DAS28 [CRP] at Weeks 2, 4, 6, 8, and 12; ACRn at Week 12; proportion of subjects achieving LDA (2.8 < clinical disease activity index [CDAI] ≤ 10) or clinical remission (CDAI ≤ 2.8) at Week 12; proportion of subjects achieving clinical remission based on CDAI ≤ 2.8 at Week 12; change from Baseline in individual ACR components (TJC, SJC, patient's assessment of pain, PtGA, PhGA, hs-CRP, HAQ – DI) at Weeks 2, 4, 6, 8, and 12; and change from Baseline for the following health outcomes (from questionnaires): Functional Assessment of Chronic Illness Therapy – fatigue [FACIT-F], Work Instability Scale – Rheumatoid Arthritis [RA-WIS], and European Quality of Life – 5 Dimensions questionnaire [EQ-5D] at Weeks 4, 8, and 12.

Pharmacokinetics:

For all subjects, blood samples for assay of ABT-494 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 pharmacokinetics (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 17 February 2015) that described the analyses for the primary, secondary, and exploratory efficacy variables, and a SAP (dated 15 July 2015) that mainly included changes to the data presentation for the efficacy analyses. Database lock occurred on 25 September 2015, after the last subject completed the 30-day follow-up visit (27 July 2015). The database was updated (unlocked/relocked) on 19 April 2016 to update a barcode for 1 PK sample and to 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. All randomized subjects received at least 1 dose of study drug, either placebo or ABT-494.

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 12 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 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.
- 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.

Statistical Methods (Continued)

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.

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 to be 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 to be counted as severe; 2) For severity assessment, an AE with unknown severity was to be 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 an inadequate response or intolerance to anti-TNF 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 = 276), the majority of subjects were female, white, and non-users of nicotine and alcohol, with a body mass index (BMI) of 25 or greater.

Summary/Conclusions (Continued)

In addition, the majority of subjects in the placebo and ABT-494 (total) groups was 45 to < 65 years of age (57.1% and 53.6%, respectively), while 25.0% and 30.0%, respectively, were ≥ 65 years of age.

No statistically significant differences were observed between the treatment groups for any demographic characteristic. Subjects (89.3% placebo; 86.4% ABT-494 [total]) reported having RA for 3 years or more (mean of approximately 10 to 12 years) and had significantly active disease per protocol-defined inclusion criteria as indicated by (placebo, ABT-494 [total]) mean TJC68 (27.8, 27.5), SJC66 (19.3, 17.2), and hs-CRP (10.1 mg/L, 14.6 mg/L). In the placebo and ABT-494 (total) groups, 76.4% and 70.5%, respectively, reported use of only 1 anti-TNF biologic; 23.6% and 29.5%, respectively, reported use of 2 or more anti-TNF biologics; and 16.1% and 20.5%, respectively, also reported use of non-anti-TNF biologics prior to Baseline.

Efficacy Results:

The efficacy of treatment with the tested ABT-494 doses (3 mg BID, 6 mg BID, 12 mg BID, and 18 mg BID) in subjects with moderately to severely active RA and an inadequate response or intolerance to anti-TNF biologic therapy was demonstrated in this Phase 2, placebo-controlled study. The study met its primary endpoint (based on LOCF analysis) and demonstrated that the proportion of subjects who achieved an ACR20 response with ABT-494 treatment (mITT population: 3 mg BID, 6 mg BID, 12 mg BID, and 18 mg BID) was statistically significantly ($P \leq 0.05$) higher at Week 12 compared with placebo. Sensitivity analyses (NRI, mixed imputation, and OC [no imputation]) also showed that a statistically significantly ($P \leq 0.05$) higher proportion of subjects achieved an ACR20 response at Week 12 in the ABT-494 3 mg BID, 6 mg BID, 12 mg BID, and 18 mg BID dose groups compared with placebo, with the exception of OC analyses for the 3 mg BID dose group. Similarly, at Week 12, statistically significantly ($P \leq 0.05$; LOCF) higher proportions of subjects in every ABT-494 dose group achieved ACR50 and ACR70 responses compared with placebo, with the exception of the 3 mg BID dose group. At Week 12, statistically significantly ($P \leq 0.05$) higher proportions of subjects in the ABT-494 12 mg BID and 18 mg BID dose groups achieved LDA and clinical remission by DAS28 [CRP].

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 CDAI, as well as assessments by patients and physicians); decreases in the number of tender and swollen joints, decreases in pain; and improvement in function and disease-related disability. In addition, at Week 12, each ABT-494 dose group had statistically significantly ($P \leq 0.05$) greater decreases in mean hs-CRP values compared with placebo. Among the ABT-494 doses, ABT-494 6 mg BID dose consistently provided robust efficacy results, and the 12 mg BID dose showed an incremental increase in various efficacy measures.

At Week 12, there was no significant mean improvement from baseline in chronic illness fatigue (FACIT-F) in any ABT-494 dose group compared to placebo and its effect on functioning and daily activities or in RA-associated work instability (for subjects who were working) (RA-WIS). At Week 12, subjects treated with ABT-494 12 mg BID showed a statistically significantly ($P \leq 0.05$) greater mean increase (improvement) from Baseline, in their current health status in 5 dimensions based on VAS (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) 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 perform their usual activities. Overall, treatment with ABT-494 resulted in numerically better results than placebo for the patient-reported outcomes studied (fatigue, work instability, and health state).

Summary/Conclusions (Continued)

Pharmacokinetic Results:

Within 12 hours of dosing, ABT-494 mean plasma concentrations ranged from 4.48 ng/mL to 19.5 ng/mL for 3 mg BID, from 9.44 ng/mL to 30.6 ng/mL for 6 mg BID, from 13.7 ng/mL to 72.6 ng/mL for 12 mg BID, and from 25.5 ng/mL to 103 ng/mL for 18 mg BID.

ABT-494 mean ABT-494 C_{max} in the intensive PK cohort was 23.4 ng/mL and 25.6 ng/mL for 3 mg BID, 41.9 ng/mL and 46.5 ng/mL for 6 mg BID, 99.0 ng/mL and 87.3 ng/mL for 12 mg BID, 148 ng/mL and 137 ng/mL for 18 mg BID on Day 1 and Week 8, respectively.

Safety Results:

The overall rates of AEs were higher for subjects treated with ABT-494 (total) compared with subjects treated with placebo (60.5% versus 44.6%). The most frequently reported AEs in the ABT-494 (total) group were urinary tract infection and headache (5.5% each), followed by upper respiratory tract infection and nausea (5.0% each). The SOC with the highest proportion of subjects with AEs was infections and infestations for both the ABT-494 (total) (29.5%) and placebo (21.4%) groups. The most frequently reported AEs considered by the investigator to have a reasonable possibility of being related to ABT-494 (total across ABT-494 dose groups) were: nausea (8 subjects, 3.6%), urinary tract infection (5 subjects, 2.3%), blood creatine phosphokinase (CPK) increased, leukopenia, upper respiratory tract infection, and headache (4 subjects each, 1.8%).

No deaths were reported for any subject during the entire study.

The overall rate of SAEs for subjects in the ABT-494 (total) group was 2.3% (5 subjects) and 1.8% (1 subject) in the placebo group. No subject treated with ABT-494 12 mg BID had an SAE. One subject treated with ABT-494 18 mg BID had an SAE of acute respiratory failure. Two subjects each had SAEs in the 3 mg (pulmonary embolism and pancreatitis) and 6 mg BID (1 subject had pulmonary embolism and deep vein thrombosis and 1 subject had transient ischemic attack and benign prostate hyperplasia) ABT-494 dose groups (3.6% each). There were 2 SAEs of pulmonary embolism (1 each in the ABT-494 3 mg BID and 6 mg BID groups, as above). No SAE of infection was reported in the ABT-494 dose groups. One subject in the placebo group had an SAE of bronchiectasis.

Ten subjects (4.5%) in the ABT-494 (total) group and 2 subjects (3.6%) in the placebo group had AEs leading to discontinuation of study drug. Treatment-emergent AEs leading to discontinuation of ABT-494 in the ABT-494 dose groups included acarodermatitis, rheumatoid arthritis, stomatitis, gastroenteritis, deep vein thrombosis, pulmonary embolism, headache, anxiety, appetite disorder, tension headache, nausea, upper respiratory tract infection, leukopenia, and hemoglobin decreased.

A total of 66 (30.0%) subjects in the ABT-494 (total) group reported treatment-emergent infections, with urinary tract infection (12 subjects, 5.5%) and upper respiratory tract infection (11 subjects, 5.0%) being the most frequently reported infections. There were 3 subjects with herpes zoster in the ABT-494 dose groups (1 subject each in the ABT-494 3 mg BID, 12 mg BID, and 18 mg BID dose groups). No reported event involved more than 1 dermatome, and none affected the eye or central nervous system; all cases resolved with concomitant medication during the study, and no subject discontinued study drug for any event of herpes zoster. There was 1 subject with malignancy (basal cell carcinoma and squamous cell carcinoma [6 mg BID]), 2 hepatic disorders (transaminases increased and blood bilirubin increased [18 mg BID]; and 1 case of anemia [18 mg BID]).

ABT-494 treatment resulted in modest increases in low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C), and the effect appeared to plateau at exposures achieved with 6 mg BID or higher, but the ratio of LDL-C:HDL-C remained unchanged through Week 12.

Summary/Conclusions (Continued)

Safety Results (Continued):

Thirteen subjects (all subjects in the ABT-494 [total] group) had CPK laboratory values > 4 × ULN.

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 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 liver function test laboratory variables (ABT-494 [total group]): 1 subject with Grade 3 ALT elevation, and 1 subject with Grade 3 total bilirubin elevation; 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 M13-550 met its primary endpoint; statistically significantly ($P \leq 0.05$) more subjects treated with ABT-494 achieved an ACR20 response at Week 12 compared with placebo. Similarly, compared with placebo, significantly ($P \leq 0.05$) higher proportions of subjects achieved ACR50 and ACR70 responses at Week 12 with most of the tested ABT-494 doses and reached a state of LDA at Week 12 as measured by either DAS28 [CRP] or CDAI. At Week 12, clinical remission by DAS28 [CRP] was achieved by a statistically significantly ($P \leq 0.05$) higher proportion of subjects in the ABT-494 12 mg BID and 18 mg BID dose group compared with placebo. Clinical remission by CDAI was not statistically significantly different for any of the ABT-494 dose groups compared with placebo. Overall, the efficacy and patient-reported outcome data demonstrated a positive treatment effect for ABT-494 in subjects with moderately to severely active RA who had shown an inadequate response or intolerance to anti-TNF biologic 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 continued development of ABT-494 for the treatment of RA.