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 on Stable Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs)

Investigator: Dr. Atul Singhal.

Study Sites: 152 sites in 26 countries (Australia, Austria, Belgium, Canada, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Korea, Latvia, New Zealand, Poland, Portugal, Puerto Rico, Russian Federation, Slovakia, Spain, Sweden, Turkey, United Kingdom, United States)

Publications: None

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 15 March 2016 Last Subject Last Visit: 27 June 2017 (Period 1)	

Objectives:

The study objective of Period 1 was to compare the safety and efficacy of upadacitinib 30 mg once daily (QD) and 15 mg QD versus placebo on a background of conventional synthetic DMARDs (csDMARDs) for the treatment of signs and symptoms of rheumatoid arthritis (RA) in bDMARD-inadequate response (bDMARD-IR) or bDMARD-intolerant 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 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

This Clinical Study Report presents the results of Period 1 (i.e., through Week 24) only.

Methodology:

This was a Phase 3 multicenter study that included two periods. Period 1 was a 24-week, randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 bDMARD. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

Methodology (Continued):

The study was designed to enroll approximately 450 subjects at approximately 300 study centers worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects had been enrolled, there was a possibility that additional subjects in screening were not enrolled.

The study duration was to include a 35-day screening period; a 24-week randomized, double-blind, parallel-group, placebo controlled treatment period (Period 1); a 216-week blinded long-term extension period (Period 2); and a 30-day follow-up period (call or visit).

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

Group 1: upadacitinib 30 mg QD (N = 150) (Day 1 to Week 12) → upadacitinib 30 mg QD (Week 12 and thereafter)

Group 2: upadacitinib 15 mg QD (N = 150) (Day 1 to Week 12) → upadacitinib 15 mg QD (Week 12 and thereafter)

Group 3: Placebo (N = 75) (Day 1 to Week 12) → upadacitinib 30 mg QD (Week 12 and thereafter)

Group 4: Placebo (N = 75) (Day 1 to Week 12) → upadacitinib 15 mg QD (Week 12 and thereafter)

Subjects should have been on a stable dose of csDMARD(s) for ≥ 4 weeks prior to the first dose of study drug and should have remained on a stable dose until Week 24; the csDMARD dose was to be decreased only for safety reasons.

Number of Subjects (Planned and Analyzed):

Planned: 450 subjects (300 upadacitinib, 150 placebo); Analyzed: 498 subjects (329 upadacitinib, 169 placebo)

Diagnosis and Main Criteria for Inclusion:

Adult males and females enrolled in this study were at least 18 years old with a diagnosis of RA for ≥ 3 months and fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. 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, and high sensitivity C-reactive protein ≥ 3 mg/L (central lab) at screening. Subjects have been treated with bDMARD therapy for RA in the past and failed at least 1 bDMARD therapy prior to first dose of study drug as defined by either not showing an adequate response to at least 1 bDMARD after a treatment of ≥ 3 months or having had to discontinue at least 1 bDMARD due to intolerability or toxicity, irrespective of treatment duration. Subjects were to have been on csDMARD therapy ≥ 3 months and on a stable dose of csDMARD therapy (restricted to methotrexate, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide) for ≥ 4 weeks prior to the first dose of study drug. Subjects were excluded if they had prior exposure to any janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib); had a history 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 × upper limit of normal (ULN); serum alanine transaminase (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 15 mg extended release capsules for oral administration (bulk lot number: 15-005364, 16-001615)

Upadacitinib 30 mg extended release capsules for oral administration (bulk lot number: 15-005365, 15-005424, 15-005425, 16-001432)

Duration of Treatment: Period 1: 24 weeks; Period 2: up to 4 years

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

Matching placebo, capsules for oral administration (bulk lot number: 15-005363, 15-005362, 16-001360)

Criteria for Evaluation

For Period 1 (through Week 24), secondary and other efficacy variables defined in the statistical analysis plan were updated after finalization of Protocol Amendment 2 and are the variables presented, and include the following:

Efficacy:

The primary endpoint for US/Food and Drug Administration (FDA) regulatory purposes is the proportion of subjects achieving ACR20 response (ACR20) at Week 12. The primary endpoint for European Union (EU)/European Medicines Agency (EMA) regulatory purposes is the proportion of subjects achieving Low Disease Activity (LDA) based on disease activity score 28 (DAS28) (C-reactive protein [CRP]) $\leq$ 3.2 at Week 12.

Ranked key secondary endpoints (at Week 12) for US/FDA regulatory purposes were: 1) change from baseline in DAS28 (CRP); 2) change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI); 3) LDA as measured by DAS28 (CRP); 4) change from baseline in Short Form-36 (SF-36) physical component summary (PCS).

Ranked key secondary endpoints (at Week 12) for EU/EMA regulatory purposes were: 1) change from baseline in DAS28 (CRP); 2) ACR20 response rate; 3) change from baseline in HAQ-DI; 4) change from baseline in SF-36 PCS.

Other key secondary endpoints (at Week 12, if not specified) for both US/FDA and EU/EMA regulatory purposes were: 1) proportion of subjects achieving ACR 50 response (ACR50) rate; 2) proportion of subjects achieving ACR 70 response (ACR70) rate; 3) proportion of subjects achieving ACR20 response at Week 1.

Additional efficacy analyses included the following endpoints at all visits through Week 24: 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 Clinical Disease Activity Index (CDAI) and Simple Disease Activity Index (SDAI); change from baseline in morning stiffness (severity and duration); proportion of subjects achieving LDA and proportion of subjects achieving clinical remission (CR) based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria; proportion of subjects achieving change from baseline in HAQ-DI ≤ -0.3 among those with baseline HAQ DI $\geq$ 0.3 and post-hoc, the proportion of subjects with change from baseline in HAQ-DI ≤ -0.22; ACR/EULAR Boolean remission; and the following endpoints at Weeks 4, 12 and 24: change from baseline in EuroQoL-5D-5L; change from baseline in Insomnia Severity Index (ISI); change from baseline in SF-36.

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

Criteria for Evaluation (Continued)

Safety:

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

Statistical Methods

Efficacy:

Primary Endpoint: Comparison of the primary endpoint was made between each upadacitinib dose group and the combined placebo groups using the Cochran-Mantel-Haenszel test adjusted for main stratification factors. For the primary analysis, Non-Responder Imputation (NRI) was used. The analysis was repeated using Observed Cases (OC). 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 Endpoints: For binary endpoints, frequencies and percentages were reported for each treatment group. Similar analyses as for the primary endpoint were conducted. For the major RA continuous endpoints DAS28 and HAQ-DI change from baseline at Week 12, statistical inference was conducted using analysis of covariance (ANCOVA) coupled with multiple imputation (MI) for missing data handling. Specifically, the ANCOVA model was to include treatment as the fixed factor, and the corresponding baseline value and the stratification factor prior bDMARD use (Stratum 1: failed 1 or 2 biologics with the same mechanism of action; Stratum 2: failed $\geq$ 3 prior bDMARDs with the same mechanism of action and/or multiple mechanisms of action) as the covariates. For other continuous endpoints, statistical inference was conducted using the Mixed Effect Model Repeat Measurement (MMRM) model with fixed effects of treatment, visit and treatment by-visit interaction, prior bDMARD use (stratum 1/stratum 2), and baseline value as covariate. For both the MI and MMRM analyses, the least square (LS) mean and 95% confidence interval (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 each upadacitinib dose group with the combined placebo group. Both nominal p value and adjusted p-value through the graphical multiplicity procedure were to be provided.

Additional Efficacy Variables: For binary endpoints, point estimate and 95% CI using normal approximation were to be provided for the response rate for each randomized treatment group. Point estimate, 95% CI, and p-value were to be provided for the treatment comparison between each upadacitinib dose group and the combined placebo group using the Cochran Mantel Haenszel test, adjusting for stratification factor of prior bDMARD use. Only nominal p-value was to be provided, and the 95% CI was to be based on normal approximation. NRI was to be used as primary analysis. For continuous endpoints, the 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-values between each upadacitinib dose group and the combined placebo group was to be provided using MMRM model with fixed effects of treatment, visit and treatment by-visit interaction, prior bDMARD use, and baseline value as covariate. Only nominal p-value was to be provided.

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. 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 (MedDRA) 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 safety data were not imputed.

Summary/Conclusions

Efficacy Results:

In this blinded, placebo-controlled period, upadacitinib at doses of 15 mg and 30 mg QD with a background of csDMARD therapy for 12 weeks was effective in the treatment of subjects with moderately to severely active RA who have had an inadequate response or intolerance to at least 1 bDMARD. The study met its primary endpoints at Week 12, with a highly statistically significantly greater percentage of subjects achieving an ACR20 response in both the upadacitinib 15 mg and 30 mg groups compared with the placebo group. Similarly, a highly statistically significantly greater proportion of subjects in both the upadacitinib 15 mg and 30 mg groups achieved LDA based on DAS28 (CRP) $\leq$ 3.2 compared with the placebo group. The study also met all ranked and other key secondary endpoints with high statistical significance in the upadacitinib dose groups compared with the placebo group, with the exception of ACR70 in the upadacitinib 15 mg group at Week 12. Notably, a similar proportion of subjects originally assigned to placebo who switched to upadacitinib 15 mg at Week 12 achieved ACR70 at Week 24 compared to the ACR 70 response rate at Week 12 among those initially randomized to upadacitinib 30 mg. Continued improvement beyond Week 12 was also demonstrated with the majority (> 50%) of subjects in both upadacitinib dose groups achieving LDA based on DAS28 (CRP) at Week 24.

Rapid onset of efficacy was noted with both upadacitinib doses achieving statistical significance for several efficacy variables as early as Week 1, and improvement was sustained through Week 12. For subjects who were on upadacitinib 15 or 30 mg from baseline through Week 24, efficacy response was either maintained or further improved. Efficacy results in this study were consistent with those observed in the Phase 2 study (Study M13-550), in a similar population.

Pharmacokinetic Results:

Within the 24-hour dosing interval, the mean plasma concentrations for upadacitinib ranged from 6.48 ng/mL to 37.3 ng/mL for subjects who received upadacitinib 15 mg QD (whether from the start of the study or switching from placebo) and from 12.1 ng/mL to 66.4 ng/mL for subjects who received upadacitinib 30 mg QD (whether from the start of the study or switching from placebo). The observed upadacitinib concentrations were consistent with the predicted concentrations based on prior pharmacokinetic evaluations of upadacitinib.

Safety Results:

In this blinded, placebo-controlled study treatment with upadacitinib for 12 weeks and through 24 weeks of continued blinded treatment, upadacitinib at doses of 15 mg and 30 mg was generally well tolerated as assessed by the frequency of TEAEs, including serious adverse events (SAEs), adverse events of special interest (AESIs), clinical laboratory values, and vital signs values.

Summary/Conclusions (Continued)

Safety Results (Continued):

Through Week 24, 2 deaths were reported in the study: 1 subject in the upadacitinib 15 mg group with a cause of death reported as cardiac arrest (adjudicated to undetermined/unknown) and 1 subject in the upadacitinib 30 mg group with a cause of death of pulmonary embolism and cardiac failure (adjudicated to non-cardiovascular death). Both deaths were assessed as having no reasonable possibility of being related to study drug.

Through Week 12 the most frequently reported TEAEs (≥ 5% of subjects in any treatment group) were upper respiratory tract infection, nasopharyngitis, urinary tract infection, and rheumatoid arthritis. The most frequently reported TEAEs through Week 24 were the same as through Week 12, with the addition of headache.

Through Week 12, the percentage of subjects with TEAEs leading to discontinuation of study drug was higher in the upadacitinib 30 mg group (9.1%) than in the upadacitinib 15 mg (2.4%) and placebo (5.3%) groups. Through Week 24, the rate of TEAEs leading to discontinuation of study drug continued to be higher in the upadacitinib 30 mg (31.5 events [E]/patient-years [PY]) compared with the upadacitinib 15 mg group (19.2 E/PY).

Through Week 12, the percentage of subjects with SAEs was higher in the upadacitinib 30 mg group (7.3%) compared with the upadacitinib 15 mg group (4.9%) and there were no SAEs reported in the placebo group. Similarly, through Week 24, the rate of SAEs was higher in the upadacitinib 30 mg group (33.8 E/100 PY) compared with the upadacitinib 15 mg group (28.2 E/100 PY).

Through Week 12, the frequency of AESIs in the upadacitinib groups was generally similar compared with the placebo group, with the exception of serious infection, neutropenia, and blood creatine phosphokinase (CPK) elevation, which were reported by a higher percentage of subjects in the upadacitinib groups. Through Week 12, no subject in any treatment group had treatment emergent non-melanoma skin cancer (NMSC), lymphoma, gastrointestinal (GI) perforation, renal dysfunction, or active/latent tuberculosis (TB). Through Week 12, herpes zoster infections were reported in 6 subjects. All events of herpes zoster were considered by the investigator to have a reasonable possibility of being related to study drug with the exception of the event of herpes zoster in the placebo group. Two events of herpes zoster in the upadacitinib 30 mg group were serious. Oral candidiasis was the only treatment emergent opportunistic infection reported through Week 12 (1 subject in the upadacitinib 15 mg group and 2 subjects in the upadacitinib 30 mg group). Through Week 12, there were 3 cases of malignancies: 1 subject in the upadacitinib15 mg group had malignant melanoma in situ (Day 82), and 2 subjects in the upadacitinib 30 mg group had a treatment-emergent malignancy of prostate cancer (Day 8 and Day 84). The percentage of drug-related hepatic disorders was similar across the treatment groups. Through Week 12, there was a single major adverse cardiovascular event (MACE) of non-fatal stroke in a subject who received upadacitinib 15 mg, which was reported by the investigator as having no reasonable possibility of being related to study drug. This subject had cardiovascular risk factors at study entry. AESIs also included abnormal labs reported by investigators as TEAEs. Through Week 12, there were no TEAEs of anemia. Equal numbers of subjects had TEAEs of lymphopenia across all treatment groups: 2 subjects each for upadacitinib 15 mg, 30 mg, and placebo groups. Through Week 12, TEAEs of neutropenia and blood CPK elevation were only reported in the upadacitinib groups. No subject had rhabdomyolysis or discontinued study drug due to a TEAE of blood CPK elevation.

Summary/Conclusions (Continued)

Safety Results (Continued):

Safety data through Week 24 analyzed as events per 100 PY showed that the rates of serious infection, hepatic disorder, neutropenia, herpes zoster, anemia, and blood CPK elevation appeared to be dose-dependent. The rates of any malignancy other than NMSC, rates of GI perforation, and rates of lymphopenia were similar for subjects in the upadacitinib 15 mg and 30 mg groups. Through Week 24, no subject in any treatment group had treatment emergent NMSC, lymphoma, or active/latent TB. Through Week 24, the rate of serious infections was higher in the upadacitinib 30 mg group than in the 15 mg group (8.2 E/100 PY vs 4.5 E/100 PY). Through Week 24, serious herpes zoster was reported in 2 subjects in the upadacitinib 30 mg group; both had ophthalmic involvement and one case involved multiple dermatomes. There was 1 additional event of opportunistic infection from Week 12 through Week 24 which was an event of mucocutaneous candidiasis (upadacitinib 30 mg). Between Week 12 and Week 24 one additional treatment emergent malignancy of bladder cancer was reported in a subject in the upadacitinib 15 mg group. There was a higher rate of non-serious hepatic disorder reported in the upadacitinib 30 mg group (21.0 E/100 PY) compared with the upadacitinib 15 mg group (7.9 E/100 PY). Through Week 24, there was 1 serious event of GI perforation in the upadacitinib 30 mg group which was life-threatening in severity. Through Week 24, 3 events of renal dysfunction were reported in the upadacitinib groups only. There were 3 additional adjudicated cardiovascular events from Week 12 to Week 24: 2 subjects in the upadacitinib 15 mg group (coronary artery disease [adjudicated to cardiovascular procedure] and cardiac arrest [adjudicated to undetermined/unknown] which resulted in death) and 1 subject in the upadacitinib 30 mg group (non-fatal myocardial infarction). Subjects with adjudicated cardiovascular events had cardiovascular risk factors at study entry.

Two subjects had events coded to the preferred term pulmonary embolism through Week 12 (1 in the 15 mg and 1 in the 30 mg dose group); no pulmonary embolism or deep vein thrombosis events were observed during treatment with placebo. Between Week 12 and Week 24, 4 more events coded to the preferred term pulmonary embolism were reported in subjects during upadacitinib treatment. These 6 events were retrospectively adjudicated in a blinded fashion after database lock for Period 1. The Cardiovascular Adjudication Committee (CAC) determined that 4 of these events were confirmed pulmonary embolism events: 1 event was determined by the CAC to have insufficient evidence to be a confirmed pulmonary embolism and 1 event was considered by the CAC to be not assessable with the available information and was adjudicated to non-cardiovascular death.

For AESIs of abnormal labs, the rate of events of anemia was higher in the upadacitinib 30 mg group (8.2 E/100 PY) compared with the upadacitinib 15 mg group (4.5 E/100 PY). Through Week 24, neutropenia was reported in the upadacitinib groups only, while the rate of lymphopenia was higher in the placebo group. Through Week 24, blood CPK elevation was reported in the upadacitinib groups only; no subject had rhabdomyolysis or discontinued study drug due to a TEAE of blood CPK elevation.

Among subjects with TEAEs of lymphopenia or neutropenia, no subject discontinued study drug due to these TEAEs.

Summary/Conclusions (Continued)

Safety Results (Continued):

Through Week 12 and through Week 24, group mean values for key hematology variables (hemoglobin, hematocrit, lymphocytes, neutrophils, platelets, and IgM and IgG) were generally within the normal reference range at baseline and at all visits for the upadacitinib and placebo groups. Through Week 12, 4 subjects (1 each in 15 mg and placebo and 2 in 30 mg) had Grade 3 or 4 hemoglobin values that were decreased at ≥ 2 time points during the treatment period. Through Week 24, the number of subjects with Grade 3 decreases in neutrophil values were comparable in the upadacitinib 30 mg group (5 subjects, 2.1%, each) and the upadacitinib 15 mg group (3 subjects, 1.3%). Two subjects in the upadacitinib 15 mg group each had a decrease in neutrophil value that was Grade 4. Of these 10 subjects with Grade 3 or Grade 4 decreases in neutrophil values, 3 subjects in the upadacitinib 15 mg group had Grade 3 or 4 values at ≥ 2 time points during the treatment period.

Grade 3 increases in blood CPK values were reported in 3 subjects who received upadacitinib (1 in 15 mg and 2 in 30 mg). One subject in the upadacitinib 30 mg group had a Grade 4 increase in blood CPK. None had rhabdomyolysis. Few subjects had increases in ALT or AST values that were Grade 3 or Grade 4. No subject had an increase in serum creatinine value that was Grade 3 or Grade 4. No Grade 3 or 4 increases in serum creatinine were observed in any subjects who received upadacitinib. Greater increases in both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed with upadacitinib treatment compared with placebo.

Mean changes from baseline to Week 12 and through Week 24 for vital signs in all the upadacitinib groups were not considered to be clinically meaningful compared with placebo.

Conclusions:

Through Week 12 of Study M13-542, superiority was consistently demonstrated for upadacitinib 15 mg and 30 mg QD versus placebo for both clinical responses and patient-reported health outcome results in subjects with moderately to severely active RA who were on a stable dose of csDMARDs and have had an inadequate response or intolerance to at least 1 bDMARD. The benefit:risk profile of both doses of upadacitinib is assessed as favorable based on review of the efficacy and safety results.

Date of Report: 23Jul2018

Protocol Changes

At the time of the data cutoff for this Period 1 clinical study report, the original protocol (21 January 2016, 3 subjects enrolled) had 2 global amendments and 9 country-specific amendments. The majority of changes to the protocol were responses to regulatory feedback, clarifications and editorial changes. The amendments, number of subjects enrolled under each amendment, country-specific protocol changes, substantial protocol changes were as follows:

- Amendment 1 (29 February 2016, 427 subjects enrolled) included revisions to the inclusion criteria to clarify requirements of pregnancy testing and women of childbearing potential, to avoid ambiguity regarding RA classification criteria. Text was added to clarify contraception requirements for background RA medication and follicle stimulating hormone (FSH) testing for females, including adding countries with local requirements. Criteria were added for adjusting or adding background medication at Week 24 if subjects did not achieve LDA as defined by CDAI. Text was added to clarify tuberculosis (TB) assessment and testing, ECG procedures, and the CDAI calculation. Preliminary results from ongoing relative bioavailability and Phase 2 studies were added.
- Amendment 1.01 (Sweden only) (06 May 2016, 3 subjects enrolled) was updated to include information of potential risks and benefits from the Investigator Brochure and discontinuation criteria language to Period 2. Discontinuation criteria for subjects were revised to reflect LDA as stopping criterion at Week 48/52 for subjects who have been exposed to bDMARDs from < 2 distinct mechanisms of action (MOA). Clarified stopping criteria for the remainder of the subjects.
- Amendment 1.02 (France only) (09 May 2016, 5 subjects enrolled) updated the study duration for Period 2 from 216 weeks to 24. Text was clarified to state that subjects who develop any malignancy were to be discontinued from study drug. Exclusion criteria were updated to remove "except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix" to clarify target group. Serum pregnancy test was added to be done at Baseline visit. Removed text regarding annual TB

testing and chest x-ray every 48 weeks. Deleted "every 48 weeks thereafter" for 12-Lead electrocardiogram (ECG).

- Amendment 1.03 (Denmark only) (16 June 2016, 0 subjects) updated study duration for Period 2 from 216 weeks to 96 weeks and clarified Week 120 as the final visit.
- Amendment 2 (10 October 2016, 60 subjects) was updated to clarify that there were different primary efficacy variables for different regulatory purposes. Revisions updated inclusion criteria text to accommodate geographic differences in MTX dosing, to remove failure of csDMARDs, and to be more in line with expected pharmacodynamics of these drugs and standard practice. Revisions were made to the exclusion criteria to clarify the highest risk for gastrointestinal (GI) perforation with interleukin (IL)-6 and JAK inhibitors is for the lower GI tract, to update laboratory values within the screening period to reflect normal laboratory value reference ranges in the elderly population, and to reflect lack of QTc prolongation with upadacitinib. Guidance text was provided for washout of csDMARDs and permitted background RA therapy. Traditional Chinese medicine was added as prohibited. ECG and in vivo biomarkers at the final/premature discontinuation visit were added to the schedule of activities.
- Amendment 2.01 (Sweden only) (26 October 2016, 1 subject enrolled) was updated clarify that there were different primary efficacy variables for different regulatory purposes. Revisions updated inclusion criteria text to accommodate geographic differences in MTX dosing, to remove failure of csDMARDs, and to be more in line with expected pharmacodynamics of these drugs and standard practice. Revisions were made to the exclusion criteria to clarify the highest risk for GI perforation with IL-6 and JAK inhibitors is for the lower GI tract, to update laboratory values within the screening period to reflect normal laboratory value reference ranges in the elderly population, and to reflect lack of QTc prolongation with upadacitinib. Guidance text was provided for washout of csDMARDs and permitted background RA therapy. Oral traditional Chinese medicine was added as prohibited medication. Updated text regarding the selection of doses in the study with more recent data from the Phase 1 study. Added creatine phosphokinase (CPK) eCRF to

be completed as appropriate. Added that ECG and in vivo biomarkers will be done at final/premature discontinuation visit.

- Amendment 2.02 (France only) (26 October 2016, 0 subjects enrolled) was updated clarify that there were different primary efficacy variables for different regulatory purposes. Revisions updated inclusion criteria text to accommodate geographic differences in MTX dosing, to remove failure of csDMARDs, and to be more in line with expected pharmacodynamics of these drugs and standard practice. Revisions were made to the exclusion criteria to clarify the highest risk for GI perforation with IL-6 and JAK inhibitors is for the lower GI tract, update laboratory values within the screening period to reflect normal laboratory value reference ranges in the elderly population, and to reflect lack of QTc prolongation with upadacitinib. Guidance text was provided for washout of csDMARDs and permitted background RA therapy. Oral traditional Chinese medicine was prohibited. Updated text regarding the selection of doses in the study with more recent data from the Phase 1 study. A CPK eCRF was added to be completed, as appropriate. ECG and in vivo biomarkers at the final/premature discontinuation visit were added to the schedule of activities.
- Amendment 2.03 (Denmark only) (26 October 2016, 0 subjects enrolled) was updated clarify that there were different primary efficacy variables for different regulatory purposes. Revisions updated inclusion criteria text to accommodate geographic differences in MTX dosing, to remove failure of csDMARDs, and to be more in line with expected PD of these drugs and standard practice. Revisions were made to the exclusion criteria to clarify the highest risk for GI perforation with IL-6 and JAK inhibitors is for the lower GI tract, update laboratory values within the screening period to reflect normal laboratory value reference ranges in the elderly population, and to reflect lack of QTc prolongation with upadacitinib. Guidance text was provided for washout of csDMARDs and permitted background RA therapy. Oral traditional Chinese medicine was prohibited. Updated text regarding the selection of doses in the study with more recent data from the Phase 1 study. CPK eCRF was added to be completed as appropriate. ECG and in vivo biomarkers at the final/premature discontinuation visit were added to the schedule of activities.

- Amendment 2.02.01 (France only) (09 December 2016, 0 subjects) added text to provide clarification of hepatic and renal AE collection.
- Amendment 2.02.02 (France only) (18 April 2017, 0 subjects enrolled) extended the observation period from 48 weeks to 144 weeks in order to allow continued treatment with study drug.
- Amendment 2.02.03 (France only) (21 June 2017, 0 subjects) extended the observation period from 48 weeks to 120 weeks in order to allow continued treatment with study drug.

The original protocol and protocol amendments are provided in Appendix 16.1__1.

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

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