Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Upadacitinib		
Name of Active Ingredient: Upadacitinib		

Title of Study: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Once Daily Monotherapy to Methotrexate (MTX) Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis

Coordinating Investigator: Dr. Jacob Aelion, MD

Study Sites: 236 sites in 43 countries (Argentina, Australia, Belarus, Belgium, Bosnia, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czech Republic, Estonia, Germany, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Kazakhstan, Latvia, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Slovakia, Slovenia, South Africa, Spain, Switzerland, Taiwan, Tunisia, Turkey, Ukraine, United Kingdom, United States)

Publications: None

Studied Period (Years): First Subject First Visit: 23 February 2016 Last Subject Last Visit (Week 24): 15 March 2018	**Phase of Development:** 3

Objectives: The study objectives of Period 1 of this study were the following: (1) To compare the safety and efficacy of upadacitinib 7.5 mg QD monotherapy (for subjects in Japan only), 15 mg QD monotherapy, and 30 mg QD monotherapy versus weekly MTX monotherapy for the treatment of signs and symptoms of RA in MTX-naïve subjects with moderately to severely active RA; (2) To compare the efficacy of upadacitinib 15 mg QD monotherapy and upadacitinib 30 mg QD monotherapy versus weekly MTX monotherapy for prevention of structural progression in MTX-naïve subjects with moderately to severely active RA.

The study objective of Period 2 is to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD (for subjects in Japan only), 15 mg QD, and 30 mg QD in subjects with RA who have completed Period 1.

This clinical study report presents results obtained through Week 24 in Period 1. Results from the overall global study population include subjects from Japan, but exclude the upadacitinib 7.5 mg QD monotherapy group. The Japan substudy included all subjects from Japan, including the upadacitinib 7.5 mg QD monotherapy group.

Methodology: This is a Phase 3 multicenter study that includes 2 periods and a Japan substudy. Period 1 is a 48-week randomized, double-blind, parallel-group, active comparator controlled treatment period designed to compare the safety and efficacy of upadacitinib 7.5 mg QD monotherapy (for subjects in Japan only), 15 mg QD monotherapy, and 30 mg QD monotherapy versus MTX monotherapy in adult MTX-naïve subjects with moderately to severely active RA. Period 1 is also designed to compare the efficacy of upadacitinib 15 mg QD monotherapy and 30 mg QD monotherapy versus MTX monotherapy for the prevention of structural progression. Period 2 is a long-term extension (up to 4 years) to evaluate the long-term safety, tolerability, and efficacy of upadacitinib (7.5, 15, or 30 mg QD) in subjects with RA who have completed Period 1.

Subjects were to be randomized in a 1:1:1 ratio to treatment Groups 2, 3, and 4 below, except for subjects from Japan, who were to be randomized in a 2:1:1:1 ratio to Groups 1, 2, 3, and 4:

Group 1: Upadacitinib 7.5 mg QD monotherapy (subjects in Japan only; N = 75)

Group 2: Upadacitinib 15 mg QD monotherapy (N = 300; includes 37 subjects from Japan)

Group 3: Upadacitinib 30 mg QD monotherapy (N = 300; includes 37 subjects from Japan)

Group 4: MTX monotherapy (N = 300; includes 37 subjects from Japan)

Subjects who completed the Week 48 visit (end of Period 1) were to have entered the long-term extension, Period 2 (192 weeks). Subjects were to have continued study treatment per assignment at the end of Period 1 in a blinded fashion.

Number of Subjects (Planned and Analyzed): Planned: 975 subjects (675 upadacitinib, 300 MTX); Randomized: 1002 subjects (687 upadacitinib, 315 MTX); Analyzed (Full Analysis Set): 1000 subjects (686 upadacitinib, 314 MTX)

Diagnosis and Main Criteria for Inclusion: Adult male and female subjects who met all the inclusion criteria and who did not meet any of the exclusion criteria were eligible for enrollment into the study. Subjects enrolled in this study were at least 18 years of age with duration of symptoms consistent with RA for ≥ 6 weeks and fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. Subjects must have been naïve to MTX or, if already on MTX, have received no more than 3 weekly MTX doses with requirement to complete a 4-week MTX washout before the first dose of study drug. Subjects with prior exposure to csDMARDs other than MTX may have been enrolled if completed the defined washout period or washout should have been at least five times the mean terminal elimination half-life of a drug. Eligible study subjects must have had ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at screening and baseline visits; high sensitivity C-reactive protein (hsCRP) ≥ 5 mg/L (central lab, ULN 2.87 mg/L) at screening; and ≥ 1 bone erosion on x-ray (by local reading) or in the absence of documented bone erosion, both positive rheumatoid factor (RF) and positive anti-cyclic citrullinated peptide (anti-CCP) autoantibodies at screening.

Subjects were excluded if they were intolerant to MTX; had prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib) or any bDMARD(s); had a history of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA; and had laboratory values that met the following criteria within the screening period prior to the first dose of study drug: serum aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN); serum alanine aminotransferase (ALT) > 2 × ULN; estimated glomerular filtration rate by simplified 4 variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73 m^2; total white blood cell count < 2,500/µL; absolute neutrophil count < 1,500/µL; platelet count < 100,000/µL; absolute lymphocyte count < 800/µL; and hemoglobin < 10 g/dL.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Upadacitinib 7.5 mg extended-release tablets for oral administration (bulk lot number: 15-006685, 16-001353, 16-004624) Upadacitinib 15 mg extended-release tablets for oral administration (bulk lot number: 15-005420, 15-005423, 15-006833, 15-006834, 16-004204, 16-005428, 16-005429, 17-002018, 1000184791, 1000229221, 15-006832, 16-001357, 17-000986) Upadacitinib 30 mg extended-release tablets for oral administration (bulk lot number: 15-005424, 15-006954, 16-004206, 16-005602, 16-005603, 17-001119, 1000187240, 1000203907, 15-006955, 16-001431, 17-001118)
Duration of Treatment: Period 1: 48 weeks; Period 2: Up to 4 years
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: MTX 7.5 mg capsule for oral administration (bulk lot number: 58509.5, 15-004789, 15-005213, 16-001721, 16-006740, 17-002068, 15-004789, 16-004218) MTX 10 mg capsule for oral administration (bulk lot number: 58509.6, 15-005208, 16-001722, 16-006741, 17-002243, 15-004790, 16-004217) Matching placebo for MTX, capsule for oral administration (bulk lot number: 15-005328, 15-005749) Matching placebo for upadacitinib, tablet for oral administration (bulk lot number: 15-005362, 16-003282, 17-002079, 15-006982, 16-001360, 16-003281)

Criteria for Evaluation

Efficacy: The primary endpoint for US/FDA regulatory purposes was the proportion of subjects achieving ACR50 response at Week 12. The primary endpoint for EU/EMA regulatory purposes was the proportion of subjects achieving Clinical Remission (CR) (defined by DAS28 [CRP] < 2.6) at Week 24. For Japan/PMDA regulatory purposes, the primary endpoints are the proportion of subjects achieving ACR20 response at Week 12 and change from baseline in modified Total Sharp Score (mTSS) at Week 24. The primary endpoints for Japan/PMDA were based on the overall global population, which include only the upadacitinib 15 mg and 30 mg groups; the upadacitinib 7.5 mg group is included in the Japan substudy only.

Ranked key secondary endpoints for US/FDA regulatory purposes were: 1) change from baseline in DAS28 (CRP) at Week 12; 2) change from baseline in HAQ-DI at Week 12; 3) change from baseline in modified Total Sharp Score (mTSS) at Week 24; 4) proportion of subjects achieving Low Disease Activity (LDA) based on DAS28 (CRP) ≤ 3.2 at Week 12; 5) proportion of subjects achieving CR based on DAS28 (CRP) < 2.6 at Week 24; 6) change from baseline in Short Form-36 (SF-36) Physical Component Score (PCS) at Week 12.

Ranked key secondary endpoints at Week 24 for EU/EMA regulatory purposes were: 1) change from baseline in DAS28 (CRP); 2) change from baseline in HAQ-DI; 3) ACR50 response rate; 4) change from baseline in modified Total Sharp Score (mTSS); 5) proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2; 6) change from baseline in SF-36 PCS; 7) proportion of subjects with no radiographic progression (defined as change from baseline in mTSS ≤ 0) at Weeks 24.

Ranked key secondary endpoints for Japan/PMDA regulatory purposes were: 1) change from baseline in DAS28 (CRP) at Week 12; 2) change from baseline in HAQ-DI at Week 12; 3) proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12; 4) proportion of subjects achieving CR based on DAS28 (CRP) < 2.6 at Week 24; 5) change from baseline in SF-36 PCS at Week 12.

Other key secondary endpoints for US/FDA regulatory purposes were: 1) ACR20 response rate at Week 12; 2) ACR70 response rate at Week 12; 3) proportion of subjects with no radiographic progression at Week 24.

Other key secondary endpoints for EU/EMA regulatory purposes were: 1) ACR20 response rate at Week 24; 2) ACR70 response rate at Week 24.

Other key secondary endpoints for Japan/PMDA regulatory purposes were: 1) ACR50 response rate at Week 12; 2) ACR70 response rate at Week 12; 3) proportion of subjects with no radiographic progression at Week 24.

Additional efficacy endpoints were to be summarized for all visits (that measurements were collected) in Period 1 by randomized treatment groups: ACR20/50/70 response rates; change from baseline in individual components of ACR response; change from baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]); change from baseline in CDAI and SDAI; proportion of subjects achieving LDA or CR by DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI); change from baseline in morning stiffness (severity and duration); proportion of subjects with change from baseline in HAQ-DI ≤ –0.22; proportion of subjects with change from baseline in HAQ-DI ≤ –0.3; ACR/EULAR Boolean remission; change from baseline in EQ-5D-5L at Weeks 12, 24, and 48; change from baseline in FACIT-F at Weeks 12 and 24; change from baseline in WPAI at Weeks 12 and 48; change from baseline in SF-36 at Weeks 12 and 24; change from baseline in mTSS at Week 24; proportion of subjects with no radiographic progression (defined as change from baseline in mTSS ≤ 0) at Week 24; change from baseline in radiographic JSN and erosion scores at Week 24.

Criteria for Evaluation (Continued)

Pharmacokinetic:

Blood samples for upadacitinib plasma concentrations were obtained throughout the study.

Safety:

Adverse events (AEs), physical examination, laboratory assessments, electrocardiogram (ECG), and vital signs data were assessed throughout the study.

Statistical Methods

Efficacy:

Primary Endpoints: For ACR20 and ACR50 at Week 12, and CR based on DAS28 (CRP) at Week 24, point estimate and 95% CI of the response rate for each randomized treatment group was provided. Comparisons of the primary endpoint were made between each upadacitinib dose group and the MTX group using the Cochran-Mantel-Haenszel test adjusting for geographic region. Point estimate, 95% CI and p-value for the treatment comparison were presented. Both nominal p-values constructed using the Cochran-Mantel-Haenszel test and adjusted p-value through the graphical multiplicity procedure were provided. For the primary analysis, non-responder imputation (NRI) was used. Subjects who meet the joint count rescue criteria at Week 16 or 20 were treated as non-responders at Week 24 for the primary analysis.

For mean change from baseline in mTSS at Week 24, both linear extrapolation and as observed (AO) analyses were conducted. Linear extrapolation results were used for the purpose of multiplicity control. To analyze the mean change from baseline in mTSS at Week 24, the point estimate and 95% CI were reported for each randomized treatment group. Between-group comparisons for each upadacitinib treatment group and the MTX group were performed using ANCOVA model with treatment and geographic region as the fixed factors and the corresponding baseline value as the covariate. Both nominal p-value and adjusted p-value through the graphical multiplicity procedure were provided.

The analysis of ACR20 and ACR50 at Week 12 was to be repeated using Observed Cases and the analysis of CR at Week 24 was repeated using As Observed as a sensitivity analysis without any imputation. These analyses were conducted on the FAS based on randomized treatment groups.

Supportive NRI analysis for ACR20, ACR50 and CR and supportive linear extrapolation and AO analysis for change from baseline in mTSS were also conducted on the Per Protocol Analysis Set.

Primary efficacy analyses (except mTSS) were also performed in demographic subgroups including age, sex, weight, body mass index, race, and geographical region to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics were also conducted.

Secondary Endpoints: For Week 12 binary endpoints, similar NRI and OC analyses as for the primary endpoint of ACR20 and ACR50 at Week 12 were conducted. For non-mTSS Week 24 binary endpoints, similar NRI and AO analyses as for the primary endpoint of CR at Week 24 were conducted.

For the analysis of the proportion of subjects with no radiographic progression at Week 24, both linear extrapolation and AO analyses were conducted. Linear extrapolation results were used for the purpose of multiplicity control. Point estimate and 95% CI of the response rate for each randomized treatment group were provided. Comparisons were made between each upadacitinib dose group and the MTX group using the Cochran-Mantel-Haenszel test adjusting for geographic region. Point estimate, 95% CI and p-value for the treatment comparison were presented.

Statistical Methods (Continued)

Efficacy (Continued):

For all continuous key secondary endpoints other than mTSS, statistical inference was conducted using analysis of covariance (ANCOVA) coupled with MI for missing data handling. Specifically, the ANCOVA model included treatment and geographic region as the fixed factors and the corresponding baseline value as the covariates. The LS mean and 95% CI were reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value were reported comparing each upadacitinib dose group with the MTX group. For subjects who met the rescue criteria at Week 16 or 20, data after rescue was overwritten by last observation carried forward (LOCF).

Both nominal p-value and adjusted p-value through the graphical multiplicity procedure were provided for primary and ranked key secondary endpoints. For other secondary endpoints, only nominal p-values were provided.

Additional Efficacy Variables: For continuous variables, statistical inference at each visit was conducted using analysis of covariance (ANCOVA) with treatment and geographic region as the fixed factors and the corresponding baseline value as the covariate. Only nominal p-values were provided. For subjects who met the rescue criteria defined by not achieving 20% improvement in TJC/SJC (for Week 12 through Week 24) in two consecutive visits, or subjects who met the rescue switching criteria at Week 26 defined by not reaching CDAI CR and not achieving 20% improvement in TJC/SJC), data after rescue was overwritten by LOCF for primary analysis. As observed (AO) data regardless of rescue was also summarized using descriptive statistics.

For binary endpoints, frequencies and percentages were reported for each randomized treatment group. Similar CMH analyses as for the primary endpoint were conducted and only nominal p-values were provided. For the primary analysis, non-responder imputation was used. In addition, subjects who met the rescue criteria of not achieving 20% improvement in TJC/SJC in two consecutive visits (for Week 12 through Week 24) or subjects who met the rescue switching criteria at Week 26 defined by not reaching CDAI CR and not achieving 20% improvement in TJC/SJC were treated as non-responders at visits after rescue. AO data regardless of rescue was also summarized using frequencies and percentages.

Plots by randomized treatment group over time were provided for selected efficacy parameters including ACR20/50/70, LDA and CR by DAS28 (CRP) and CDAI, and change from baseline in DAS28 (CRP), HAQ-DI, and pain.

Japan Substudy: For the Japan substudy, efficacy analyses were conducted for selected variables. The primary and key secondary endpoints and the subsequent multiplicity control were only applicable for the global analysis of subjects randomized to MTX, upadacitinib 15 mg QD, and upadacitinib 30 mg QD.

For the Japan substudy, no multiplicity adjustments were applied and only nominal p-values were provided for all efficacy analyses. In addition, model adjustment for region was not applicable for the Japan substudy. The nominal p-values in Japan substudy should be interpreted with caution due to limited sample size.

Subgroup analysis for the primary endpoints was only applicable for the global analysis. No subgroup analysis was planned for Japan substudy due to limited sample size.

Statistical Methods (Continued)

Pharmacokinetic:

Individual upadacitinib plasma concentrations at each study visit were tabulated and summarized with appropriate statistical methods.

Safety:

Safety analyses up to Week 24 were carried out using the Safety Analysis Set by the "as treated" treatment groups of upadacitinib 15 mg QD, upadacitinib 30 mg QD and MTX. Missing safety data were not imputed.

The standard safety analyses included reporting of adverse events (AEs), laboratory, and vital signs measurements up to Week 24. Frequency tables of subjects with treatment-emergent adverse events (TEAEs) by system organ class (SOC) and by preferred term (PT) as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary were provided by treatment group. Exposure adjusted event rate (EAER) per 100 patient-years (PY) and exposure adjusted incidence rate (EAIR) per 100 PY were provided. Mean changes from baseline in all continuous laboratory parameters and vital signs variables at each visit were summarized by "as treated" treatment group. Frequency tables of subjects meeting criteria for potentially clinically significant vital sign values and for potentially clinically significant laboratory values were provided by treatment group.

For the Japan substudy, there was an additional upadacitinib 7.5 mg QD group. Selected safety analyses were conducted for the Japan substudy by the "as treated" treatment groups of upadacitinib 7.5 mg QD, upadacitinib 15 mg QD, upadacitinib 30 mg QD and MTX. Missing safety data were not imputed.

Summary/Conclusions

Efficacy Results:

Global Study Population:

Through Week 12 of Period 1, upadacitinib at doses of 15 mg and 30 mg QD was superior compared with MTX in the treatment of signs and symptoms of RA in MTX-naïve subjects with moderately to severely active RA; upadacitinib at 15 mg and 30 mg QD was also superior compared with MTX in improvement of physical function, and inhibiting radiographic progression. The study met its primary endpoints, with a highly statistically significantly greater percentage of subjects achieving an ACR50 response at Week 12 (US/FDA), CR based on DAS28 (CRP) < 2.6 at Week 24 (EU/EMA), and an ACR20 response at Week 12 (Japan/PMDA) in both the upadacitinib 15 mg and 30 mg groups compared with the MTX group. Additionally, at Week 24, statistically significantly smaller mean increase in mTSS from baseline in the upadacitinib 15 mg and 30 mg groups were observed compared with the MTX group. These primary endpoints are met with pre-specified multiplicity adjustment for Japan/PMDA, US/FDA, and EU/EMA respectively. The study also met all ranked key secondary endpoints (multiplicity adjusted) and other key secondary endpoints (nominal significance) with clinically meaningful and highly statistically significant improvement in the upadacitinib 15 mg and 30 mg groups compared with the MTX group at Week 12 and Week 24.

Rapid onset of efficacy was noted with both upadacitinib doses achieving statistical significance for several efficacy variables as early as Week 2, and improvement was sustained through Week 24.

Summary/Conclusions (Continued)

Japan Substudy:

Through Week 24 of Period 1, upadacitinib 7.5 mg, 15 mg, and 30 mg QD demonstrated significant improvement in RA signs and symptoms, physical function, and disability compared with MTX in adult Japanese MTX-naïve subjects with moderately to severely active RA; upadacitinib at 15 mg and 30 mg QD were also more effective than MTX in inhibiting radiographic progression.

At Week 12, a statistically significantly greater percentage of subjects achieved an ACR20/50/70 response in the upadacitinib 7.5 mg, 15 mg, and 30 mg groups compared with the MTX group, with the exception of the upadacitinib 30 mg group for ACR20, where the response was numerically higher compared with the MTX group, but not statistically significant. Despite the small sample size of the JAS population, clinically meaningful and statistically significant improvement in the upadacitinib 7.5 mg, 15 mg, and 30 mg groups compared with the MTX group were observed for change from baseline in DAS28 (CRP), HAQ-DI, and SF-36 at Week 12, proportion of subjects achieving LDA based on DAS28 (CRP) at Week 12, and proportion of subjects achieving CR based on DAS28 (CRP) at Week 24. At Week 24, despite the small sample size of the JAS population, inhibition of radiographic progression was observed in the upadacitinib 15 mg and 30 mg groups, as shown by a statistically significantly smaller mean increase in mTSS from baseline in the upadacitinib 15 mg and 30 mg groups compared with the MTX group; a greater inhibition of radiographic progression was observed at Week 24 in the upadacitinib 7.5 mg group compared with the MTX group, but the difference was not statistically significant.

Rapid onset of efficacy was noted with the upadacitinib doses achieving statistical significance versus MTX for the majority of efficacy variables as early as Week 2 (first post-baseline visit), and improvement was sustained for the majority of variables through Week 24.

Pharmacokinetic Results:

The observed upadacitinib concentrations were consistent with the predicted concentrations based on prior pharmacokinetic evaluations of upadacitinib. Within 24 hours of dosing, upadacitinib mean plasma concentrations ranged from 5.89 ng/mL to 26.7 ng/mL for 15 mg QD and from 12.3 ng/mL to 78.8 ng/mL for 30 mg QD.

Sparse pharmacokinetic data from a relatively small number of Japanese subjects who received upadacitinib 7.5 mg was available from this study. Results from the upadacitinib 7.5 mg group will be included, along with other doses and studies, in the population pharmacokinetic analyses to allow for a more robust pharmacokinetic assessment.

Safety Results:

Global Study Population:

In Study M13-545, treatment with upadacitinib monotherapy for 24 weeks at doses of 15 mg and 30 mg QD was generally well-tolerated as assessed by the frequency of TEAEs, including SAEs, AESIs, clinical laboratory values, and vital signs values.

Through Week 24, the most frequently reported TEAEs (≥ 5% of subjects in any treatment group) were increased blood CPK, upper respiratory tract infection, urinary tract infection, nasopharyngitis, and nausea. The percentage of subjects with TEAEs leading to discontinuation of study drug was highest in the MTX group (5.1%), followed by the upadacitinib 15 mg group (4.4%), and the upadacitinib 30 mg group (3.8%). The percentage of subjects with SAEs was higher in the upadacitinib 30 mg group (6.4%), but comparable between the upadacitinib 15 mg (4.7%) and MTX groups (4.1%).

Summary/Conclusions (Continued)

Six deaths were reported through Week 24. Two deaths were reported in the upadacitinib 15 mg group. One subject died due to metastatic malignant melanoma and hepatic vein thrombosis (adjudicated by the external CAC as not a VTE). After the Week 24 database lock, hepatic vein thrombosis was revised by the investigator to tumor infiltration of the hepatic vein. Source data (CT scan) indicating tumor infiltration was available before the database lock. The other subject died due to myocardial infarction (adjudicated by the external CAC as non-fatal myocardial infarction) and subsequent hypoxic-ischemic encephalopathy. Three deaths were reported in the upadacitinib 30 mg group: 1 subject died due to pneumonia and sepsis, 1 subject died due to sudden death (adjudicated by the external CAC as cardiovascular death), and 1 subject died due to peritonitis. One subject in the MTX group died due to acute myocardial infarction (adjudicated by the external CAC as cardiovascular death). The investigators assessed the myocardial infarction, hypoxic-ischemic encephalopathy, and peritonitis as having a reasonable possibility of being related to study drug.

Through Week 24, the percentage of subjects with AESIs was generally comparable across treatment groups, with the exception of anemia, CPK elevation, and herpes zoster, which were reported in a higher percentage of subjects in the upadacitinib 15 mg and 30 mg group compared with the MTX group. No TEAEs of lymphoma or active/latent TB were reported.

The percentage of treatment-emergent serious infections was higher in the upadacitinib 30 mg group (2.5%), but comparable between the upadacitinib 15 mg (1.6%) and MTX groups (1.3%). The percentage of subjects with treatment-emergent herpes zoster was higher in both the upadacitinib 15 mg and 30 mg groups (2.2% each) compared with the MTX group (0.3%). No events of herpes zoster were considered by the investigator to be serious. Only 2 opportunistic infections were reported: pneumonia cryptococcal (1 subject in the upadacitinib 15 mg group) and asymptomatic cytomegalovirus test positive (1 subject in the upadacitinib 30 mg group).

The treatment-emergent malignancies included ovarian cancer in the MTX group, and squamous cell carcinoma (PT was updated to squamous cell carcinoma of the lung after database lock), metastatic malignant melanoma, and uterine carcinoma in situ in the upadacitinib 15 mg group; these events were reported on Day 56, 91, 110, and 154, respectively, relative to the first dose of study drug. None of these malignancies were considered by the investigator to have a reasonable possibility of being related to study drug. There were 4 subjects who had adjudicated MACE events: 3 events of cardiovascular deaths (1 subject each in the upadacitinib 15 mg, 30 mg, and MTX groups) and 2 events of non-fatal myocardial infarction (1 subject each in the upadacitinib 15 mg [same subject with cardiovascular death] and 30 mg groups). Adjudicated VTEs included deep vein thrombosis (1 subject in upadacitinib 30 mg) and pulmonary embolism (1 subject in MTX). Other cardiovascular events (non-fatal) included hospital-based treatment for heart failure (1 subject in MTX who also had the pulmonary embolism mentioned above) and transient ischemic attack (1 subject in upadacitinib 15 mg). All adjudicated cardiovascular events were considered by the investigator as having no reasonable possibility of being related to study drug, with the exception of transient ischemic attack (1 subject) and non-fatal myocardial infarction and cardiovascular death (1 subject) in the upadacitinib 15 mg group.

Drug-related hepatic disorders were largely hepatic enzyme elevations and the percentage of subjects with treatment-emergent drug-related hepatic disorders was as follows upadacitinib 15 mg group (6.0%), followed by the MTX group (5.4%), and lowest in the upadacitinib 30 mg group (4.5%). No Hy's law case was identified.

Summary/Conclusions (Continued)

AESIs also included abnormal labs reported by investigators as TEAEs (anemia, neutropenia, lymphopenia, and CPK elevation). Overall, the upadacitinib 30 mg group had a higher percentage of subjects with anemia or CPK elevation compared with the upadacitinib 15 mg and MTX groups. No subject discontinued due to a TEAE of anemia, neutropenia, lymphopenia, or blood CPK increased.

In general, group mean values for hematology variables (hemoglobin, hematocrit, lymphocytes, neutrophils, platelets, and IgM and IgG) were within the normal laboratory range at baseline and at all visits for all treatment groups through Week 24. At the subject level, however, a higher percentage of subjects in the upadacitinib 30 group compared with the upadacitinib 15 mg and MTX groups had Grade 3 or Grade 4 decreases in hemoglobin, neutrophil, leukocyte, or platelet values. Of the 67 subjects with Grade 3 or Grade 4 decreases in hemoglobin values, the majority of these values were transient and occurred at only 1 time point during the treatment period. No Grade 3 or Grade 4 decreases in hemoglobin value led to treatment discontinuation. One subject in the upadacitinib 30 mg group had a decrease in neutrophil, lymphocyte, and leukocyte values that were Grade 4 with infectious events of pneumonia and sepsis around the time of neutropenia, lymphopenia, and leukopenia (approximately –4 days); this subject died due to pneumonia and sepsis. This same subject had Grade 3 and Grade 4 decreases in leukocyte values at $\geq$ 2 time points (3 time points). A Grade 4 decrease in platelet count, which occurred at 1 time point only, was reported in 1 subject in the upadacitinib 30 mg group.

Through Week 24, Grade 3 and Grade 4 increases in blood CPK values were reported in the upadacitinib 15 mg and upadacitinib 30 mg groups only. No subjects with Grade 3 or Grade 4 increases in blood CPK values discontinued study drug due to an increased CPK value and all subjects were asymptomatic, with the exception of 1 subject who had muscle pain; this subject had a Grade 3 increase in blood CPK value at 1 time point only.

The percentage of subjects with increases in ALT values that were Grade 3 was higher in the MTX group (11 subjects [3.5%]), but comparable between the upadacitinib 15 mg (4 subjects [1.3%]) and upadacitinib 30 mg (5 subjects [1.6%]) groups. Few subjects had increases in ALT values that were Grade 4 (2 subjects [0.6%] in upadacitinib 15 mg, 0 subjects in upadacitinib 30 mg, 3 subjects [1.0%] in MTX). The percentage of subjects with increases in AST values that were Grade 3 was highest in the MTX group (8 subjects [2.6%]), followed by the upadacitinib 30 mg group (4 subjects [1.3%]), and lowest in the upadacitinib 15 mg group (1 subject [0.3%]). Increases in AST values that were Grade 4 were reported in the upadacitinib 15 mg group only (2 subjects [0.6%]). No subjects had an increase in serum creatinine value that was Grade 3 or Grade 4.

Treatment with upadacitinib 15 mg and 30 mg resulted in numerically greater mean increases from baseline in LDL-C, HDL-C, and cholesterol at Week 24 compared with MTX; however, the ratios of total cholesterol:HDL-C and LDL-C:HDL-C remained unchanged from baseline through Week 24 for the upadacitinib 15 mg, upadacitinib 30 mg, and MTX groups.

Mean changes from baseline through Week 24 for vital signs in the upadacitinib dose groups were not considered to be clinically meaningful compared with the MTX group.

Summary/Conclusions (Continued)

Japan Substudy:

In this blinded, controlled treatment period, treatment with upadacitinib for 24 weeks at doses of 7.5 mg, 15 mg, and 30 mg QD in the Japanese population was generally well-tolerated as assessed by the frequency of TEAEs, including SAEs and AESIs.

Through Week 24 TEAEs reported by ≥ 10% of subjects in any treatment group were blood CPK increased, constipation, nasopharyngitis, stomatitis, and rheumatoid arthritis. The incidence of blood CPK increased appeared to be dose-dependent. One death was reported through Week 24: 1 subject in the upadacitinib 30 group died due to sudden death (adjudicated by the external CAC as cardiovascular death). The investigator assessed the death as having no reasonable possibility of being related to study drug. The percentage of subjects with SAEs was higher in the upadacitinib 7.5 mg and 30 mg groups compared with the upadacitinib 15 mg and MTX groups. The percentage of subjects with TEAEs leading to discontinuation of study drug was higher in the upadacitinib 7.5 mg group compared with the upadacitinib 15 mg, upadacitinib 30 mg, and MTX groups.

Through Week 24, the percentage of subjects experiencing most AESIs was low and similar among all of the treatment groups. The most common AESIs were elevations in CPK and hepatic disorder; all events of CPK elevations and hepatic disorders were nonserious.

Conclusions:

Through Week 24 of Period 1 for Study M13-545, superiority was consistently demonstrated for upadacitinib 15 mg and 30 mg QD versus MTX for both clinical responses (signs and symptoms) and patient-reported health outcome results in adult MTX-naïve subjects with moderately to severely active RA. Upadacitinib 15 mg and 30 mg were also more effective than MTX in the inhibition of structural progression. The benefit:risk profile of both doses of upadacitinib is assessed as favorable based on the efficacy and safety results through Week 24 of the study.

The sample size of the Japan substudy was too small to allow for definite conclusions.

Date of Report: 27Aug2018

Protocol Changes

At the time of the data cutoff for this clinical study report (15 March 2018), the original protocol (01 October 2015, 00 subjects) had 5 global amendments, 6 country-specific amendments, and 2 global administrative changes. The majority of changes to the protocol were responses to regulatory feedback, clarifications, and editorial changes.

The amendments, administrative changes, and number of subjects enrolled under each amendment were as follows:

- Amendment 1 (15 January 2016, 02 subjects)
  - Updated to identify the existing study objectives as being part of Period 1 and added study objectives for the long-term extension, Period 2, which had been added to the study design.
  - Added 7.5 mg treatment group for subjects in Japan only to Objective 1.
  - Added frequency of MTX administration.
  - Updated text to reflect the change in study duration, to change the study design to include a 48-week randomized, double-blind treatment period (Period 1), and to add a long-term extension (Period 2).
  - Added 7.5 mg treatment group for subjects in Japan only and increased the number of subjects to be enrolled accordingly.
  - Described how the blind will be maintained.
  - Added language regarding study drug dose reduction and the initiation of or change in background RA medication(s).
  - Added the following exclusion criteria: females who are considering becoming pregnant during the study or for approximately 180 days after the last dose of study drug; male subject who is considering fathering a child or donating sperm during the study or for approximately 180 days after the last dose of study drug; subjects with a history of gastrointestinal (GI) perforation or a history of associated GI diseases; subjects with conditions that could interfere with drug absorption; subjects who have been the recipient of an organ transplant; subjects who had clinically

relevant or significant ECG abnormalities; subjects with a positive result of beta-D-glucan (for subjects in Japan only).

- Clarified permitted RA therapies during Period 1. Added permitted RA therapies during Period 2.
- Updated durations of prohibited therapies based on updated study design.
- Added criteria for rescue therapy at Week 26.
- Clarified informed consent details.
- Clarified tuberculosis (TB) testing procedures during Periods 1 and 2.
- Added requirement that a positive result for hepatitis B surface (HBs) antibody (Ab)/anti-HBs requires hepatitis B virus (HBV) deoxyribonucleic acid (DNA) polymerase chain reaction testing (for subjects in Japan only).
- Added testing for varicella zoster virus (for subjects in Japan only).
- Updated study visits for pharmacokinetic sampling based on updated study design.
- Primary, secondary, and other variables were updated to reflect current scientific rationale and analyses to be conducted for this study.
- Added efficacy assessments for the long-term extension, Period 2.
- Added text to reflect current discontinuation procedures.
- Clarified that subjects will receive both 2 capsules once weekly (MTX or matching placebo) and 1 tablet QD (ABT-494 or matching placebo) to maintain the double blind. Added language regarding blinding and the Week 24 interim analysis.
- Clarified that administration of both daily and weekly study drug must be stopped if study drug treatment is interrupted or withdrawn in Periods 1 or 2.
- Updated rules regarding study drug interruption for Period 1 to reflect the change in study duration and added for the long-term extension, Period 2.
- Updated the AST or ALT specific toxicity management guidelines.

- Administrative Change 1 (22 January 2016)
  - Revised transcription errors.

- Amendment 2 (29 February 2016, 126 subjects)
  - Updated text to provide clarification for discontinuation criteria.
  - Updated Inclusion Criterion 2 text to avoid ambiguity regarding RA classification criteria. Updated Inclusion Criterion 9 text to clarify pregnancy testing and women of childbearing potential.
  - Updated text to clarify RA optimization therapies.
  - Added criteria for adjusting or adding background medication at Week 26 if subjects do not achieve LDA as defined by CDAI or do not achieve > 20% improvement from baseline in both tender joint count (TJC) and swollen joint count (SJC).
  - Updated text to clarify Independent Joint Assessor. Updated text to clarify TB assessment and testing. Added text that all subjects to have ECG performed at screening and every 48 weeks.
- Amendment 2.01 (Japan only) (07 March 2016, 7 subjects)
  - Updated text to provide clarification for discontinuation criteria.
  - Updated Inclusion Criterion 2 text to avoid ambiguity regarding RA classification criteria.
  - Updated Inclusion Criterion 9 text to clarify pregnancy testing and women of childbearing potential.
  - Updated text to clarify RA optimization therapies.
  - Added criteria for adjusting or adding background medication at Week 26 if subjects do not achieve LDA as defined by CDAI or 3 do not achieve > 20% improvement from baseline in both TJC and SJC.
- Amendment 3 (31 May 2016, 199 subjects)
  - Added criteria for rescue therapy between Weeks 12 and 24 and between Weeks 36 and 40 if subjects do not achieve ≥ 20% improvement from baseline in both TJC and SJC.
  - Updated text to clarify exceptions for rescue therapy.
  - Added text to follow MTX local label for concomitant treatment contraindications.

- Amendment 3.01 (Japan only) (25 July 2016, 18 subjects)
  - Added criteria for rescue therapy between Weeks 12 and 24 and between Weeks 36 and 40 if subjects do not achieve ≥ 20% improvement from baseline in both TJC and SJC.
  - Updated Inclusion Criterion 2 text to avoid ambiguity regarding RA classification criteria.
  - Updated text to clarify exceptions for rescue therapy.
  - Updated background medications.
  - Added text to follow MTX local label for concomitant treatment contraindications.
  - Updated text to clarify exceptions for rescue therapy.
  - Updated text to clarify hsCRP and varicella zoster virus testing.
- Amendment 4 (18 August 2016, 534 subjects)
  - Updated Inclusion Criterion 2 text to select subject population based on duration of symptoms consistent with RA.
  - Updated text to clarify when to administer live vaccines and to provide examples of inactivated vaccines.
  - Added text to describe the addition of MTX for Week 26 rescue therapy.
  - Added requirement to perform pregnancy testing if follicle-stimulating hormone results are consistent with premenopausal status. Updated text to account for local contraception requirements.
  - Added text to clarify different primary efficacy variable for different regulatory purposes.
  - Updated time points for key secondary variables to allow for rescue therapy at Week 12.
  - Added text for local country requirements for Colombia.
- Amendment 4.01 (Japan only) (18 October 2016, 113 subjects)
  - Updated time points for key secondary variables to allow for rescue therapy at Week 12.

- To maintain the double blind nature of the study, the MTX dose reduction language was updated to allow single dose reductions up through Week 26 only.
- Added inclusionary criteria regarding traditional Chinese medicine for Inclusion Criteria 8.
- Updated text to clarify when to administer live vaccines and to provide examples of inactivated vaccines.
- Added text to describe the addition of MTX for Week 26 rescue therapy.
- Added requirement to perform pregnancy testing if follicle-stimulating hormone results are consistent with premenopausal status. Updated text to account for local contraception requirements.
- Added text regarding beta D-glucan testing at screening for Japan only.
- Added text to clarify different primary efficacy variable for different regulatory purposes.
- Updated time points for key secondary variables to allow for rescue therapy at Week 12.
- Updated text to clarify protocol deviation reporting criteria.
- Added text for local country requirements for Colombia.

- Administrative Change 2 (02 November 2016)
  - Clarified MTX dose reduction language to specify that single dose reductions are allowed until Week 26 only.
  - Updated figures to correctly reflect the rescue therapy MTX dosing change that was made in Amendment 4 and clarified duration of blinding in Period 2.
- Amendment 4.02 (China only) (21 December 2016, 03 subjects)
  - Added MTX dosing and titration requirements for China.
  - Updated Inclusion Criterion 8 text to include traditional Chinese medicine requirements.
  - Updated Exclusion Criterion 9 to add HBV exclusionary requirement for China.

- Amendment 5 (26 December 2017, 00 subjects)
  - Revised to reflect the recently approved International Nonproprietary Name.
  - Clarified who will remain blinded during Period 1 and that additional unblinded analyses may be conducted after the first unblinded analysis for regulatory purposes.
  - Clarified that study drug dose changes are not permitted during unblinded Period 2.
  - Clarified that 30-day follow-up visit should be completed for subjects who do not continue in Period 2 after Period 1 has been completed.
  - Clarified that for subjects who discontinue study drug and continue on study, a second premature discontinuation visit is not required if the subject later withdraws from study.
  - Clarified 30-day follow-up visit when subject withdraws consent during Period 1 and Period 2.
  - Added paragraph on oral traditional Chinese medicines that cannot be initiated or changed during the study.
  - Clarified use of grapefruit and updated the list of examples of commonly used strong cytochrome (CYP)3A inhibitors and inducers.
  - Clarified that live vaccines must not be administered at least 30 days after last dose of study drug.
  - Added injectable hormonal contraception.
  - Added clarification on requirements for contraception for females if childbearing potential status changes during the course of the study.
  - Updated to clarify TB testing requirements during the study. Revised to prevent unnecessary initiation of TB prophylaxis in subjects with indeterminate QuantiFERON-TB test results by allowing local testing. Revised to include rifapentine as excluded medication for TB prophylaxis.
  - Updated to allow a pulmonologist to perform an assessment of the chest x-ray.
  - Updated to clarify QTcF cannot be calculated due to pacemaker or supraventricular or ventricular conduction abnormalities.

- Updated x-ray time points for subjects who prematurely discontinue from study drug but continue in the study to optimize x-ray assessments at Weeks 24 and 48.
- Clarified that serum samples may be used for assay of study drugs if needed.
- Updated text for primary variables, ranked key secondary endpoints, other key secondary endpoints, additional endpoints, Period 2 variables to be aligned with the SAP.
- Clarified that study drug dose changes are not permitted during unblinded Period 2.
- Reduced malignancy and lymphoproliferative disorders to malignancy (all types), which encompasses all types of malignancy, including lymphoproliferative malignancies. Removed hemoglobin effects as the term anemia encompasses all hemoglobin effects of interest. Included embolic and thrombotic events as adverse events of special interest (AESI), based on data reported for JAK inhibitors.
- Updated definition for assessing the relationship of AEs to use of study drug per sponsor guidelines.
- Updated Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting text per sponsor guideline.
- Clarified that subject should discontinue study drug for an ECG abnormality that is considered clinically significant with reasonable possibility that the event is related to study drug.
- Clarified all abnormal lab tests that are considered clinically significant by the investigator should be followed to a satisfactory resolution.
- Clarified toxicity management for ALT, AST, and international normalized ratio (INR).
- Added wording for management of subjects with hepatitis B core (HBc) Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening and laboratory values during study which may indicate active hepatitis.
- Clarified toxicity management criteria for serum creatinine levels within normal reference range. Clarified procedures for elevated creatine

phosphokinase (CPK) value (greater than or equal to 4 × ULN) but without any clinical signs and symptoms to allow continuation of treatment.

- Updated different primary efficacy variables for different regulatory purposes.

- Amendment 5.01 (Japan only) (06 February 2018, 00 subjects)
  - Revised to reflect the recently approved International Nonproprietary Name.
  - Clarified who will remain blinded during Period 1 and that additional unblinded analyses may be conducted after the first unblinded analysis.
  - Clarified that study drug dose changes are not permitted during unblinded Period 2.
  - Clarified that 30-day follow-up visit should be completed for subjects who do not continue in Period 2 after Period 1 has been completed.
  - Clarified that for subjects that discontinue study drug and continue on study, a second premature discontinuation visit is not required if the subject later withdraws from study.
  - Clarified 30-day follow-up visit when subject withdraws consent during Period 1 and Period 2.
  - Clarified use of grapefruit and updated the list of examples of commonly used strong CYP3A inhibitors and inducers.
  - Clarified that live vaccines must not be administered at least 30 days after last dose of study drug.
  - Added injectable hormonal contraception.
  - Added clarification on requirements for contraception for females if childbearing potential status changes during the course of the study.
  - Updated to clarify TB testing requirements during the study. Revised to prevent unnecessary initiation of TB prophylaxis in subjects with indeterminate QuantiFERON-TB test results by allowing local testing. Revised to include rifapentine as excluded medication for TB prophylaxis.
  - Added radiologist or pulmonologist to perform an assessment of the chest x-ray.

- Updated to clarify QTcF cannot be calculated due to pacemaker or supraventricular or ventricular conduction abnormalities.
- Updated x-ray time points for subjects that prematurely discontinue from study drug but continue in the study to optimize x-ray assessments at Weeks 24 and 48.
- Clarify that serum samples may be used for assay of study drugs if needed.
- Updated text for primary variables, ranked key secondary endpoints, other key secondary endpoints, additional endpoints, Period 2 variables to be aligned with the SAP.
- Clarified that study drug dose changes are not permitted during unblinded Period 2.
- Reduced malignancy and lymphoproliferative disorders to malignancy (all types), which encompasses all types of malignancy, including lymphoproliferative malignancies. Removed hemoglobin effects as the term anemia encompasses all hemoglobin effects of interest. Included embolic and thrombotic events as AESI, based on data reported for JAK inhibitors.
- Updated definition for assessing the relationship of AEs to use of study drug per sponsor guidelines.
- Updated SUSAR reporting text per sponsor guideline.
- Clarified that subject should discontinue study drug for an ECG abnormality that is considered clinically significant with reasonable possibility that the event is related to study drug.
- Clarified all abnormal lab tests that are considered clinically significant by the investigator should be followed to a satisfactory resolution.
- Clarified toxicity management for ALT, AST, and INR.
- Added wording for management of subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening and laboratory values during study which may indicate active hepatitis.
- Clarified toxicity management criteria for serum creatinine levels within normal reference range. Clarified procedures for elevated CPK value

(greater than or equal to 4 × ULN) but without any clinical signs and symptoms to allow continuation of treatment.

- Updated different primary efficacy variables for different regulatory purposes.

- Amendment 5.02 (China only) (07 February 2018, 0 subjects)
  - Revised to reflect the recently approved International Nonproprietary Name.
  - Clarified who will remain blinded during Period 1 and that additional unblinded analyses may be conducted after the first unblinded analysis.
  - Clarified that study drug dose changes are not permitted during unblinded Period 2.
  - Clarified that 30-day follow-up visit should be completed for subjects who do not continue in Period 2 after Period 1 has been completed.
  - Clarified that for subjects that discontinue study drug and continue on study, a second premature discontinuation visit is not required if the subject later withdraws from study.
  - Clarified 30-day follow-up visit when subject withdraws consent during Period 1 and Period 2.
  - Clarified use of grapefruit and to update the list of examples of commonly used strong CYP3A inhibitors and inducers.
  - Clarified that live vaccines must not be administered at least 30 days after last dose of study drug.
  - Added injectable hormonal contraception.
  - Added clarification on requirements for contraception for females of childbearing potential status changes during the course of the study.
  - Updated to clarify TB testing requirements during the study. Revised to prevent unnecessary initiation of TB prophylaxis in subjects with indeterminate QuantiFERON-TB test results by allowing local testing. Revised to include rifapentine as excluded medication for TB prophylaxis.
  - Updated to allow a pulmonologist to perform an assessment of the chest x-ray.

- Updated to clarify QTcF cannot be calculated due to pacemaker or supraventricular or ventricular conduction abnormalities.
- Updated x-ray time points for subjects that prematurely discontinue from study drug but continue in the study to optimize x-ray assessments at Weeks 24 and 48.
- Clarify that serum samples may be used for assay of study drugs if needed.
- Reduced malignancy and lymphoproliferative disorders to malignancy (all types), which encompasses all types of malignancy, including lymphoproliferative malignancies. Removed hemoglobin effects as the term anemia encompasses all hemoglobin effects of interest. Included embolic and thrombotic events as AESI, based on data reported for JAK inhibitors.
- Updated definition for assessing the relationship of AEs to use of study drug per sponsor guidelines.
- Updated SUSAR reporting text per sponsor guideline.
- Clarified that subject should discontinue study drug for an ECG abnormality that is considered clinically significant with reasonable possibility that the event is related to study drug.
- Clarified all abnormal lab tests that are considered clinically significant by the investigator should be followed to a satisfactory resolution.
- Clarified toxicity management for ALT, AST, and INR.
- Added wording for management of subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening and laboratory values during study which may indicate active hepatitis.
- Clarified toxicity management criteria for serum creatinine levels within normal reference range. Clarified procedures for elevated CPK value (greater than or equal to 4 × ULN) but without any clinical signs and symptoms to allow continuation of treatment.
- Updated different primary efficacy variables for different regulatory purposes.

The protocol changes described in the amendments and administrative changes did not affect the interpretation of the study results.

The original protocol, protocol amendments, and administrative changes not incorporated into a previous amendment are provided in Appendix 16.1__1.

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