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 Study in Healthy Adult Volunteers and Adult Subjects with Rheumatoid Arthritis to Evaluate the Safety, Tolerability, and Pharmacokinetics After Multiple Dosing of ABT-494		
Coordinating Investigator: [redacted]		
Study Sites: Five investigative sites in the United States were selected to perform the study and received drug supplies, subjects were enrolled at only 3 of the sites. Study site information is on file at AbbVie.		
Publications: None		
Studied Period (Years): First Subject First Visit: 05 November 2012 Last Subject Last Visit: 13 December 2013	**Phase of Development:** 1	

Objectives:

Primary:

- To evaluate the safety, tolerability, and pharmacokinetics after multiple ascending oral doses of ABT-494 in healthy adult subjects in Substudy 1.
- To assess the safety, tolerability, and pharmacokinetics after multiple oral doses of ABT-494 in subjects with rheumatoid arthritis (RA) who are on a stable methotrexate (MTX) regimen in Substudy 2.

Secondary:

- To determine the effects of multiple doses of ABT-494 on the pharmacokinetics of MTX in Substudy 2.
- To determine the effect of MTX on the multiple dose pharmacokinetics of ABT-494 in Substudy 2.

Exploratory:

- To investigate whether ABT-494 inhibits Jak Kinase (Jak) activity by assessing its effects on certain lymphocyte subsets (i.e., natural killer [NK] cells), signal transduction activators of transcription (STAT) phosphorylation and potentially other exploratory biomarkers in Substudies 1 and 2.
- To study the effects of ABT-494 on messenger ribonucleic acid (mRNA) related to inflammation and drug mechanism in Substudy 2.
- To explore potential disease response signals in Substudy 2.
- To investigate the effect of tofacitinib on lymphocyte subsets (i.e., NK cells), STAT phosphorylation and potentially other exploratory biomarkers in Substudy 3.

Methodology:

Adult male and female subjects (N = 53) in general good health, and adult male and female subjects with mild to moderate RA who were on stable MTX treatment (N = 14) participated in the study. Subjects were not dosed in more than one dose group within a substudy. In each substudy, each dose of study drug was administered (if confined) or taken (if outpatient) following breakfast for the morning dose and dinner/snack for the evening dose. Each dose of study drug was taken orally with approximately 240 mL of water.

Substudy 1 – Multiple Ascending Dose in Healthy Volunteers (MAD/HV) was a randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability and pharmacokinetics of multiple ascending oral doses of ABT-494 in healthy subjects. Forty-four (N = 44) subjects participated in the study and randomized into four groups (Groups 1 – 4), each with 11 subjects. Within each group, subjects were randomly assigned (8:3 ratio) to receive ABT-494 or matching placebo twice a day (BID) for 13 consecutive days and once in the morning on Day 14, with food. The ABT-494 doses administered were 3 mg, 6 mg, 12 mg, and 24 mg BID for Groups 1, 2, 3 and 4, respectively. Serial blood samples for ABT-494 assay were drawn on Day 1 prior to and for 12 hours after the morning dose (prior to the evening dose). On Day 14, blood samples for ABT-494 assay were drawn prior to and for 72 hours after the morning dose. Blood samples were also drawn prior to the morning dose on Days 5, 6, 7, and 13 to measure ABT-494 trough concentrations.

Substudy 2 – Multiple Dosing in RA Subjects on a Stable Dose of MTX (MD/RA) was a randomized, double-blind, parallel-group, placebo-controlled study designed to assess the safety, tolerability and pharmacokinetics of multiple oral doses of ABT-494 in subjects with mild to moderate RA who were on stable MTX treatment and in otherwise general good health. Fourteen (N = 14) subjects participated in the study and were randomized into one of four dosing arms (Arms 1 – 4). Subjects received 6 mg, 12 mg, or 24 mg ABT-494 BID in Arms 1, 2 or 3, respectively, or placebo in Arm 4. Subjects received study drug (ABT-494 or placebo) for 26 consecutive days with food (Study Days 3 through 28) and a single morning dose of study drug on Study Day 29. Subjects were on MTX therapy for at least 3 months and on a stable dose of 10 to 25 mg/week of MTX for at least 4 weeks prior to the first dose of study drug administered on Study Day 3 and continued their weekly stable dose of MTX on Study Days 1, 8, 15, 22 and 29. Serial blood samples for MTX assay were drawn prior to the morning dose on Study Day 1 until 48 hours after MTX dose (prior to the first dose of study drug) and prior to the morning dose on Study Day 29 until 48 hours after MTX dose on Day 29. Serial blood samples for ABT-494 assay were drawn on Day 3 and Day 28 from prior to the morning dose until 12 hours post-study drug dose (prior to the evening study drug dose) and prior to the morning dose on Day 29 until 48 hours post dose.

Substudy 3 – Multiple Dosing of Tofacitinib in Healthy Volunteers (Tofa/HV) was a single-arm, open-label study designed to collect safety, tolerability, pharmacokinetics and biomarker information following the administration of multiple doses of tofacitinib to healthy subjects. Nine (N = 9) subjects participated in the study. They received 5 mg tofacitinib BID for 13 consecutive days (Day 1 – 13) and once in the morning on Day 14. Serial PK samples for tofacitinib assay were drawn on Day 1 from prior to the morning dose until 12 hours post-study drug dose (prior to the evening study drug dose) and prior to the morning dose on Day 14 until 72 hours post dose.

Methodology (Continued):

Assays: Plasma concentrations of ABT-494, tofacitinib and MTX were determined using a validated liquid chromatography (LC) method with mass spectrometric (MS) detection. The lower limits of quantitation (LLOQ) for ABT-494, tofacitinib and MTX in plasma were established at 0.0503 ng/mL, 0.637 ng/mL and 1.00 ng/mL, respectively. Urine concentrations of ABT-494 and MTX were determined using a validated LC method with MS detection. The LLOQ for ABT-494, and MTX in urine were established at 1.01 ng/mL and 0.0500 µg/mL, respectively.

Number of Subjects (Planned and Analyzed):

Planned: 85, Entered: 67, Completed: 67, Evaluated for Pharmacokinetics: 51, Evaluated for Safety: 67, Evaluated for Pharmacodynamics: 67.

Substudy 1

		Mean ± SD (Minimum – Maximum)			
Group	**N**	**Age (Years)**	**Weight (kg)**	**Height (cm)**	**BMI (kg/m^2)**
Placebo	12	30.7 ± 5.0 (25 – 40)	78.4 ± 13.6 (57 – 96)	177 ± 6.2 (167 – 187)	25.0 ± 3.4 (20 – 30)
3 mg BID ABT-494	8	33.6 ± 9.4 (23 – 48)	70.8 ± 7.4 (59 – 80)	171 ± 9.8 (155 – 185)	24.4 ± 3.0 (21 – 29)
6 mg BID ABT-494	8	37.0 ± 11.1 (26 – 54)	75.7 ± 13.6 (56 – 89)	173 ± 8.5 (157 – 181)	25.3 ± 3.2 (21 – 29)
12 mg BID ABT-494	8	34.0 ± 7.3 (25 – 48)	73.7 ± 8.6 (62 – 92)	169 ± 6.5 (159 – 180)	25.9 ± 2.5 (22 – 29)
24 mg BID ABT-494	8	28.4 ± 11.3 (22 – 56)	76.1 ± 9.9 (62 – 91)	175 ± 6.4 (165 – 184)	24.9 ± 3.0 (20 – 28)
Total ABT-494	32	33.3 ± 9.9 (22 – 56)	74.1 ± 9.9 (56 – 92)	172 ± 7.9 (155 – 185)	25.1 ± 2.9 (20 – 29)

Substudy 2

		Mean ± SD (Minimum – Maximum)			
Group	**N**	**Age (Years)**	**Weight (kg)**	**Height (cm)**	**BMI (kg/m^2)**
Placebo	3	58.7 ± 14.3 (43 – 71)	62.5 ± 6.9 (55 – 67)	165 ± 9.9 (154 – 173)	22.9 ± 0.5 (22 – 23)
6 mg BID ABT-494	4	54.0 ± 9.4 (44 – 62)	76.7 ± 17.6 (57 – 93)	171 ± 11.4 (160 – 187)	26.1 ± 4.5 (22 – 32)
12 mg BID ABT-494	3	57.7 ± 4.7 (54 – 63)	71.3 ± 11.7 (63 – 85)	168 ± 6.0 (162 – 173)	25.2 ± 4.1 (21 – 29)
24 mg BID ABT-494	4	65.8 ± 5.4 (58 – 70)	85.7 ± 14.6 (71 – 101)	172 ± 3.9 (166 – 174)	29.0 ± 4.5 (23 – 33)
Total ABT-494	11	59.3 ± 8.3 (43 – 71)	78.5 ± 14.9 (57 – 101)	171 ± 7.3 (160 – 187)	26.9 ± 4.3 (21 – 33)

Number of Subjects (Planned and Analyzed) (Continued):

Substudy 3					
		Mean ± SD (Minimum – Maximum)			
Group	**N**	**Age (Years)**	**Weight (kg)**	**Height (cm)**	**BMI (kg/m^2)**
5 mg BID Tofacitinib	9	33.2 ± 8.9 (20 – 47)	71.2 ± 9.2 (60 – 83)	169 ± 9.4 (156 – 185)	25.0 ± 2.4 (20 – 28)

SD = Standard Deviation

Diagnosis and Main Criteria for Inclusion:

Subjects were male and female volunteers between 18 and 55 years in Substudies 1 and 3, or between 18 and 75 years in Substudy 3 at Screening. Subjects in the study were judged to be in general good health (other than RA for at least 6 months for Substudy 2 subjects) based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG). Females were postmenopausal for at least 2 years or surgically sterile, and were not pregnant or breastfeeding. Males did not donate sperm and used condoms from the first dose of study drug until 90 days after the last dose of study drug.

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

	Substudy 1		Substudy 2	
	ABT-494	**Placebo for ABT-494**	**ABT-494**	**Placebo for ABT-494**
Mode of Administration	Oral	Oral	Oral	Oral
Dosage Form	Capsule	Capsule	Capsule	Capsule
Strength (mg)	3	0	3	0
Bulk Product Lot Number	12-002768	10-005233	12-008070	10-005233
Finishing Lot	12-006337	12-006914	13-000246	
Retest Date	31 October 2013	31 December 2014	31 December 2013	
Manufacturer	AbbVie	AbbVie	AbbVie	

	Substudy 3
	Tofacitinib (Xeljanz)
Mode of Administration	Oral
Dosage Form	Tablet
Strength (mg)	5
Bulk Product Lot Number	13-001432
Finishing Lot	13-001435
Retest Date	31 March 2014
Manufacturer	Pfizer

Duration of Treatment:

Subjects in Substudy 1 (MAD/HV) received ABT-494 or matching placebo twice a day for 13 consecutive days and once in the morning on Day 14. Subjects in Substudy 2 (MD/RA) received ABT-494 or matching placebo twice a day for 26 consecutive days with food (Study Days 3 through 28) and a single morning dose of ABT-494 or matching placebo on Study Day 29. Subjects Substudy 3 (Tofa/HV) received tofacitinib twice a day for 13 consecutive days and once in the morning on Day 14.

Criteria for Evaluation

Pharmacokinetic:

ABT-494, MTX and tofacitinib pharmacokinetic parameters were determined using non compartmental methods.

ABT-494 parameters (Substudies 1 and 2) included: the maximum observed concentration (C_{max}), the time to C_{max} (T_{max}), trough plasma concentration (C_{trough}) the terminal phase elimination rate constant (β), the terminal phase elimination half-life ($t_{1/2}$), the terminal phase functional half-life ($t_{1/2}F$), the area under the plasma concentration-time curve (AUC) from time 0 to 12 hours (AUC_{0-12}), the apparent oral clearance (CL/F), and apparent volume of distribution during the terminal elimination phase (Vd_{β}/F), and the fraction of the unchanged drug excreted in urine (f_e) and renal clearance (CL_r). Additional pharmacokinetic parameter values included accumulation ratio (R_{ac}).

MTX parameters (Substudy 2) included: C_{max}, T_{max}, C_{trough}, β, $t_{1/2}$, $t_{1/2}F$, the AUC from time 0 to last measurable concentration (AUC_t), the AUC from time 0 to infinite time (AUC_{∞}), the AUC from time 0 to 48 hours (AUC_{0-48}), CL/F, Vd_{β}/F, R_{ac}, f_e and CL_r.

Tofacitinib parameters (Substudy 3) included: C_{max}, T_{max}, C_{trough}, β, $t_{1/2}$, $t_{1/2}F$, AUC_{0-12}, CL/F and Vd_{β}/F.

Pharmacodynamic:

Pharmacodynamic assessment included ex-vivo, in-vivo and disease response biomarkers and clinical assessments. Ex-vivo variables (Substudies 1, 2 and 3) included interleukin (IL)-6-induced STAT3 phosphorylation, IL-7-induced STAT5 phosphorylation and granulocyte macrophage colony-stimulating factor (GMCSF) induced STAT5 phosphorylation. In-vivo variables (Substudies 1, 2 and 3) included NK, natural killer T cells (NKT), B cells, total T cell and reticulocytes. Additionally, disease response biomarkers and clinical assessments for Substudy 2 were collected and included: swollen joint count (SJC), tender joint count (TJC), physician global assessment of disease activity using a visual analog scale (VAS), patient global assessment of diseases activity using Visual Analog Scale (VAS), patient assessment of pain using VAS, and Health Assessment Questionnaire – Disability Index (HAQ-DI) score.

Safety:

Safety was evaluated based on assessments of adverse events, vital signs, physical examination, and laboratory tests assessments.

Statistical Methods

Enrollment for Substudy 2 was prematurely discontinued; no statistical analysis for safety, pharmacodynamic or pharmacokinetic variables was performed for Substudy 2 due to limited available data. Only descriptive summary statistics were provided, except an analysis of covariance (ANCOVA) was performed on ABT-494 pharmacokinetic parameters to compare healthy subjects in Substudy 1 to subjects with RA in Substudy 2.

Statistical Methods (Continued)

Pharmacokinetic:

Pharmacokinetic parameters of ABT-494 were summarized by study day and by dose level in Substudies 1 and 2. For Substudy 2, pharmacokinetic parameters of MTX were summarized by study day and by ABT-494 dose level. In Substudy 3, pharmacokinetic parameters of tofacitinib were summarized by study day.

Analyses for Substudy 1 were performed to assess attainment of ABT-494 steady state, linear kinetics and dose proportionality of ABT-494 and ABT-494 accumulation. Additionally, an analysis of covariance was performed to compare healthy subjects in Substudy 1 and patients with RA in Substudy 2.

Pharmacodynamic:

Biomarkers: Analyses were performed for each of IL-6-induced STAT3 phosphorylation, IL-7-induced STAT5 phosphorylation and GMCSF induced STAT5 phosphorylation as measured in a whole blood ex-vivo assay. For Substudy 1, a repeated measures analysis was performed on the percent inhibition of phosphorylation obtained on Study Day 14 with the baseline measurement of phosphorylation as a covariate and an analysis was performed for each variable at each time of measurement after the beginning of the ABT-494 regimen.

Disease response biomarkers and clinical assessments: Disease response biomarkers and clinical assessments of rheumatoid arthritis activity were only collected in Substudy 2. Descriptive statistics were provided.

Pharmacokinetic/Pharmacodynamic Modeling:

Population PK/PD Analysis analyses were conducted to characterize the pharmacokinetics of ABT-494 and tofacitinib in plasma and to correlate pharmacokinetic profiles to the ex-vivo IL-6 and IL-7-induced STAT phosphorylation after ABT-494 or tofacitinib dosing. The analyses were conducted using a mixed-effects modeling approach. A model was constructed to describe the pharmacokinetics of ABT-494 in healthy subjects and in subjects with RA. A second model was constructed to describe the pharmacokinetics of tofacitinib in healthy subjects. The empirical Bayesian individual pharmacokinetic parameters from the final pharmacokinetic models were used to build exposure-response models and the data for ABT-494 and tofacitinib were fit simultaneously. Relevant covariate-parameter relationships were investigated in each model using forward inclusion/backward elimination procedures.

Safety:

All subjects who received at least one dose of study drug were included in the safety analyses. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by dose level. Laboratory test values and vital signs measurements that were above or below the reference range were identified. For Substudy 1, an ANCOVA was performed on hematology, clinical chemistry and standard urinalysis variables data on Study Day 14. For ECG, blood pressure and heart rate a linear mixed effects model analysis was performed on the scheduled measurements during the 12 hours after the first ABT-494 dose. A second analysis was performed on the scheduled measurements during the 12 hours after the last dose of the regimen (Day 14). For Substudy 3, change from baseline was summarized for clinical laboratory variables at the end of the regimen.

Summary/Conclusions

Pharmacokinetic Results:

The mean ± SD pharmacokinetic parameters of ABT-494 after BID administration of ABT-494 to healthy subjects in Substudy 1 are presented in the following tables.

	Substudy 1[a]			
ABT-494 Pharmacokinetic Parameters (Units)	**Group 1 3 mg BID ABT-494 (N = 8)**	**Group 2 6 mg BID ABT-494 (N = 8)**	**Group 3 12 mg BID ABT-494 (N = 8)**	**Group 4 24 mg BID ABT-494 (N = 8)**
	Study Day 1			
C_{max} (ng/mL)	19.0 ± 5.02	29.4 ± 3.16	58.1 ± 10.9	126 ± 18.1
T_{max} (h)	1.6 ± 0.8	2.0 ± 0.3	1.9 ± 0.7	1.9 ± 0.4
AUC_{0-12} (ng•h/mL)	75.3 ± 20.5	134 ± 15.9	270 ± 63.2	540 ± 74.0
C_{max}/Dose (ng/mL)/mg	6.33 ± 1.67	4.91 ± 0.53	4.84 ± 0.91	5.25 ± 0.75
AUC_{0-12}/Dose (ng•h/mL)/mg	25.1 ± 6.83	22.3 ± 2.64	22.5 ± 5.26	22.5 ± 3.08

a. ABT-494 administered BID under non-fasting conditions on Study Days 1 – 13, single dose administered on Study Day 14.

	Substudy 1[a]			
ABT-494 Pharmacokinetic Parameters (Units)	**Group 1 3 mg BID ABT-494 (N = 8)**	**Group 2 6 mg BID ABT-494 (N = 8)**	**Group 3 12 mg BID ABT-494 (N = 8)**	**Group 4 24 mg BID ABT-494 (N = 8)**
	Study Day 14			
C_{max} (ng/mL)	18.5 ± 5.41	28.8 ± 3.67	57.6 ± 11.0	119 ± 16.9
T_{max} (h)	1.7 ± 0.9	2.1 ± 0.4	2.2 ± 0.5	1.8 ± 0.3
AUC_{0-12} (ng•h/mL)	78.3 ± 20.3	138 ± 16.7	271 ± 52.7	529 ± 62.6
C_{trough} (ng/mL)	1.46 ± 0.50	2.29 ± 0.41	4.54 ± 1.55	9.50 ± 2.57
$t_{1/2}$ (h)[b,c]	15.7 ± 10.6	13.6 ± 8.5	7.6 ± 4.8	8.0 ± 4.2
$t_{1/2}F$ (h)[b,d]	3.2 ± 0.4	3.3 ± 0.3	3.2 ± 0.5	3.3 ± 0.4
CL/F (L/h)	40.7 ± 10.6	43.9 ± 5.35	45.5 ± 8.04	46.1 ± 6.40
C_{max}/Dose (ng/mL)/mg	6.16 ± 1.80	4.80 ± 0.61	4.80 ± 0.91	4.95 ± 0.71
AUC_{0-12}/Dose (ng•h/mL)/mg	26.1 ± 6.75	23.1 ± 2.78	22.6 ± 4.39	22.0 ± 2.61
C_{trough}/Dose (ng•h/mL)/mg	0.49 ± 0.17	0.38 ± 0.07	0.38 ± 0.13	0.40 ± 0.11
CL_r (L/h)	7.46 ± 2.34	8.05 ± 1.83	9.70 ± 2.28	8.58 ± 2.78
f_e (%)	18.8 ± 4.99	18.7 ± 5.76	21.4 ± 3.80	18.7 ± 5.92
R_{ac} C_{max}[e]	0.9 (0.7 – 1.3)	1.0 (0.8 – 1.1)	1.0 (0.8 – 1.3)	1.0 (0.8 – 1.0)
R_{ac} AUC_{0-12}[f]	1.1 (0.9 – 1.2)	1.0 (0.9 – 1.2)	1.0 (0.9 – 1.1)	1.0 (0.8 – 1.3)

Summary/Conclusions (Continued)

Pharmacokinetic Results (Continued):

a. ABT-494 administered BID under non-fasting conditions on Study Days 1 – 13, single dose administered on Study Day 14.

b. Harmonic mean ± pseudo-standard deviation.

c. Terminal elimination half-life.

d. Functional half-life calculated as: $\ln(2)/(\ln[C_{max}/C_{trough}]/12)$.

e. $R_{ac}\ C_{max}$ = Accumulation ratio (calculated as the ratio of C_{max} on Study Day 14 to C_{max} on Study Day 1); median and range (minimum to maximum) are presented.

f. $R_{ac}\ AUC_{0-12}$ = Accumulation ratio (calculated as the ratio of AUC_{0-12} on Study Day 14 to AUC_{0-12} on Study Day 1); median and range (minimum to maximum) are presented.

The mean ± SD pharmacokinetic parameters of ABT-494 after BID dosing of ABT-494 in subjects with mild to moderate RA on stable doses of MTX (with and without concomitant dosing) in Substudy 2 are presented in the following tables.

	Substudy 2[a]		
ABT-494 Pharmacokinetic Parameters (Units)	**Arm 1: 6 mg BID ABT-494 (N = 4)**	**Arm 2: 12 mg BID ABT-494 (N = 3)**	**Arm 3: 24 mg BID ABT-494 (N = 3)**
	Study Day 3		
C_{max} (ng/mL)	39.4 ± 17.7	66.3 ± 6.77	150 ± 8.39
T_{max} (h)	2.3 ± 1.3	1.8 ± 0.3	1.3 ± 0.3
AUC_{0-12} (ng•h/mL)	169 ± 43.1	296 ± 43.8	492 ± 111
C_{max}/Dose (ng/mL)/mg	6.56 ± 2.94	5.53 ± 0.56	6.24 ± 0.35
AUC_{0-12}/Dose (ng•h/mL)/mg	28.2 ± 7.18	24.7 ± 3.65	20.5 ± 4.62
CL_r (L/h)	5.82 ± 2.06	3.57 ± 0.40[b]	8.58 ± 1.02
f_e (%)	15.7 ± 4.3	8.38 ± 0.69[b]	17.3 ± 2.16

a. ABT-494 administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable doses of MTX administered on Study Days 1, 8, 15, 22 and 29.

b. N = 2.

Summary/Conclusions (Continued)
Pharmacokinetic Results (Continued):

	Substudy 2[a]		
ABT-494 Pharmacokinetic Parameters (Units)	**Arm 1: 6 mg BID ABT-494 (N = 4)**	**Arm 2: 12 mg BID ABT-494 (N = 3)**	**Arm 3: 24 mg BID ABT-494 (N = 3)**
	Study Day 28		
C_{max} (ng/mL)	47.1 ± 7.47	71.1 ± 14.8	129 ± 39.0
T_{max} (h)	1.5 ± 0.4	1.8 ± 0.3	2.3 ± 1.4
AUC_{0-12} (ng•h/mL)	231 ± 48.5	334 ± 49.4	637 ± 143
C_{trough} (ng/mL)	5.81 ± 3.06	5.41 ± 0.98	15.3 ± 1.86
CL/F (L/h)	26.7 ± 4.96	36.4 ± 5.44	39.1 ± 9.79
C_{max}/Dose (ng/mL)/mg	7.84 ± 1.25	5.93 ± 1.23	5.37 ± 1.62
AUC_{0-12}/Dose (ng•h/mL)/mg	38.5 ± 8.09	27.9 ± 4.12	26.5 ± 5.94
C_{trough}/Dose (ng•h/mL)/mg	0.97 ± 0.51	0.45 ± 0.08	0.64 ± 0.08
CL_r (L/h)	6.94 ± 4.04	6.27 ± 2.79	6.31 ± 0.96
f_e (%)	24.7 ± 13.7	17.4 ± 7.81	16.7 ± 4.56
R_{ac} C_{max}[b]	1.3 (0.9 – 1.9)	1.1 (0.9 – 1.2)	0.8 (0.7 – 1.1)
R_{ac} AUC_{0-12}[c]	1.4 (1.0 – 1.8)	1.2 (0.9 – 1.4)	1.3 (1.2 – 1.4)

a. ABT-494 administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable doses of MTX administered on Study Days 1, 8, 15, 22 and 29.

b. R_{ac} C_{max} = Accumulation ratio (calculated as the ratio of C_{max} on Study Day 28 to C_{max} on Study Day 3); median and range (minimum to maximum) are presented.

c. R_{ac} AUC_{0-12} = Accumulation ratio (calculated as the ratio of AUC_{0-12} on Study Day 28 to AUC_{0-12} on Study Day 3); median and range (minimum to maximum) are presented.

Summary/Conclusions (Continued)
Pharmacokinetic Results (Continued):

	Substudy 2[a]		
ABT-494 Pharmacokinetic Parameters (Units)	**Arm 1: 6 mg BID ABT-494 (N = 4)**	**Arm 2: 12 mg BID ABT-494 (N = 3)**	**Arm 3: 24 mg BID ABT-494 (N = 3)**
	Study Day 29		
C_{max} (ng/mL)	42.4 ± 8.85	60.8 ± 4.01	154 ± 39.5
T_{max} (h)	2.1 ± 0.8	2.2 ± 0.8	1.0 ± 0.5
AUC_{0-12} (ng•h/mL)	215 ± 49.2	338 ± 14.5	665 ± 89.8
C_{trough} (ng/mL)	4.63 ± 3.48	6.44 ± 1.09	14.9 ± 4.37
$t_{1/2}$ (h)[b, c]	9.5 ± 3.6	14.4 ± 5.3	11.5 ± 7.6
$t_{1/2}F$ (h)[b, d]	3.5 ± 0.9	3.7 ± 0.2	3.6 ± 0.1
CL/F (L/h)	29.0 ± 5.92	35.6 ± 1.56	36.5 ± 4.70
C_{max}/Dose (ng/mL)/mg	7.06 ± 1.48	5.07 ± 0.33	6.40 ± 1.64
AUC_{0-12}/Dose (ng•h/mL)/mg	35.8 ± 8.19	28.1 ± 1.21	27.7 ± 3.74
C_{trough}/Dose (ng•h/mL)/mg	0.77 ± 0.58	0.54 ± 0.09	0.62 ± 0.18
CL_r (L/h)	4.93 ± 2.41	4.96 ± 3.34	8.60 ± 1.30
f_e (%)	16.1 ± 5.33	14.2 ± 9.76	23.6 ± 1.80
Day 29/Day 28 C_{max} Ratio[e]	0.9 (0.8 – 1.1)	0.9 (0.7 – 1.0)	1.2 (1.1 – 1.4)
Day 29/Day 28 AUC_{0-12} Ratio[e]	0.9 (0.9 – 1.0)	1.0 (0.9 – 1.1)	1.0 (0.9 – 1.2)

a. ABT-494 administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable dose of MTX administered on Study Days 1, 8, 15, 22 and 29.

b. Harmonic mean ± pseudo-standard deviation.

c. Terminal elimination half-life.

d. Functional half-life.

e. Median and range (minimum to maximum) are presented.

Summary/Conclusions (Continued)

Pharmacokinetic Results (Continued):

The mean ± SD pharmacokinetic parameters of MTX after administration of stable dose of MTX with and without concomitant dosing of ABT-494 to subjects with mild to moderate RA in Substudy 2 are presented in the following tables.

	Substudy 2[a]			
MTX Pharmacokinetic Parameters (Units)	**Arm 1: 6 mg BID ABT-494 (N = 4)**	**Arm 2: 12 mg BID ABT-494 (N = 3)**	**Arm 3: 24 mg BID ABT-494 (N = 3)**	**Arm 4: ABT-494 Placebo (N = 4)**
	Study Day 1			
C_{max} (ng/mL)	245 ± 63.6	278 ± 44.0	196 ± 58.6	318 ± 138
T_{max} (h)	3.1 ± 2.0	2.7 ± 0.6	2.0 ± 1.7	2.0 ± 0.7
AUC_t (ng•h/mL)	1450 ± 510	1640 ± 381	945 ± 350	1620 ± 479
AUC_∞ (ng•h/mL)	1470 ± 494	1670 ± 393	966 ± 365	1640 ± 470
$t_{1/2}$ (h)[b]	4.0 ± 2.6	4.0 ± 0.3	3.0 ± 1.1	3.9 ± 0.5
CL/F (L/h)	11.8 ± 6.43	8.36 ± 1.28	16.9 ± 8.89	11.2 ± 3.81
C_{max}/Dose (ng/mL)/mg	18.0 ± 10.0	20.7 ± 4.61	13.9 ± 4.29	18.8 ± 9.50
AUC_t/Dose (ng•h/mL)/mg	97.2 ± 36.0	120 ± 19.7	67.8 ± 27.4	97.4 ± 39.3
AUC_∞/Dose (ng•h/mL)/mg	98.9 ± 35.6	122 ± 20.0	69.3 ± 28.1	98.7 ± 38.8
CL_r (L/h)	6.63 ± 3.79	6.13 ± 1.93	7.46 ± 0.70	4.32 ± 1.12
f_e (%)	58.0 ± 28.6	74.3 ± 18.6	53.9 ± 25.1	44.9 ± 25.1

a. ABT-494 or placebo administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable doses of MTX administered on Study Days 1, 8, 15, 22 and 29.

b. Harmonic mean ± pseudo-standard deviation.

Summary/Conclusions (Continued)
Pharmacokinetic Results (Continued):

	Substudy 2[a]			
MTX Pharmacokinetic Parameters (Units)	**Arm 1: 6 mg BID ABT-494 (N = 4)**	**Arm 2: 12 mg BID ABT-494 (N = 3)**	**Arm 3: 24 mg BID ABT-494 (N = 3)**	**Arm 4: ABT-494 Placebo (N = 4)**
	Study Day 29			
C_{max} (ng/mL)	228 ± 23.0	255 ± 99.9	256 ± 29.3	354 ± 182
T_{max} (h)	1.6 ± 0.5	2.7 ± 0.3	2.5 ± 0.5	2.1 ± 1.4
AUC_t (ng•h/mL)	1480 ± 426	1750 ± 784	1340 ± 315	1570 ± 462
AUC_∞ (ng•h/mL)	1490 ± 424	1780 ± 791	1373 ± 324	1590 ± 458
$t_{1/2}$ (h)[b]	4.7 ± 1.3	4.2 ± 0.6	3.1 ± 1.3	3.8 ± 0.3
CL/F (L/h)	10.9 ± 3.43	8.14 ± 1.03	10.6 ± 1.61	11.3 ± 2.66
C_{max}/Dose (ng/mL)/mg	16.2 ± 7.21	18.0 ± 2.11	18.1 ± 1.75	21.3 ± 13.1
AUC_t/Dose (ng•h/mL)/mg	96.5 ± 25.4	122 ± 14.4	94.1 ± 16.0	92.1 ± 28.9
AUC_∞/Dose (ng•h/mL)/mg	97.5 ± 25.4	124 ± 14.7	96.4 ± 16.1	93.2 ± 28.4
CL_r (L/h)	5.43 ± 2.02	4.78 ± 2.28	6.43 ± 0.75	5.80 ± 1.08
f_e (%)	51.1 ± 20.1	58.8 ± 25.8	62.6 ± 3.99	56.5 ± 26.4
C_{max} Ratio[c]	1.0 (0.8 – 1.1)	0.8 (0.8 – 1.1)	1.2 (1.0 – 2.2)	1.1 (1.0 – 1.2)
AUC_∞ Ratio[d]	1.0 (0.8 – 1.4)	0.9 (0.9 – 1.3)	1.1 (1.0 – 3.1)	0.9 (0.8 – 1.2)

a. ABT-494 or placebo administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable doses of MTX administered on Study Days 1, 8, 15, 22 and 29.

b. Harmonic mean ± pseudo-standard deviation.

c. C_{max} Ratio = calculated as the ratio of C_{max} on Study Day 29 to C_{max} on Study Day 1; median and range (minimum to maximum) are presented

d. AUC_∞ Ratio = calculated as the ratio of AUC_∞ on Study Day 29 to AUC_∞ on Study Day 1; median and range (minimum to maximum) are presented.

Summary/Conclusions (Continued)

Pharmacokinetic Results (Continued):

The mean ± SD pharmacokinetic parameters of tofacitinib after BID administration to healthy subjects in Substudy 3 are presented in the following table.

	Substudy 3[a]	
Tofacitinib Pharmacokinetic Parameters (Units)	**5 mg BID Tofacitinib (N = 9)**	
	Day 1	**Day 14**
C_{max} (ng/mL)	42.0 ± 10.0	40.9 ± 6.29
T_{max} (h)	0.8 ± 0.3	0.9 ± 0.5
AUC_{0-12} (ng•h/mL)	139 ± 13.4	135 ± 14.2
C_{trough} (ng/mL)	--	1.23 ± 0.44
$t_{1/2}$ (h)[b]	--	2.3 ± 0.4
CL/F (L/h)	--	37.4 ± 4.05
C_{max}/Dose (ng/mL)/mg	8.39 ± 2.00	8.19 ± 1.26
AUC_{0-12}/Dose (ng•h/mL)/mg	27.8 ± 2.68	27.0 ± 2.84
C_{trough}/Dose (ng•h/mL)/mg	--	0.25 ± 0.09

a. Tofacitinib was administered BID on Study Days 1 through 13; single dose of Tofacitinib was administered in the morning on Study Day 14.

b. Harmonic mean ± pseudo-standard deviation.

Population pharmacokinetic analysis of the combined dataset from healthy volunteers and the limited number of subjects with RA evaluated in this study suggested that ABT-494 clearance is approximately 20% lower in subjects with RA who are on stable doses of MTX compared to healthy volunteers.

Pharmacodynamic Results:

Following the administration of multiple ABT-494 doses to healthy subjects, IL-6-induced STAT3 phosphorylation and IL-7-induced STAT5 phosphorylation were inhibited with maximum inhibition observed 1 hour after dosing. Inhibition of IL-6- and IL-7-induced STAT phosphorylation induction after 1 hour ranged from 52% to 80% and from 21% to 82% for IL-6 and IL-7, respectively, across all ABT-494 BID dose groups.

There was a statistically significant trend for decrease in NK and NKT cell counts from baseline with increasing ABT-494 dose, with greater reduction in the 12 mg and 24 mg, dose groups compared to placebo. Of note, there was a substantial increase in NK cell counts (+ 65.6%) from baseline in the placebo group on Day 15. No statistically significant trend for change in NK and NKT cell counts with ABT-494 dose was observed on Day 35. The small sample size and individual variability in these measurements limit the conclusions from this dataset.

Summary/Conclusions (Continued)

PharmacokineticPharmacodynamic Modeling Results:

The effects of ABT-494 or tofacitinib on IL-6- and IL-7-induced STAT phosphorylation were described by E_{max} models. The model-estimated EC_{50} values for inhibition of IL-6-induced phosphorylation were 23.1 ng/mL for ABT-494 and 37.1 ng/mL for tofacitinib. Based on a molecular weight of 380.4 for ABT-494 and 312.4 for tofacitinib, the corresponding EC_{50} estimates are 60.7 and 119 nM, respectively, suggesting that ABT-494 is more potent in inhibiting IL-6-induced phosphorylation than tofacitinib. The model-estimated EC_{50} values for inhibition of IL-7-induced phosphorylation were 47.7 ng/mL for ABT-494 and 24.7 ng/mL for tofacitinib (125 nM and 79.1 nM, respectively), suggesting that tofacitinib is more potent in inhibiting IL-7-induced STAT phosphorylation than ABT-494.

Safety Results:

Multiple doses of ABT-494 were administered up to 24 mg BID in healthy subjects for 14 days in Substudy 1 and ABT-494 administered on a background with stable doses of MTX in subjects with RA for 28 days in Substudy 2. Multiple doses of 5 mg tofacitinib were administered BID to healthy subjects for 14 days in Substudy 3.

Overall there were no dose-limiting toxicities or safety concerns with ABT-494 from the multiple dosing of ABT-494 in either healthy volunteers or in subjects with RA. There was no observed trend in regards to the adverse events reported. All adverse events were considered mild or moderate in severity. No deaths, other serious adverse events or treatment discontinuations due to adverse events occurred during the study. Headache was the only adverse event reported by more than two subjects in any ABT-494 regimen (2/8, 25%; Substudy 1: 3 mg and 12 mg ABT-494 BID), all other adverse events for ABT-494 BID regimens in both Substudies 1 and 2 were reported by a maximum of one subject each. One adverse event (1/9, 11.1%) of pruritis was reported in Substudy 3 after administration of 5 mg tofacitinib BID to healthy subjects.

Results of other safety analyses including individual subject changes, changes over time and individually clinically significant values for vital signs, ECG and laboratory measurements were unremarkable for each treatment group.

Conclusions:

Following multiple oral dosing to healthy subjects, ABT-494 steady-state concentrations were achieved by Day 13. However, there was a small difference (~13%) in ABT-494 mean pre-dose plasma concentrations between Days 5 and 13. ABT-494 steady-state exposure (AUC, C_{max} and C_{trough}) did not deviate significantly from dose-proportionality in the dose range of 3 mg to 24 mg BID. ABT-494 displayed minimal to no accumulation with BID dosing. ABT-494 functional half-life, estimated from C_{max} to C_{trough} ratio at steady-state, was approximately 3 hours. ABT-494 terminal elimination half-life ranged from 8 to 16 hours. The fraction of ABT-494 dose eliminated unchanged in urine ranged from 19% to 21%.

In subjects with RA on stable MTX treatment, ABT-494 mean T_{max} was approximately 2 hours, under non-fasting conditions, similar to healthy volunteers. ABT-494 median accumulation ratio with BID dosing ranged from 0.8 to 1.4. ABT-494 functional $t_{1/2}$ was approximately 4 hours, and the terminal $t_{1/2}$ ranged from 9 to 14 hours. ABT-494 exposures were comparable when concomitantly administered with and without MTX. Similarly, MTX exposures were comparable when administered with and without ABT-494.

Summary/Conclusions (Continued)

Conclusions:

Plasma concentrations of tofacitinib reached peak levels at approximately 1 hour after dosing on Days 1 and 14 of a 5 mg twice daily dosing regimen in healthy volunteers. The harmonic mean terminal elimination half-life of tofacitinib was 2.3 hours.

Population pharmacokinetic analysis of the combined dataset from healthy volunteers and the limited number of subjects with RA evaluated in this study suggested that ABT-494 clearance is approximately 20% lower in subjects with RA who are on stable doses of MTX compared to healthy volunteers.

Following the administration of multiple ABT-494 doses to healthy subjects, IL-6-induced STAT3 phosphorylation and IL-7-induced STAT5 phosphorylation were inhibited with maximum inhibition observed 1 hour after dosing. Inhibition of IL-6 and IL-7 induction after 1 hour ranged from 52% to 80% and from 21% to 82% for IL-6 and IL-7, respectively, across all ABT-494 BID dose groups. In the lower dose range studied (3 mg BID and 6 mg BID), the magnitude of IL-6 inhibition was numerically greater than the magnitude of IL-7 inhibition. At the highest dose tested (24 mg BID), the magnitude of IL-6 inhibition was similar to the magnitude of IL-7 inhibition. This is consistent with the Jak1 selectivity of ABT-494. The clinical significance of this is not known.

Population PK/PD modeling of IL-6- and IL-7-induced STAT phosphorylation following the administration of ABT-494 or tofacitinib showed the effect on these biomarkers was dependent on the plasma concentrations, and that ABT-494 was more potent in inhibiting IL-6-induced STAT phosphorylation and less potent in inhibiting IL-7-induced STAT phosphorylation compared to tofacitinib.

There was a trend for decreases in NK and NKT cell counts in healthy volunteers treated with increasing doses of ABT-494 for 14 days. The clinical relevance of these observations is not known. Based on the known mechanism of action of ABT-494, the changes at higher doses of ABT-494 are not unexpected. There were no statistically significant trend for changes in B cells, T cells, and reticulocytes.

Safety and tolerability of ABT-494 from Study M13-845 were consistent with observations in the first-in-human, single ascending dose study with ABT-494 (Study M13-401). There was no clear association of adverse events with any ABT-494 dose group. No severe, serious, or fatal adverse events were reported or led to discontinuation of study drug.