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) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)

Coordinating Investigator: Charles Birbara, MD

Study Sites: 286 study sites located in 41 countries (Argentina, Australia, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Kazakhstan, Republic Of Korea, Latvia, Lithuania, Malaysia, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan [Province Of China], Turkey, Ukraine, United Kingdom, United States)

Publications: None

Studied Period (Years): First Subject First Visit: 01 December 2015 Last Subject Last Visit: 02 February 2018 (Week 26)	**Phase of Development:** 3

Objectives:

The study objectives of Period 1 of this study are:

1. To compare the efficacy of upadacitinib 15 mg once daily (QD) versus placebo, and versus adalimumab, for the treatment of signs and symptoms of rheumatoid arthritis (RA) in subjects with moderately to severely active RA who are on a stable background of methotrexate (MTX) and who have an inadequate response to MTX.
2. To compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression in RA subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX.
3. To compare the safety and tolerability of upadacitinib 15 mg QD versus placebo, and versus adalimumab, in subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX.

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

Objectives (Continued):

The cutoff date for this clinical study report was 02 February 2018, when all subjects were expected to have completed their Week 26 visit (ranked key radiographic endpoints of the study). Week 26 is the end of the placebo-controlled phase of the study, including data for multiplicity controlled analysis of primary and ranked key secondary efficacy endpoints. This clinical study report presents data obtained through each subject's Week 26 visit of Period 1, with the exception of the following data that were not available prior to the data cutoff for this report: all Week 26 data for 1 subject who missed their scheduled Week 26 visit and Week 26 radiographic data for 2 additional subjects.

Methodology:

This is a Phase 3 multicenter study that includes 2 periods. Period 1 is a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg QD versus placebo, and versus adalimumab, for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of MTX and had an inadequate response to MTX. Period 1 was also designed to compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression. Period 2 is a long-term extension to evaluate the safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who had completed Period 1.

The study duration was to include a 35-day screening period; a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled treatment period (Period 1); a long-term extension period (blinded to sites and subjects until the last subject completes Period 1) (up to 5 years) (Period 2); a 30‑day follow-up period (call or visit); and a 70-day follow-up call.

Subjects who met eligibility criteria were to be randomized in a 2:2:1 ratio to one of three treatment groups:

Group 1: upadacitinib 15 mg QD (N = 600)

Group 2: placebo (N = 600)

Group 3: adalimumab (40 mg every other week [eow]) (N = 300)

Subjects were to receive both oral study drug QD (either upadacitinib 15 mg or matching placebo) and subcutaneous study drug eow (either adalimumab 40 mg or matching placebo) until the study is unblinded. At Week 26, all subjects receiving placebo were to be switched to upadacitinib 15 mg QD regardless of response.

Subjects were to have been on oral or parenteral MTX therapy for ≥ 3 months, on a stable MTX dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week), and were to remain on a stable dose throughout the study; the MTX dose may have been decreased only for safety reasons. In addition, all subjects were to take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Folic acid dosing and timing of regimen were to be followed according to the investigator's instructions. Starting at the Week 26 visit (after Week 26 assessments were performed) and thereafter, initiation of or change in background RA medication(s) including corticosteroids, non-steroidal anti-inflammatory drugs, and acetaminophen/paracetamol was allowed as per local label. Starting at Week 48 (after Week 48 assessments were performed) and thereafter, initiation of or change in conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) was allowed as per local label (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide).

Methodology (Continued):

Rescue therapy was to be offered to subjects who met the following criteria:

Placebo:

- Subjects who did not achieve a ≥ 20% improvement in tender joint count (TJC) and swollen joint count (SJC) at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded upadacitinib treatment.
- At Week 26, all remaining subjects were switched to blinded upadacitinib treatment regardless of clinical response.

Adalimumab:

- Subjects who did not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded upadacitinib treatment.
- At Week 26, all remaining subjects who did not achieve low disease activity (LDA) according to Clinical Disease Activity Index (CDAI) (LDA defined as CDAI ≤ 10) at Week 26 were to be switched to blinded upadacitinib treatment.

Upadacitinib:

- Subjects who did not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded adalimumab treatment.
- At Week 26, all remaining subjects who did not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 were to be switched to blinded adalimumab treatment.

An unblinded analysis was conducted when all subjects were expected to have completed their Week 26 visit for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of Period 1.

Number of Subjects (Planned and Analyzed): Planned: 1500 subjects; Analyzed: 1629

Diagnosis and Main Criteria for Inclusion:

Adult males and females enrolled in this study were at least 18 years of age with a diagnosis of RA for ≥ 3 months who also fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA who have had an inadequate response to MTX treatment. Local guidelines for MTX dosage may have applied. Eligible study subjects were to have had ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein level ≥ 5 mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at Screening. Subjects were also to have had the following at Screening: ≥ 3 bone erosions on x-ray; or ≥ 1 bone erosion and a positive rheumatoid factor; or ≥ 1 bone erosion and a positive anti-cyclic citrullinated peptide autoantibody.

Diagnosis and Main Criteria for Inclusion (Continued):

Subjects were excluded if they had prior exposure to any Janus kinase inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib) or adalimumab, or who had been treated with other biologic disease-modifying anti-rheumatic drug (bDMARD) therapy for ≥ 3 months who were considered inadequate responders (lack of efficacy) to bDMARD therapy as determined by the investigator. Subjects were also excluded if they 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 transaminase (AST) > 2 × ULN; serum alanine aminotransferase (ALT) > 2 × ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/minute/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 15 mg extended-release tablets for oral administration (bulk lot number: 15-005420, 15-005421, 15-005422, 15-005423, 15-006832, 15-006833, 16-005073, 16-005417, 16-005426, 17-002015, 17-001973)

Duration of Treatment: Period 1: 48 weeks; Period 2: up to 5 years

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

Adalimumab 40 mg/0.8 mL subcutaneous injection solution for subcutaneous administration (bulk lot number: 15-000609, 15-005080, 16-001720, 16-005133, 17-002006)

Matching placebo for adalimumab, subcutaneous injection solution for subcutaneous administration (bulk lot number: 14-002885, 15-005865, 16-000470, 16-004292, 17-002248)

Matching placebo for upadacitinib, tablet for oral administration (bulk lot number: 15-005362, 15-006982, 16-003281, 17-002079)

Criteria for Evaluation

Efficacy:

The primary endpoint for US/Food and Drug Administration (FDA) regulatory purposes is the proportion of subjects achieving ACR 20% (ACR20) response at Week 12. The primary endpoint for European Union (EU)/European Medicines Agency (EMA) regulatory purposes is the proportion of subjects achieving clinical remission (CR) (based on Disease Activity Score 28 [DAS28] C-reactive protein [CRP] < 2.6) at Week 12.

Criteria for Evaluation (Continued)

Efficacy (Continued):

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for US/FDA regulatory purposes were: 1) change from Baseline in DAS28 (CRP) at Week 12; 2) change from Baseline in modified Total Sharp Score (mTSS) at Week 26; 3) change from Baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 12; 4) ACR 50% (ACR50) response rate at Week 12 (non-inferiority of upadacitinib versus adalimumab); 5) change from Baseline in Short Form-36 (SF-36) physical component summary (PCS) at Week 12; 6) proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12; 7) proportion of subjects achieving CR based on DAS28 (CRP) at Week 12; 8) proportion of subjects achieving LDA based on CDAI at Week 12; 9) change from Baseline in morning stiffness (duration) at Week 12; 10) change from Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) at Week 12; 11) ACR50 response rate at Week 12 (superiority of upadacitinib versus adalimumab); 12) change from Baseline in Patient's Assessment of Pain at Week 12 (superiority of upadacitinib versus adalimumab); and 13) change from Baseline in HAQ-DI at Week 12 (superiority of upadacitinib versus adalimumab).

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for EU/EMA regulatory purposes were: 1) change from Baseline in mTSS at Week 26; 2) proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12; 3) change from Baseline in DAS28 (CRP) at Week 12; 4) change from Baseline in HAQ-DI at Week 12; 5) ACR20 response rate at Week 12; 6) proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of upadacitinib versus adalimumab); 7) change from Baseline in SF-36 PCS at Week 12; 8) proportion of subjects achieving LDA based on CDAI at Week 12; 9) change from Baseline in morning stiffness (duration) at Week 12; 10) change from Baseline in FACIT-F at Week 12; and 11) proportion of subjects with no radiographic progression (defined as change from Baseline in mTSS ≤ 0) at Week 26.

Primary and ranked key secondary endpoints were multiplicity adjusted for strong type I error control for US/FDA and EU/EMA regulatory purposes.

Other key secondary endpoints (upadacitinib versus placebo) for US/FDA regulatory purposes were: 1) ACR50 response rate at Week 12; 2) ACR 70% (ACR70) response rate at Week 12; and 3) proportion of subjects with no radiographic progression (defined as change from Baseline in mTSS ≤ 0) at Week 26.

Other key secondary endpoints (upadacitinib versus placebo) for EU/EMA regulatory purposes were: 1) ACR50 response rate at Week 12; and 2) ACR70 response rate at Week 12.

Additional efficacy analysis included the following endpoints (upadacitinib versus placebo and adalimumab) at all visits in Period 1: change from Baseline in individual components of ACR response; ACR20/50/70 response rates; change from Baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]); change from Baseline in CDAI and Simple Disease Activity Index (SDAI); proportion of subjects achieving LDA or proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria; 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; and ACR/EULAR Boolean remission.

Additional efficacy analysis included the following endpoints (upadacitinib versus placebo and adalimumab) at Weeks 12, 26, and 48 only: change from Baseline in SF-36 PCS; change from Baseline in FACIT-F; change from Baseline in Work Instability Scale for Rheumatoid Arthritis; and change from Baseline in EuroQoL-5D-5L.

Criteria for Evaluation (Continued)

Efficacy (Continued):

Additional efficacy analysis included the following endpoints (upadacitinib versus placebo and adalimumab) at Weeks 26 and 48 only: change from Baseline in mTSS; proportion of subjects with no radiographic progression (defined as change from Baseline in mTSS ≤ 0); and change from Baseline in joint space narrowing (JSN) score and joint erosion score.

Pharmacokinetic:

Blood samples for upadacitinib plasma concentrations were obtained throughout Period 1.

Safety:

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

Statistical Methods

Efficacy:

Primary Endpoint: Comparisons of the primary endpoint were made between the upadacitinib 15 mg QD group and the placebo group using the Cochran-Mantel-Haenszel test adjusting for stratification factor of prior bDMARD use (Yes/No). For the primary analysis, non-responder imputation (NRI) was used. Supportive analysis was also conducted on the Per Protocol Analysis Set. The primary efficacy analyses 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 and stratification factors were also conducted.

Secondary Clinical Endpoints: For binary endpoints, frequencies and percentages were reported for each treatment group. Similar analyses as for the primary endpoint were conducted. Additionally, for ACR50 response rate, analysis was conducted to test the non-inferiority of upadacitinib versus adalimumab using the 95% confidence interval (CI) of treatment difference against a non-inferiority margin of 10% for US/FDA regulatory purposes. Similar non-inferiority analysis was conducted for LDA based on DAS28 (CRP) with a 10% margin for EU/EMA regulatory purposes. Superiority of upadacitinib versus adalimumab was tested using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD use. For the major RA continuous endpoints DAS28 and HAQ-DI change from Baseline, statistical inference was conducted using analysis of covariance (ANCOVA) coupled with Multiple Imputation (MI) for missing data handling. Specifically, the ANCOVA model included treatment as the fixed factor, and the corresponding Baseline value and the stratification factor prior bDMARD use (Yes/No) as the covariates. For other continuous endpoints, statistical inference was conducted using the Mixed Effect Model Repeat Measurement (MMRM) model with the main stratification factor being prior bDMARD use (Yes/No). From both the MI and MMRM analyses, the least square (LS) mean and 95% CI were to be reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value were to be reported comparing the upadacitinib group with the placebo group. For change from Baseline in patient's global assessment of pain and change from Baseline in HAQ-DI, superiority of upadacitinib versus adalimumab was tested.

Statistical Methods (Continued)

Efficacy (Continued):

mTSS-Related Secondary Endpoints: Linear extrapolation was used for all mTSS-related endpoints. Analysis based on As Observed (AO) data was also performed. In the linear extrapolation analysis, the Week 26 data was imputed via linear extrapolation using x-ray data from the Baseline window and the Week 14 window for the following subjects: subjects rescued to a different study drug at Week 14, subjects who prematurely discontinued study drug prior to Week 18, and subjects otherwise (i.e., not rescued to a different study drug at Week 14, not prematurely discontinued study drug prior to Week 18) missing x-ray data in the Week 26 window but have available x-ray data in the Week 14 window. For proportion of subjects with no radiographic progression, frequencies and percentages were reported for each treatment group. Similar analyses as for the primary endpoint were conducted, with the exception that linear extrapolation was used for imputation. For change from Baseline in mTSS, statistical inference was conducted using the ANCOVA model with treatment and prior bDMARD use (Yes/No) as the fixed factors and the corresponding Baseline value as the covariates. In the event that data severely deviated from the normal distribution, non-parametric analyses such as the Wilcoxon rank sum test may have been considered for treatment comparison. From the linear extrapolation analysis, the point estimate and 95% CI were to be reported for each randomized treatment group; the point estimate, 95% CI, and p-value were to be reported comparing the upadacitinib group with the placebo group.

Additional Clinical Efficacy Variables: For binary endpoints, frequencies and percentages were reported for each randomized treatment group. Similar analyses as for the primary endpoint were conducted. For the primary analysis, NRI was used. In addition, subjects who met the rescue criteria (based on joint improvement) at either Week 14, 18 or 22 were treated as non-responders at visits after rescue treatment switching. For subjects who meet the rescue criteria (based on CDAI LDA) at Week 26, data after rescue treatment switching were overwritten by the last response prior to rescue. AO data, regardless of rescue, were also summarized using frequencies and percentages. For continuous variables, statistical inference was conducted using ANCOVA with treatment and prior bDMARD use (Yes/No) as the fixed factor and the corresponding Baseline value as the covariate. For subjects who met the rescue criteria at either Week 14, 18, 22, or 26, data after rescue treatment switching was overwritten by Last Observation Carried Forward for the primary analysis. AO data, regardless of rescue treatment switching, was also summarized using descriptive statistics.

Additional mTSS-Related Efficacy Variables: This clinical study report only presents results from TSS-related variables through Week 26. For proportion of subjects with no radiographic progression and change from Baseline in mTSS, analyses are described above. For change from Baseline in JSN score and joint erosion score, linear extrapolation analysis was performed as described above. Analysis was repeated on AO data, regardless of rescue treatment switching or study drug discontinuation, for all mTSS-related efficacy variables.

Pharmacokinetic:

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

Statistical Methods (Continued)

Safety:

Safety analyses were based on treatments actually received. The following 2 main sets of safety analyses were provided:

1. **Safety Analysis through Week 14** – safety data prior to availability of rescue therapy
2. **Safety Analysis through Week 26 (Censored at Treatment Switching)** – safety data through Week 26, excluding safety data obtained after subjects received rescue therapy (i.e., switched treatment).

Safety analysis through Week 26 (including data obtained after subjects switched from original randomized treatment to rescue therapy) was provided for select measures. Safety was assessed by AEs, physical examination, laboratory assessments, ECG, and vital signs. Frequency tables and lists of subjects with treatment-emergent AEs (TEAEs) by preferred term as in the Medical Dictionary for Regulatory Activities dictionary, by system organ class, by severity, and by relationship to the study drug as assessed by the investigator were provided. The changes from Baseline in vital signs and laboratory values were examined. Shift of laboratory values from Baseline to defined time points was tabulated. Missing data were not imputed.

Summary/Conclusions

Efficacy Results:

Through Week 26 of Period 1, upadacitinib at a dose of 15 mg QD was more effective than placebo and adalimumab in treating signs and symptoms of RA and in improving physical function in subjects with moderately to severely active RA who were on background MTX and had inadequate response to MTX; upadacitinib was also more effective than placebo in inhibiting structural progression. The study met its primary endpoints at Week 12, with a highly statistically significantly greater percentage of subjects achieving an ACR20 response (US/FDA primary endpoint) and CR based on DAS28 (CRP) < 2.6 (EU/EMA primary endpoint) in the upadacitinib group compared with the placebo group. The study also met all multiplicity-controlled ranked key secondary endpoints with statistical significance in the upadacitinib 15 mg QD dose group compared with the placebo group. All pre-specified, multiplicity-controlled ranked non-inferiority and superiority comparisons of upadacitinib versus adalimumab (change from Baseline in patient's global assessment of pain [superiority] and HAQ-DI [superiority]; proportion of subjects achieving LDA based on DAS28 [CRP] ≤ 3.2 [non-inferiority] and ACR50 response rate [non-inferiority and superiority]) were also achieved in favor of upadacitinib. The other key secondary endpoints also achieved nominal statistical significance versus placebo. Rapid onset of efficacy was noted with the upadacitinib dose achieving statistical significance versus placebo for all components of the ACR response beginning at Week 2 and for the majority of other efficacy variables as early as Week 2; improvement was sustained through Week 12 and was either maintained or further improved after Week 12.

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 15 mg QD, upadacitinib mean plasma concentrations ranged from 5.74 to 32.4 ng/mL.

Summary/Conclusions (Continued)

Safety Results:

In this blinded, placebo- and active comparator-controlled treatment period, continuous treatment with upadacitinib for up to 26 weeks at a dose of 15 mg QD was generally well-tolerated as assessed by the frequency of TEAEs, including serious AEs (SAEs), AEs leading to discontinuation of study drug, AEs of special interest (AESIs), clinical laboratory values, and vital signs values.

Through Week 26, 4 deaths were reported: 1 subject in the adalimumab group died due to craniocerebral injury, 1 subject in the placebo group died due to sudden death (adjudicated by the external Cardiovascular Adjudication Committee [CAC] as cardiovascular death), 1 subject in the placebo group died due to pneumocystis jirovecii pneumonia, and 1 subject in the adalimumab group died due to left ventricular failure (adjudicated by the external CAC as cardiovascular death). Pneumocystis jirovecii pneumonia was the only event leading to death that was assessed by the investigator as having a reasonable possibility of being related to study drug. No deaths were reported in the upadacitinib group.

Through Week 14 (prior to availability of rescue therapy switch), no TEAEs were reported by ≥ 5% of subjects in any treatment group; only upper respiratory tract infection and nasopharyngitis were reported by ≥ 5% of subjects in any treatment group through Week 26 (censored at treatment switching).

Through Week 14, the percentage of subjects with TEAEs leading to discontinuation of study drug was higher in the adalimumab group (16 subjects [4.9%]) compared with the upadacitinib (18 subjects [2.8%]) and placebo (12 subjects [1.8%]) groups. The percentage of subjects with SAEs was comparable across all treatment groups (18 subjects [2.8%] in the upadacitinib group, 8 subjects [2.4%] in the adalimumab group, and 14 subjects [2.1%] in the placebo group). In general, SAEs were observed evenly across treatment groups. Similar results were observed through Week 26 (censored at treatment switching): TEAEs leading to discontinuation (20 subjects [6.1%] in the adalimumab group versus 23 subjects [3.5%] in the upadacitinib group and 15 subjects [2.3%] in the placebo group) and SAEs (24 subjects [3.7%] in the upadacitinib group, 14 subjects [4.3%] in the adalimumab group, and 19 subjects [2.9%] in the placebo group).

Through Week 14, the percentage of subjects with AESIs was generally comparable across treatment groups, with the exception of hepatic disorders, neutropenia, and creatine phosphokinase (CPK) elevation, which were reported in a higher percentage of subjects in the upadacitinib group compared with the adalimumab and placebo groups; and serious infections, which were reported in similar percentages in the upadacitinib and adalimumab groups, but higher than the placebo group. Similar results were observed through Week 26 (censored at treatment switching).

Through Week 14, serious infections were reported by 10 subjects (1.5%) in the upadacitinib group, 4 subjects (1.2%) in the adalimumab group, and 5 subjects (0.8%) in the placebo group. Nonserious herpes zoster was reported by 5 subjects (0.8%) in the upadacitinib group and 1 subject (0.3%) in the adalimumab group. The opportunistic infections reported were esophageal candidiasis (1 subject in the upadacitinib group), oral candidiasis (2 subjects in the upadacitinib group and 1 subject in the adalimumab group), and pneumocystis jirovecii pneumonia (2 subjects in the placebo group). Treatment-emergent malignancies were reported in the adalimumab and placebo groups only and included 2 basal cell carcinomas (1 subject each in the adalimumab and placebo groups) and 1 cervical carcinoma in the placebo group. The 2 events of basal cell carcinoma were reported on Day 48 and Day 59, and the event of cervical carcinoma was reported on Day 82, 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. No subject in any treatment group had treatment-emergent lymphoma.

Summary/Conclusions (Continued):

Safety Results (Continued):

Through Week 14, adjudicated major adverse cardiovascular event (MACE) were reported in the adalimumab and placebo dose groups only and included non-fatal stroke (1 subject in the adalimumab group), cardiovascular death (1 subject in the placebo group), and non-fatal myocardial infarction (2 subjects in the placebo group). Adjudicated venous thrombotic events included deep vein thrombosis (1 subject in the upadacitinib group) and pulmonary embolism (3 subjects in the adalimumab group and 1 subject in the placebo group). All adjudicated cardiovascular events were considered by the investigator as having no reasonable possibility of being related to study drug, with the exception of pulmonary embolism in 1 subject in the adalimumab group.

Through Week 26 (censored at treatment switching), serious infections were reported by 12 subjects (1.8%) in the upadacitinib group, 5 subjects (1.5%) in the adalimumab group, and 5 subjects (0.8%) in the placebo group. From Week 14 to Week 26, 2 additional subjects in the placebo group reported nonserious herpes zoster while subjects were on their original randomized treatment. Opportunistic infections reported included oral candidiasis (1 subject in the upadacitinib group and 1 subject in the placebo group) and fungal esophagitis (1 subject in the placebo group). No additional malignancies were reported. One additional adjudicated MACE of cardiovascular death (1 subject in the adalimumab group) and 1 additional adjudicated venous thrombotic event of pulmonary embolism (1 subject in the upadacitinib group) with known risk factors was reported. Both adjudicated cardiovascular events were considered by the investigator as having no reasonable possibility of being related to study drug.

For both the through Week 14 and through Week 26 (censored at treatment switching) analysis sets, the majority of hepatic disorders were mild to moderate in severity and were largely hepatic enzyme elevations. They were more frequently reported by subjects in the upadacitinib group compared to the adalimumab and placebo groups. Overall, the upadacitinib group had a higher percentage of subjects with an AESI of neutropenia or CPK elevation compared with the adalimumab and placebo groups. No subject discontinued study drug due to a TEAE of blood CPK increased. Through Week 14, no subject discontinued study drug due to a TEAE of neutropenia; 1 subject discontinued study drug (upadacitinib) from Week 14 through Week 26 while on their original randomized treatment.

In general, group mean values for key hematology variables (hemoglobin, hematocrit, lymphocytes, neutrophils, platelets, and immunoglobulin [Ig]M and IgG) were within the normal reference range at Baseline and at all visits for all treatment groups for both the through Week 14 and through Week 26 (censored at treatment switching) analysis sets. While the percentage of subjects with Grade 3 decreases in neutrophil values was comparable across groups, 3 subjects (all in the upadacitinib group and all during the first 14 weeks of the study) had Grade 4 decreases in neutrophil values; 2 of the 3 subjects reported an infectious TEAE (tooth abscess, urosepsis) that had resolved just prior to the onset of neutropenia. The percentage of subjects with Grade 3 decreases in hemoglobin values were comparable in the upadacitinib (16 subjects [2.5%]) and placebo (18 subjects [2.8%]) groups, but slightly lower in the adalimumab group (4 subjects [1.2%]); similar finding were observed for Grade 4 decreases through Week 14 (4 subjects [0.6%] in both the upadacitinib and placebo groups, and 1 subject [0.3%] in the adalimumab group) and Grade 3 decreases through Week 26 (censored at treatment switching) (24 subjects [3.7%] in the upadacitinib group and 19 subjects [2.9%] in the placebo group versus 6 subjects [1.8%] in the adalimumab group). Through Week 26 (censored at treatment switching), the percentage of subjects with Grade 4 decreases in hemoglobin values was comparable among all treatment groups (5 subjects [0.8%] in the upadacitinib group, 2 subjects [0.6%] in the adalimumab group, and 6 subjects [0.9%] in the placebo group).

Summary/Conclusions (Continued):

Safety Results (Continued):

Through Week 14, Grade 3 increases in blood CPK values were reported in the upadacitinib and placebo groups only and were reported in a similar percentage of subjects (3 subjects [0.5%] in the upadacitinib and 2 subjects [0.3%] in the placebo group). Grade 4 increases in blood CPK values were reported in 1 subject in the upadacitinib and 1 subject in the adalimumab group. Through Week 26 (censored at treatment switching), Grade 3 increases in blood CPK values were reported by 5 subjects (0.8%) in the upadacitinib group, 3 subjects (0.5%) in the placebo group, and 1 subject (0.3%) in the adalimumab group; from Week 14 through Week 26, 1 additional subject (upadacitinib group) reported Grade 4 increases in blood CPK while on their original randomized treatment. No subject with Grade 3 or Grade 4 increases in blood CPK values discontinued study drug due to an increased CPK value or had rhabdomyolysis, and all subjects were asymptomatic with the exception of a subject from the upadacitinib group who had a single Grade 3 increase in blood CPK value during the first 14 weeks of the study that was associated with transient muscle weakness.

Through Week 14, the percentage of subjects with Grade 3 increases in ALT values was higher in the upadacitinib group (16 subjects [2.5%]) compared with the adalimumab (4 subjects [1.2%]) and placebo (9 subjects [1.4%]) groups. Similar results were observed through Week 26 (censored at treatment switching): (25 subjects [3.8%] in the upadacitinib group versus 4 subjects [1.2%] in the adalimumab group and 13 subjects [2.0%] in the placebo group). Through Week 14, the percentage of subjects with Grade 3 increases in AST values was comparable across treatment groups (10 subjects [1.5%] in the upadacitinib group, 4 subjects [1.2%] in the adalimumab group, and 3 subjects [0.5%] in the placebo group). Through Week 26 (censored at treatment switching), the percentage of subjects with Grade 3 increases in AST values was highest in the upadacitinib group (13 subjects [2.0%]), followed by the adalimumab group (4 subjects [1.2%]), and the placebo group (4 subjects [0.6%]). Through Week 14, the percentage of subjects with Grade 4 increases in ALT values was comparable among treatment groups (3 subjects [0.5%] in the upadacitinib group, 2 subjects [0.6%] in the adalimumab group, and 1 subject [0.2%] in the placebo group). Similar results were observed through Week 26 (censored at treatment switching): (3 subjects [0.5%] in the upadacitinib group, 2 subjects [0.6%] in the adalimumab group, and 2 subjects [0.3%] in the placebo group). Grade 4 increases in AST values were reported in 2 subjects (0.3%) in the upadacitinib group and 1 subject (0.3%) in the adalimumab group (all during the first 14 weeks of the study).

Through Week 26 (censored at treatment switching), Grade 3 increases in serum creatinine values were infrequent and reported in only 1 subject in the upadacitinib group and 1 subject in the adalimumab group (both during the first 14 weeks of the study); no subject in any treatment group had a serum creatinine increased value that was Grade 4. Through Week 14, treatment with upadacitinib resulted in mean increases from Baseline in low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and total cholesterol compared with adalimumab and placebo; however, the ratios of total cholesterol:HDL-C and LDL-C:HDL-C remained unchanged from Baseline through Week 14 for the upadacitinib, adalimumab, and placebo groups. Similar results were observed through Week 26 (censored at treatment switching).

Mean changes from Baseline through Week 14 in vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, temperature) in the upadacitinib group were small and not considered to be clinically meaningful. Similar results were observed through Week 26 (censored at treatment switching).

Summary/Conclusions (Continued):

Safety Results (Continued):

Through Week 26 (after treatment switching), no death, malignancy other than nonmelanoma skin cancer, gastrointestinal perforation, renal dysfunction, active/latent tuberculosis, adjudicated MACE, or adjudicated venous thromboembolic event was reported after treatment switching. The following select AESIs were observed after switching and up to Week 26: 3 serious infections (sepsis and cellulitis [1 subject each on upadacitinib], and pneumonia [1 subject on adalimumab]), 1 opportunistic infection (esophageal candidiasis [1 subject on upadacitinib]), 2 herpes zoster (1 subject on upadacitinib and 1 subject on adalimumab), and 1 malignancy (basal cell carcinoma [1 subject on upadacitinib]). The basal cell carcinoma was considered by the investigator to have no reasonable possibility of being related to study drug.

Conclusions:

Through Week 26 of Period 1 for Study M14-465, superiority was consistently demonstrated for upadacitinib 15 mg QD versus placebo and adalimumab in treating signs and symptoms of RA and in improving physical function in subjects with moderately to severely active RA who were on a stable background of MTX and had an inadequate response to MTX. Upadacitinib was also more effective than placebo in inhibiting structural progression using both linear extrapolation and AO analyses. The safety of upadacitinib was generally comparable to adalimumab. The benefit-risk profile of upadacitinib 15 mg QD is assessed as favorable based on the efficacy and safety results through Week 26 of the study.

Date of Report: 28Aug2018

Protocol Changes

At the time of the data cutoff for this clinical study report (02 February 2018), the original protocol (30 September 2015, 9 subjects enrolled) had 5 global amendments, 9 country-specific amendments, and 2 global administrative changes. The majority of changes to the protocol were responses to regulatory feedback, clarifications, and editorial changes.

Administrative Change 1 (17 December 2015) was written to correct study visits for blood samples for exploratory research and validation studies. Administrative Change 2 (28 September 2017) was written to make a minor administrative correction.

The amendments, number of subjects enrolled under each amendment, country-specific protocol changes, and substantial protocol changes were as follows:

- Amendment 1 (11 December 2015, 13 subjects)
  - Changed the duration of Period 1 from 52 weeks to 48 weeks.
  - Added the following: a long-term extension period (Period 2); stable dose of MTX requirements; that csDMARD background therapy other than MTX is not allowed during Period 1; rescue criteria; study visits for rescue therapy; discontinuation procedures; follow-up procedures; contraception recommendations and pregnancy testing; requirement for a 12-lead ECG and physical exam at Week 48; international normalized ratio (INR) reflex and follicle stimulating hormone (FSH) to laboratory tests; instructions for chest x-ray requirements; use of an external DMC; the Summary of Product Characteristics as the reference document for adalimumab SUSAR reporting; an interim analysis after completion of the Week 26 visit and Week 48 visit; and a definition for screen failure.
  - Updated the following: primary, secondary, and other efficacy variables; x-ray study visits; procedures for laboratory samples during the screening period; hsCRP value requirement at Screening; contraception requirements; randomization stratification; assumptions used to determine sample size; and AST and ALT specific toxicity management guidelines.

- Clarified the following: washout requirements for rituximab; prior bDMARD therapy and washout periods; AEs to be assessed at Screening; randomization scheme; language regarding independent joint assessors; hsCRP level requirement; the AE collection period; site monitoring, archiving, and sponsor support provided to sites; and exploratory research/validation studies.
- Added the following exclusion criteria: females who are considering becoming pregnant during the study or for approximately 150 days after the last dose of study drug; males who are considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug; and subjects who are considered inadequate responders to bDMARD therapy as determined by the Investigator, have a history of gastrointestinal (GI) perforation or a history of associated GI diseases, have conditions that could interfere with drug absorption, have a history of demyelinating disease, have received an organ transplant, or had clinically relevant or significant ECG abnormalities.

- Amendment 2 (08 January 2016, 509 subjects)
  - Corrected study visits for blood samples for exploratory research and validation studies.
  - Clarified the primary endpoint and key secondary endpoints for the EU.
- Amendment 0.01 (Canada only) (13 January 2016, 2 subjects)
  - Updated text to reflect revisions implemented with global protocol Amendment 1 (11 December 2015).
  - Updated absolute neutrophil count and absolute lymphocyte count specific toxicity management guidelines.
  - Added text that non-investigational product (standard of care) must be obtained commercially.
- Amendment 2.02 (Korea only) (23 March 2016, 0 subjects)
  - Removed "chloroquine" as a potential background csDMARD and true abstinence as a highly effective method of birth control for both males and females.

- Amendment 3 (01 April 2016, 785 subjects)
  - Updated rescue therapy criteria at Week 26.
  - Clarified that starting at Week 48, subjects who failed to show at least 20% improvement in TJC and SJC compared to Baseline at 2 consecutive visits should discontinue study drug treatment.
  - Clarified subpopulation requirements for patients with prior exposure to bDMARDs.
- Amendment 2.01 (France only) (15 April 2016, 2 subjects)
  - Updated text to reflect revisions implemented with global protocol Amendment 2 (08 January 2016).
  - Updated study activities table to include serum pregnancy text at central lab for Baseline Visit and revised 30-Day follow-up Visit header by removing "Call."
  - Removed text references and descriptions of Period 2.
  - Clarified that subjects who develop any malignancy will be discontinued.
  - Clarified pregnancy test performed on women of childbearing potential as target group.
- Amendment 3.01 (Korea only) (21 April 2016, 7 subjects)
  - Updated text to reflect revised rescue therapy.
  - Removed "chloroquine" as a potential background csDMARD and true abstinence as a highly effective method of birth control for both males and females.
  - Clarified the following: that starting at Week 48, subjects who failed to show at least 20% improvement in TJC and SJC compared to Baseline at 2 consecutive visits should discontinue study drug treatment; subpopulation requirements for patients with prior exposure to bDMARDs; and that the duration of contraception after discontinuation of the csDMARD should be based on the local label.
- Amendment 0.01.01 (Canada only) (26 April 2016, 6 subjects)
  - Updated text to reflect revisions implemented with global protocol Amendment 3 (01 April 2016).

- Amendment 4 (11 January 2017, 291 subjects)
  - Added the following: that oral traditional Chinese medicine is prohibited; requirement to perform pregnancy testing if FSH results are consistent with pre-menopausal status; and local country requirements for Canada, Hong Kong, Korea, Malaysia, Singapore, and Taiwan.
  - Removed blood samples for assay of adalimumab and for assay of anti-adalimumab antibodies.
  - Updated the following: the key secondary endpoints list to match new emphasis on head-to-head comparison of upadacitinib to adalimumab; the list of additional endpoints; text to allow concomitant medication modifications at Week 26; required duration of contraception to reflect new data obtained from chronic animal toxicology studies and that additional local contraception requirements may apply; pregnancy and sperm donation waiting periods following oral study drug administration; and clinical laboratory tests to remove creatine kinase-muscle/brain, and add minimum residual B-cell panel, antinuclear antibodies/dsDNA (reflex) antibodies, and human immunodeficiency virus (HIV) testing.
  - Specified the pregnancy reporting period required for oral and subcutaneous study drug.
  - Clarified the following: rescue therapy; central imaging; re-screening labs and Premature Discontinuation Visits for subjects who prematurely discontinue from study drug; exceptions for administering live vaccines; that all remaining subjects who had not been previously rescued and have not reached LDA will be rescued at Week 26; pregnancy testing; HIV testing; independent joint assessor; tuberculosis (TB) test; TB prophylaxis, x-rays of the hands and feet, and chest x-ray; that ECG will be performed at the final visit of Period 1 only if the subject does not enter Period 2 or if the subject discontinues from the study; the pharmacokinetic analyses that will be conducted; the difference in AE collection period for oral and subcutaneous study drug; conditions under which study drug would be interrupted with respect to type of surgery; statistical analysis details; and assumptions used for sample size determination.

- Made the following updates to inclusion criteria: updated MTX dosing information; updated requirements for stable doses of NSAIDs, acetaminophen, oral corticosteroids, or inhaled corticosteroids; included discontinuation requirements for oral traditional Chinese medicine; and clarified pregnancy testing requirement.
- Made the following updates to exclusion criteria: updated Exclusion Criterion 8 to include chronic and invasive infections and added HIV infection definition; updated follow-up period from 90 days to 30 days in Exclusion Criterion 7; updated Exclusion Criterion 11 to clarify that the 70-day follow‑up period pertains to the subcutaneous study drug; and updated Exclusion Criterion 21 to reflect normal reference range in the elderly population.

- Amendment 4.01 (China only) (12 January 2017, 0 subjects)
  - Added MTX dosing requirements for China and hepatitis B virus (HBV) exclusionary requirements for China.
- Amendment 4.02 (France only) (31 January 2017, 1 subject)
  - Updated text to reflect revisions implemented with global protocol Amendment 3 (01 April 2016) and global protocol Amendment 4 (11 January 2017).
  - Clarified that the duration of contraception after discontinuation of the csDMARD should be based on the local label.
- Amendment 4.03 (Canada only) (13 March 2017, 4 subjects)
  - Revised contraceptive requirements.
- Amendment 4.02.01 (France only) (20 September 2017, 0 subjects)
  - Added a long-term extension period (Period 2) (72 weeks).
- Amendment 5 (01 December 2017, 0 subjects)
  - Defined key secondary endpoints as ranked.
  - Implemented a supplemental eCRF for thrombotic events.
  - Added management language for subjects with Hepatitis B core antibody positive and negative HBV DNA at Screening and laboratory values during the study which may indicate active hepatitis.

- Updated the following: safety collection requirements for subjects that are treated with commercial adalimumab after end of study treatment; csDMARD language to enable unbiased comparison of investigational product to active comparator up to end of Period 1; text to align with permitted background corticosteroid requirements; herpes zoster vaccine language for subject safety prior to and after study drug; duration of contraception recommendations for males; study procedures to include rifapentine as an excluded medication; to allow a pulmonologist to perform an assessment of the chest x-ray; x-ray time points for subjects that prematurely discontinue from study drug but continue in the study; adverse events of special interest (AESIs) that will be monitored during the study to align in content and presentation with the current version of the product safety statistical analysis plan; and local country requirements for Canada.
- Clarified the following: that the long-term extension period is blinded until the last subject completes Period 1; TJC/SJC improvement requirements starting at Week 48 to remain on study drug; requirements for contraception for females if child-bearing potential status changes during the course of the study; the frequency of the Latent TB Risk Assessment Form completion; that an annual ECG is required for all subjects; indeterminate QuantiFERON-TB test results; that annually is considered every 48 weeks; requirements for recording lab abnormalities as AEs; efficacy variables; that starting at Week 48, at least 20% improvement in both SJC and TJC compared to Baseline is required to remain on study drug; who will remain blinded at study time points; that subjects should discontinue study drug for an ECG abnormality that is considered clinically significant with reasonable possibility that the event is related to study drug; toxicity management for ALT, AST, INR, serum creatinine, and elevated creatine phosphokinase (CPK) values; imputation method and safety analysis details; and that for CPK and serum creatinine, National Cancer Institute (NCI) Common Terminology Criteria (CTC) grading will be used.

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

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

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