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) Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX

Coordinating Investigator: Manish Jain, MD

Study Sites: 138 study sites located in 24 countries (Argentina, Austria, Belgium, Bulgaria, Chile, Czech Republic, Estonia, Greece, Hungary, Israel, Italy, Japan, Mexico, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, South Africa, Spain, Turkey, Ukraine, United States)

Publications: None

Studied Period (Years): First Subject First Visit: 23 March 2016 Last Subject Last Visit: 02 October 2017 (Period 1)	**Phase of Development:** 3

Objectives:

The study objective of Period 1 of this study was to compare the safety and efficacy (signs and symptoms) of upadacitinib 30 mg once daily (QD) alone and 15 mg QD alone versus continuing MTX alone in MTX-inadequate response subjects with moderately to severely active rheumatoid arthritis (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 only.

Methodology:

This is a Phase 3 multicenter study that includes 2 periods. Period 1 was a 14-week, randomized, double-blind, parallel-group, controlled treatment period designed to compare the safety and efficacy of upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX alone for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX). 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 have completed Period 1.

The study duration was to include a 35-day screening period; a 14-week randomized, double-blind, parallel-group, controlled treatment period (Period 1); a 226-week blinded extension period (Period 2); and a 30-day follow-up visit.

Methodology (Continued):

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 = 200) (Period 1) → upadacitinib 30 mg QD (Period 2)

Group 2: upadacitinib 15 mg QD (N = 200) (Period 1) → upadacitinib 15 mg QD (Period 2)

Group 3: MTX (N = 100) (Period 1) → upadacitinib 30 mg QD (Period 2)

Group 4: MTX (N = 100) (Period 1) → upadacitinib 15 mg QD (Period 2)

Prior to enrollment, subjects should have been receiving oral or parenteral MTX therapy ≥ 3 months and on a stable dose (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week [For subjects in Japan: MTX 7.5 to 16 mg/week]) for at least 4 weeks. No MTX washout was needed prior to randomization. All subjects were to have started on their blinded upadacitinib (15 mg QD, 30 mg QD or placebo QD) dose at Baseline. Also, starting at Baseline, all subjects were to have discontinued their current MTX treatment and started their blinded MTX treatment. Subjects were to be given oral MTX in a blinded manner (7.5 to 25 mg/week and/or placebo) based on the subject's prior stable dose of MTX. Subjects who were on a stable dose of MTX between 10 and < 15 mg/week at study entry were to be assigned to MTX 10 mg/week at randomization. For all other doses of MTX, subjects were to be assigned to blinded MTX based on their prior stable MTX dose at study entry. For subjects in Japan, if stable dose was 8, 10 or 12, or 14 or 16 mg/week, then subjects were assigned to 7.5, 10, or 15 mg/week MTX, respectively. In addition, all subjects should have taken a dietary supplement of folic acid (or equivalent) throughout Period 1 participation. Folic acid dosing and timing of regimen should have been followed according to investigator's instructions.

Subjects who completed the Week 14 visit (end of Period 1) were to enter the blinded long-term extension portion of the study, Period 2 (226 weeks).

Number of Subjects (Planned and Analyzed): Planned: 600 subjects; Analyzed: 648 (432 upadacitinib, 216 MTX)

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, but were able to tolerate ≥ 15 mg of weekly oral MTX or ≥ 10 mg/week in subjects who were intolerant of MTX at doses ≥ 12.5 mg/week. Local guidelines for MTX dosage may have applied. 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 level ≥ 3 mg/L (central lab) at Screening.

Subjects were excluded if they had prior exposure to any Janus kinase inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib) or any biologic disease-modifying anti-rheumatic drug; 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 × 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 15 mg extended-release tablets for oral administration (bulk lot number: 15-005423, 15-005421, 15-006834, 16-005072, 15-006832, 16-001357)

Upadacitinib 30 mg extended-release tablets for oral administration (bulk lot number: 15-005425, 15-005424, 15-006954, 16-001431, 15-006955)

Duration of Treatment: Period 1: 14 weeks; Period 2: 226 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
MTX 7.5, 10, 15, 17.5, 20, 22.5, or 25 mg capsule for oral administration (bulk lot number for over-encapsulated MTX capsule: 15-005213, 16-001721, 16-006740, 15-005208, 16-001722, 16-006741; bulk lot number for MTX tablet: 15-004789, 15-004790, 16-004217)

Matching placebo for MTX, capsule for oral administration (bulk lot number: 15-005749, 15-005328)

Matching placebo for upadacitinib, tablet for oral administration (bulk lot number: 15-005362, 15-006982, 16-003281, 16-001360)

Criteria for Evaluation

For Period 1 (through Week 14), secondary and other efficacy variables were updated after finalization of global protocol Amendment 3. The efficacy variables analyzed in the clinical study report are those defined in the statistical analysis plan, which include the following:

Efficacy:

The primary endpoint for US/Food and Drug Administration (FDA) regulatory purposes was the proportion of subjects achieving ACR 20% response (ACR20) at Week 14. The primary endpoint for European Union (EU)/European Medicines Agency (EMA) regulatory purposes was 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 14.

Ranked key secondary endpoints (at Week 14) 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) change from Baseline in Short Form-36 (SF-36) physical component summary (PCS) score; 4) proportion of subjects achieving LDA based on DAS28 (CRP) $\leq$ 3.2; 5) proportion of subjects achieving clinical remission (CR) based on DAS28 (CRP); and 6) change from Baseline in morning stiffness (duration).

Ranked key secondary endpoints (at Week 14) for EU/EMA regulatory purposes were: 1) change from Baseline in DAS28 (CRP); 2) change from Baseline in HAQ-DI; 3) ACR20 response rate; 4) change from Baseline in SF-36 PCS; 5) proportion of subjects achieving CR based on DAS28 (CRP); and 6) change from Baseline in morning stiffness (duration).

Other key secondary endpoints (at Week 14) for both US/FDA and EU/EMA regulatory purposes were: 1) ACR 50% response (ACR50) rate and 2) ACR 70% response (ACR70) rate.

Additional efficacy analysis included the following endpoints at all visits in Period 1: 1) change from Baseline in individual components of ACR response; 2) ACR20/50/70 response rates; 3) change from Baseline in Clinical Disease Activity Index (CDAI) and Simple Disease Activity Index (SDAI); 4) change from Baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]); 5) change from Baseline in morning stiffness (severity and duration); 6) proportion of subjects achieving LDA and proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria; 7) proportion of subjects with change from Baseline in HAQ-DI $\leq$ –0.22; 8) proportion of subjects with change from Baseline in HAQ-DI $\leq$ –0.3; and 9) ACR/EULAR Boolean remission.

Criteria for Evaluation (Continued)

Efficacy (Continued):

Additional efficacy analysis included the following endpoints at Weeks 4 and 14 only: 1) change from Baseline in EuroQoL-5D-5L and 2) change from Baseline in SF-36.

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 Endpoint: Comparisons of the primary endpoint were made between each upadacitinib dose and the combined MTX group using the Cochran-Mantel-Haenszel test adjusting for stratification factor of geographic region. 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 Endpoints: For binary endpoints, frequencies and percentages were reported for each randomized treatment group. Similar analyses as for the primary endpoint were conducted. For the major RA continuous endpoints, and 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 was to include treatment as the fixed factor, and the corresponding Baseline value and the stratification factor of geographic region 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 geographic region. From 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 MTX 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 MTX group using the Cochran-Mantel-Haenszel test adjusting for stratification factor of geographic region. Only the 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 and Observed Cases was to be used as sensitivity 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 MTX group were to be provided using MMRM model with fixed effects of treatment, visit and treatment-by-visit interaction, geographic region, and Baseline value as covariate. Only the nominal p-value was to be provided.

Statistical Methods (Continued)

Pharmacokinetic:

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

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 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:

In this blinded, controlled period, upadacitinib alone at doses of 15 mg and 30 mg QD was more effective than continuing MTX in subjects with moderately to severely active RA with inadequate response to MTX. The study met its primary endpoints at Week 14, 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 continuing MTX (cMTX) group (US/FDA primary endpoint). Comparable results were reported for LDA based on DAS28 (CRP) $\leq$ 3.2 (EU/EMA primary endpoint). The study also met all ranked and other key secondary endpoints with high statistical significance in the upadacitinib dose groups compared with the cMTX group. Numerically higher efficacy was observed for upadacitinib 30 mg as compared to upadacitinib 15 mg across all primary and key secondary endpoints, particularly for the more stringent measures of efficacy (ACR70, LDA, and CR). Rapid onset of efficacy was noted with both upadacitinib doses achieving statistical significance for the majority of efficacy variables as early as Week 2, and improvement was sustained for all visits through Week 14.

Pharmacokinetic Results:

Within the 24-hour dosing interval, the mean plasma concentrations for upadacitinib ranged from 5.61 ng/mL to 38.2 ng/mL for subjects who received upadacitinib 15 mg QD and from 9.43 ng/mL to 73.1 ng/mL for subjects who received upadacitinib 30 mg QD in this study. The observed upadacitinib plasma concentrations were generally consistent with the predicted concentrations for these dose levels based on prior pharmacokinetic evaluations of upadacitinib.

Summary/Conclusions (Continued)

Safety Results:

In this blinded, controlled treatment period, treatment with upadacitinib for 14 weeks at doses of 15 mg and 30 mg QD was well-tolerated as assessed by the frequency of TEAEs, including serious AEs (SAEs), AEs of special interest (AESIs), clinical laboratory values, and vital signs values. The most frequently reported TEAEs (≥ 5% of subjects in any treatment group) were upper respiratory tract infections. One death occurred and was reported by the investigator as resulting from a hemorrhagic stroke due to a ruptured aneurysm (adjudicated by the Cardiovascular Adjudication Committee as cardiovascular death due to hemorrhagic stroke); the investigator assessed the hemorrhagic stroke as having no reasonable possibility of being related to study drug. The percentage of subjects with TEAEs leading to discontinuation of study drug was low across all treatment groups (upadacitinib 15 mg [3.7%], upadacitinib 30 mg [2.8%], and cMTX [2.8%]). The percentage of subjects with SAEs was higher in the upadacitinib 15 mg group (5.1%) compared with the upadacitinib 30 mg and cMTX groups (2.8% each).

In general, the frequency of AESIs was largely comparable across treatment groups, with the exception of neutropenia, herpes zoster, and creatine phosphokinase (CPK) elevation, which were numerically higher in both upadacitinib groups compared to the cMTX group and highest in the upadacitinib 30 mg group. No subject in any treatment group had treatment-emergent gastrointestinal perforation, renal dysfunction, or active or latent tuberculosis. Serious infections were reported by 1 subject in the upadacitinib 15 mg group (limb abscess) and 1 subject in the cMTX group (urosepsis). Nonserious herpes zoster was reported in 3 subjects in the upadacitinib 15 mg, 6 subjects in the upadacitinib 30 mg, and 1 subject in the cMTX groups. Opportunistic infections reported in this period were oral candidiasis (2 subjects in upadacitinib 30 mg group), oropharyngeal candidiasis (1 subject in upadacitinib 30 mg group), and fungal esophagitis (1 subject in cMTX group). The treatment-emergent malignancies reported were breast cancer and non-Hodgkin's lymphoma (1 subject each in the upadacitinib 15 mg group), and basal cell carcinoma of the skin (1 subject in the cMTX group). The events of breast cancer, non-Hodgkin's lymphoma, and basal cell carcinoma were reported on Day 11, Day 98, and Day 102, respectively, relative to the first dose of study drug. Only the event of non-Hodgkin's lymphoma was considered by the investigator to have a reasonable possibility of being related to study drug. Adjudicated cardiovascular events were reported in the upadacitinib dose groups only and included 3 adjudicated major adverse cardiovascular events (cardiovascular death [1 subject in the upadacitinib 15 mg group], and non-fatal myocardial infarction and non-fatal stroke [1 subject each in the upadacitinib 30 mg group]) and a single adjudicated venous thromboembolic event of pulmonary embolism in 1 subject in the upadacitinib 15 mg group with known risk factors (diabetes; hypertension; obesity, body mass index of 44.9, on estrogen therapy at time of event). All adjudicated cardiovascular events were considered by the investigator to have no reasonable possibility of being related to study drug and were attributed to underlying cardiovascular risk factors. All drug-related hepatic disorders were reported to be asymptomatic lab abnormalities, with the exception of 1 nonserious event of hepatic cyst; frequencies of drug-related hepatic disorders were comparable across the treatment groups.

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 neutropenia or blood CPK increased compared with the upadacitinib 15 mg and cMTX groups; TEAEs of blood CPK increased were reported in the upadacitinib dose groups only. No subject discontinued due to a TEAE of neutropenia, lymphopenia, or blood CPK increased.

Summary/Conclusions (Continued)

Safety Results (Continued):

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 the upadacitinib and cMTX groups. At the subject level however, a higher percentage of subjects in the upadacitinib 30 mg dose group compared with the upadacitinib 15 mg and cMTX groups had Grade 3 or Grade 4 decreases in hemoglobin, neutrophil, or lymphocyte values. Three subjects (1 in each treatment group) had Grade 3 decreases in hemoglobin values that occurred at multiple ($\geq$ 2) time points during the treatment period. No subject had a Grade 4 decrease in neutrophil value. Only 1 subject (upadacitinib 30 mg group) had a Grade 4 decrease in lymphocyte value, which occurred at a single time point during the treatment period; no treatment-emergent infectious events were reported by this subject.

Grade 3 increases in blood CPK values were reported in the upadacitinib dose groups only (2 subjects in each group); none of these subjects discontinued the study due to an increased CPK value or had rhabdomyolysis, and all 4 subjects were asymptomatic. No Grade 4 increases in blood CPK were reported. Few subjects had increases in ALT or AST values that were Grade 3, and no Grade 4 ALT or AST values were reported. No subject had an increase in serum creatinine value that was Grade 3 or Grade 4. Treatment-with upadacitinib 15 mg and 30 mg resulted in statistically significant and clinically meaningful mean increases compared with cMTX in low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and total cholesterol. However, the ratios of total cholesterol:HDL-C and LDL-C:HDL-C remained unchanged and were not statistically significant for both the upadacitinib and cMTX groups at Week 14.

Mean changes from Baseline to Week 14 for vital signs in all the upadacitinib dose groups were not considered to be clinically meaningful compared with the cMTX group.

Conclusions:

In Period 1 of Study M15-555, superiority was consistently demonstrated for upadacitinib 15 mg and 30 mg QD alone versus continuing MTX for both clinical responses and patient-reported health outcome results in subjects with moderately to severely active RA who had an inadequate response to MTX. The benefit-risk profile of both doses of upadacitinib as monotherapy is assessed as favorable based on the efficacy and safety results through Week 14 of the study.

Date of Report: 07Jun2018

Protocol Changes

At the time of the data cutoff for this Period 1 clinical study report, the original protocol (01 October 2015, 0 subjects enrolled) had 3 global amendments, 4 country-specific amendments, 5 global administrative changes, and 3 country-specific administrative changes. The majority of changes to the protocol were responses to regulatory feedback, clarifications, and editorial changes.

Administrative Change 1 (04 March 2016), 2 (21 March 2016), 3 (12 April 2016), 5 (05 May 2016), 7 (Voluntary Harmonization Procedure [VHP] countries only) (20 January 2017), and 8 (30 March 2017) were written to update contact information or to make minor administrative corrections. Administrative Change 4 (Japan only) (13 April 2016) was written to clarify the beta-D-glucan testing for Japan. Administrative Change 6 (Japan only) (08 June 2016) was written to clarify the varicella zoster virus testing for Japan.

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

- Amendment 1 (21 January 2016, 0 subjects)
  - Updated the study design and plan to change the duration of Period 1 from to 14 weeks and added a blinded long-term extension (Period 2).
  - Added a 15 mg treatment group.
  - Increased the number of study centers and number of subjects to be enrolled.
  - Described how the blind will be maintained.
  - Added discontinuation procedures.
  - Updated procedures for laboratory samples during the screening period and defined screen failure.
  - Added follow-up procedures.
  - Updated MTX therapy and hsCRP value requirements at Screening.
  - Identified patient questionnaires to be completed.

- Added international normalized ratio (INR) reflex, follicle stimulating hormone, and varicella zoster virus specific immunoglobulin (Ig)G to clinical chemistry lab tests.
- Added requirement that a positive result for Hepatitis B surface antibody requires Hepatitis B virus DNA polymerase chain reaction (PCR) testing (for subjects in Japan only).
- Added testing for varicella zoster virus (for subjects in Japan only).
- Updated randomization and randomization stratification.
- Added language regarding the Week 14 interim analysis.
- Added text to describe the addition of an external DMC.
- Updated the AST or ALT specific toxicity management guidelines.
- 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).

- Amendment 2 (29 February 2016, 283 subjects)
  - Removed all country-specific language for Japan.
  - Updated RA classification criteria serum pregnancy testing requirements.
  - Added criteria for adjusting or adding background medication at Week 26 if subjects do not achieve LDA as defined by CDAI.
- Amendment 2.01 (Japan only) (09 March 2016, 27 subjects)
  - Added Japan-specific inclusion and exclusion criteria.
  - Updated text to reflect revisions implemented with global protocol Amendment 2 (29 February 2016).

- Amendment 2.02 (VHP countries) (27 May 2016, 128 subjects)
  - Revised to require compliance to local label with the concomitant use of MTX.
- Amendment 3 (06 October 2016, 166 subjects)
  - Updated exclusion criteria to reflect normal reference range in the elderly population and the lack of corrected QT interval prolongation with upadacitinib.
  - Added text to follow MTX local label for concomitant treatment contraindications.
- Amendment 3.01 (Japan only) (02 November 2016, 38 subjects)
  - Updated text to reflect revisions implemented with global protocol Amendment 3 (06 October 2016).
- Amendment 3.02 (VHP countries) (04 January 2017, 6 subjects)
  - Updated text to reflect revisions implemented with global protocol Amendment 3 (06 October 2016).

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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