Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Upadacitinib</td></tr>
<tr><td>Name of Active Ingredient:
Upadacitinib</td></tr>
<tr><td colspan="3">Title of Study: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs</td></tr>
<tr><td colspan="3">Coordinating Investigator: Dr. Alan Kivitz</td></tr>
<tr><td colspan="3">Study Sites: 150 sites in 35 countries (Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Kazakhstan, Korea, Latvia, Lithuania, Mexico, New Zealand, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Switzerland, Taiwan, Ukraine, United Kingdom, United States)</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 17 December 2015
Last Subject Last Visit: 21 April 2017 (Period 1)</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives: The study objectives of Period 1 of this study were the following: (1) To compare the efficacy of upadacitinib 30 mg once daily (QD) and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active rheumatoid arthritis (RA) who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs; and to compare the safety and tolerability of upadacitinib 30 mg QD and 15 mg QD versus placebo in subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs.
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.</td></tr>
</table>

Methodology: This was a Phase 3 multicenter study that included two periods. Period 1 was a 12-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 csDMARDs. 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. The study duration was to include a 35-day screening period; a 12-week randomized, double-blind, parallel-group, placebo controlled treatment period (Period 1); a blinded long-term extension period (up to 5 years) (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 = 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: Placebo (N = 100) (Period 1) → upadacitinib 30 mg QD (Period 2)

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

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. Subjects who completed the Week 12 visit (end of Period 1) were to enter the blinded long-term extension portion of the study, Period 2 (up to 5 years).

Number of Subjects (Planned and Analyzed): Planned: 600 subjects (400 upadacitinib, 200 placebo); Analyzed: 661 subjects (440 upadacitinib, 221 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 must have been receiving csDMARD therapy ≥ 3 months and on a stable dose of csDMARD therapy (restricted to methotrexate [MTX], chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide) for ≥ 4 weeks prior to the first dose of study drug. Subjects must have failed at least one of the following: MTX, sulfasalazine, or leflunomide. Subjects with inadequate response to hydroxychloroquine and/or chloroquine were to only be included if they also failed MTX, sulfasalazine, or leflunomide.

Subjects were excluded if they had prior exposure to any Janus kinase inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib); were considered inadequate responders to biological DMARD (bDMARD) therapy; 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 > 2 × upper limit of normal (ULN); serum alanine transaminase > 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 < 850/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, 15-005423, 15-005364, 15-005422, 16-005249)

Upadacitinib 30 mg extended-release tablets for oral administration (bulk lot number: 15-005425, 15-005424, 16-001433, 16-005870)

Duration of Treatment: Period 1: 12 weeks; Period 2: up to 5 years

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Matching placebo, tablets for oral administration (bulk lot number: 15-005362, 16-003281). Note: Placebo film coated tablet bulk lot 16-003281 was part of blinded lot 16-006938, however only the 15 mg bulk lot 16-005249 and 30 mg bulk lot 16-005870 bulk lot portions of blinded lot 16-006938 were shipped to sites and dispensed to subjects.

Criteria for Evaluation

Efficacy:

The primary endpoint for US/Food and Drug Administration (FDA) regulatory purposes is ACR 20% response (ACR20) at Week 12. The primary endpoint for European Union (EU)/European Medicines Agency (EMA) regulatory purposes is 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) change from baseline in Short Form-36 (SF-36) physical component summary score (PCS); 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); 6) proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) $\leq$ 10; 7) change from baseline in morning stiffness (duration); and 8) change from baseline in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F).

Ranked key secondary endpoints (at Week 12) 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); 6) proportion of subjects achieving LDA based on CDAI $\leq$ 10; 7) change from baseline in morning stiffness (duration); and 8) change from baseline in FACIT-F.

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

Criteria for Evaluation (Continued)

Efficacy (Continued):

Additional efficacy analysis included the following endpoints 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); change from baseline in morning stiffness (severity and duration); proportion of subjects achieving LDA and proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria; proportion of subjects achieving minimal clinically important difference in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ -0.3) among those with baseline HAQ-DI ≥ 0.3; ACR/EULAR Boolean remission; change from baseline in EuroQoL-5D-5L; change from baseline in SF-36; change from baseline in FACIT-F; change from baseline in Work Instability Scale for Rheumatoid Arthritis.

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: 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, and DAS28 and HAQ-DI change from baseline, statistical inference was to be 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 (Yes/No) as the covariates. For other continuous endpoints, statistical inference was to be conducted using the Mixed Effect Model Repeat Measurement (MMRM) model, with the main stratification factor being prior bDMARD use (Yes/No). 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.

Statistical Methods (Continued)

Efficacy (Continued):

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 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 and OC 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 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.

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 (PT) 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 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 to csDMARDs. 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 (US/FDA primary endpoint). Similar 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 placebo group. Notably, upadacitinib at both doses was effective in achieving more stringent measures of efficacy (ACR70, LDA, and CR). 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 for all visits through Week 12. Efficacy results in this study were consistent with what was observed in the Phase 2 study (Study M13-537) in a similar population.

Summary/Conclusions (Continued)

Pharmacokinetic Results:

The observed upadacitinib concentrations were consistent with the predicted concentrations based on prior PK evaluations of upadacitinib. Within 24 hours of dosing, upadacitinib mean plasma concentrations ranged from 5.37 to 37.5 ng/mL for 15 mg QD and from 10.5 ng/mL to 80.7 ng/mL for 30 mg QD.

Safety Results:

In this blinded, placebo-controlled period, treatment with upadacitinib for 12 weeks at doses of 15 mg and 30 mg QD was generally well-tolerated as assessed by the frequency of TEAEs, including serious adverse events (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 nausea, nasopharyngitis, upper respiratory tract infection, and headache. There were no deaths reported. The percentage of subjects with TEAEs leading to discontinuation of study drug was higher in the upadacitinib 30 mg group (5.9%) compared with the upadacitinib 15 mg and placebo groups (3.2% each). The percentage of subjects with SAEs was higher in the upadacitinib 15 mg group (4.1%) compared with the upadacitinib 30 mg and placebo group (2.7% and 2.3%, respectively). There were no TEAEs of deep vein thrombosis or pulmonary embolism reported in any treatment group.

In general, the frequency of AESIs was similar between the upadacitinib 15 mg and placebo group, with the exception of neutropenia and asymptomatic creatine phosphokinase (CPK) elevation. The rates of AESIs were numerically higher in the upadacitinib 30 mg group compared with the upadacitinib 15 mg group and placebo group. Treatment-emergent serious infections were reported in 1 subject each for the upadacitinib 15 mg group and placebo group and 3 subjects in the upadacitinib 30 mg group. No subjects in any treatment group had gastrointestinal perforation or active/latent tuberculosis. Nonserious herpes zoster was reported in 3 subjects (1 subject in each treatment group); all were single dermatomes and none were ocular. In addition, a fourth subject in the upadacitinib 30 mg group had an event of varicella zoster virus infection (primary), and 4 days later the subject developed varicella zoster pneumonia.

Opportunistic infections reported in this period were oral candidiasis (2 subjects in upadacitinib 30 mg and 1 subject in placebo) and varicella zoster pneumonia (1 subject in upadacitinib 30 mg). There were 2 cases of malignancies, which were both in the upadacitinib 30 mg group. One subject, who had a medical history of basal cell and squamous cell cancer, had a TEAE of basal cell carcinoma during the study, and the other subject was reported to have had B-cell small lymphocytic lymphoma and chronic lymphocytic leukemia. Adjudicated cardiovascular events included a single major adverse cardiovascular event of non-fatal stroke in a subject who received 30 mg upadacitinib.
Two other adjudicated non-MACE cardiovascular events included a subject with cardiovascular procedures (percutaneous coronary intervention) and a subject who was hospitalized for congestive heart failure; both subjects received upadacitinib 15 mg. All adjudicated cardiovascular events, except congestive heart failure, were reported as having no reasonable possibility of being related to study drug. All 3 subjects had cardiovascular risk factors at study entry. All drug-related hepatic disorders were reported to be asymptomatic lab abnormalities and the percentage was similar across the treatment groups.

Summary/Conclusions (Continued)

Safety Results:

AESIs also included abnormal labs reported by investigators as TEAEs (anemia, neutropenia, lymphopenia, and blood CPK increased). Overall, the upadacitinib 30 mg group had a higher percentage of subjects with lymphopenia and neutropenia compared with the upadacitinib 15 mg and placebo groups. Among subjects with TEAEs of lymphopenia or neutropenia, only 1 subject (upadacitinib 30 mg) discontinued study drug due a TEAE of lymphopenia. TEAEs of blood CPK increased (all asymptomatic) was reported in the upadacitinib dose groups only; no subjects had rhabdomyolysis due to a TEAE of blood CPK increased.

In general, group mean values for key hematology variables (hemoglobin, hematocrit, lymphocytes, neutrophils, platelets, immunoglobulin M and immunoglobulin G) were within the normal reference range at baseline and at all visits for the upadacitinib and placebo groups. At the subject level however, a higher percentage of subjects in the upadacitinib dose groups compared with the placebo group had Grade 3 or Grade 4 decreases in hemoglobin, neutrophil, or lymphocyte values, or increases in blood CPK values. Among subjects with Grade 3 or Grade 4 decreases in hemoglobin values, approximately half of these subjects had hemoglobin values that remained within the normal range. Four subjects (2 each in 15 mg and placebo) had Grade 3 or 4 hemoglobin values that were decreased at $\geq$ 2 time points during the treatment period. Only 1 subject, who was in the upadacitinib 15 mg group, had a decrease in neutrophil value that was Grade 4; no associated clinical events (infections) were reported around the time of neutropenia. Of the subjects with Grade 4 lymphocyte values who received upadacitinib, 3 subjects had infectious events (herpes simplex, upper respiratory tract infection, and viral infection) around the onset of lymphopenia.

No subjects with Grade 3 or Grade 4 increases in blood CPK had rhabdomyolysis or any clinical signs or symptoms of muscle toxicity, and no subject discontinued study due to an increased CPK value. A subject (30 mg) had a Grade 2 CPK elevation on Day 85 that was accompanied with muscle pain and muscle weakness; the investigator attributed the CPK elevation to an acute illness (respiratory tract viral infection), which also occurred on Day 85. Few subjects had increases in alanine aminotransferase or aspartate aminotransferase values that were Grade 3 or Grade 4. No subjects had an increase in serum creatinine value that was Grade 3 or Grade 4. Treatment with upadacitinib 15 mg and 30 mg resulted in statistically significant and clinically meaningful mean increases compared with placebo in low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and cholesterol. However, the ratio of total cholesterol:HDL-C and LDL-C:HDL-C remained unchanged through Week 12 and were not statistically significant for both the upadacitinib and placebo groups.

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

Conclusions:

In Period 1 of Study M13-549, 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 had an inadequate response to csDMARDs. 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: 01Mar2018

Protocol Changes

The original protocol (30 September 2015, 4 subjects) had 3 global amendments and 7 country-specific amendments during Period 1. 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 (11 December 2015, 183 subjects)
  - Updated the study design to add a blinded long-term extension (Period 2).
  - Revised inclusion criteria: Clarified requirements for subjects who had been receiving csDMARD therapy prior to study entry. Provided acceptable csDMARDS and dose requirements for inclusion. Modified dose requirement of MTX for inclusion. Updated hsCRP value requirement at screening. Updated contraception requirements for females and males.
  - Added the following exclusion criteria: subjects who are considered inadequate responders to bDMARD therapy; 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 received an organ transplant; and subjects who had clinically relevant or significant ECG abnormalities.
  - Added an interim data analysis after the completion of Period 1.
- Amendment 0.01 (Canada only) (06 January 2016, 0 subjects)
  - Implemented country-specific contraception requirements and updated to reflect revisions implemented with global protocol Amendment 1 (11 December 2015).
- Amendment 1.01 (Korea only) (15 March 2016, 2 subjects)
  - Implemented country-specific contraception requirements per Korea regulatory requirements. Additionally, chloroquine was removed as a potential background csDMARD as it is not available in Korea.

- Amendment 2 (01 April 2016, 453 subjects)
  - Addition of CDAI calculation at Week 24 to determine LDA.
  - Clarified that starting at Week 24, subjects who do not show 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits should discontinue study drug.
- Amendment 1.01.01 (Korea only) (07 April 2016, 0 subjects)
  - Added additional information regarding the SAP in Period 1 at the request of the Korean Competent Authority.
- Amendment 1.02 (France only) (20 April 2016, 2 subjects)
  - Updated study duration for Period 2 from up to 5 years to 36 weeks.
- Amendment 2.01 (Korea only) (23 May 2016, 11 subjects)
  - Revised inclusion criterion specific for Korea to allow 10 mg MTX per week and updated to reflect revisions implemented with global protocol Amendment 2 (01 April 2016)
- Amendment 2.02 (Canada only) (01 June 2016, 6 subjects)
  - Incorporated revisions implemented with global protocol Amendment 2 (01 April 2016)
- Amendment 3 (31 March 2017, 0 subjects)
  - Revised contraception recommendations for males including sperm donation time frame and clarified follicle-stimulating hormone testing requirements for females.
  - Added/updated key secondary endpoints, additional endpoints.
  - Updated statistical sections for accuracy and clarity.
  - Incorporated Canada and Korea country-specific requirements.
- Amendment 3.01 (France only) (14 April 2017, 0 subjects)
  - Incorporated applicable revisions implemented with global protocol Amendment 2 (01 April 2016) and 3 (31 March 2017).

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.

List of Investigators and Sites

Investigator Name	Site Name/Post Office Address
Ali, Mohammad	Comprehensive Rheumatology Care Suite 201A 353 New Shackle Island Road HENDERSONVILLE, TN 37075 United States
Alper, Jeffrey	Jeffrey Alper MD Research 689 Ninth Street North NAPLES, FL 34102 United States
Amin, Mona	Arizona Research Center, Inc. Suite 114 2525 W. Greenway Road PHOENIX, AZ 85023 United States
Antolini, Christopher	Denver Arthritis Clinic, PC Suite 100 200 Spruce Street DENVER, CO 80230 United States
Bagga, Hanish	Coffs Clinical Trials Suite 1 18-20 Scarba street COFFS HARBOR, NSW 2450 Australia
Baraf, Herbert	The Center for Rheumatology & Bone Research Suite 306 2730 University Boulevard West WHEATON, MD 20902 United States
Baravalle, Marcos	Instituto Rheumatologic Strusberg Av. Olmos 247 - 1st floor CORDOBA, X5000EDC Argentina

Investigator Name	Site Name/Post Office Address
Bazela, Barbara	NZOZ Centrum Reumatologiczne Indywidualna Specjalistyczna Praktyka Lekarska Lek. Med. Barbara Bazela ul. Gdynska 51 ELBLAG, 82-300 Poland
Bennett, Ralph	Arizona Arthritis & Rheumatology Research, PLLC Suite 1704550 East Bell Road PHOENIX, AZ 85032 United States
Bessette, Louis	Groupe de Recherche en Maladies Osseuses (GRMO Inc.) Suite 101 1200 Avenue de Germain-des-Pres QUEBEC CITY, QC G1V 3M7 Canada
Bilusic, Marinko	Poliklinika Bonifarm Hondlova 2/10 ZAGREB, 10000 Croatia
Bortlik, Ladislav	Artroscan s r.o. Trebovicka 5114/106 OSTRAVA-TREBOVICE, 722 00 Czech Republic
Bozic-Majstorovic, Ljubinka	Univiversity Clinical Centre of the Republic of Srpska Republic of Srpska Dvanaest beba bb BANJA LUKA, 78000 Bosnia And Herzegovina
Chernykh, Tatiana	Voronezh State Medical University n.a. N.N. Burdenko 10, Studencheskaya str. VORONEZH, 394036 Russian Federation
Choe, Jung-Yoon	Daegu Catholic University Medical Center 33 Duryugongwon-ro 17-gil, Namgu DAEGU, 42472 Korea, Republic Of

Investigator Name	Site Name/Post Office Address
Churchill, Melvin	Physician Research Collaboration, LLC Suite 120 3901 Pine Lake Road LINCOLN, NE 68516 United States
Codding, Christine	Health Research of Oklahoma Suite 409 1211 North Shartel Avenue OKLAHOMA CITY, OK 73103 United States
Covarrubias-Cobos, Jose	Centro Peninsular de Investigacion Clinica S.C.P. (CEPIC) Calle 56 numero 344 depto 29, entre calle 35 y Av. Perez Ponce Colonia Centro, Merida YUCATAN, 97000 Mexico
Craig, Gary	Arthritis Northwest, PLLC Suite 6080/7030 105 West 8th Avenue SPOKANE, WA 99204 United States
Cush, John	Baylor Research Institute Arthritis Care and Research Center Suite 550 9900 North Central Expressway DALLAS, TX 75231 United States
Daikh, Brian	Rheumatology Associates, PA 51 Sewall Street PORTLAND, ME 04102 United States
DeJesus, Alex	Accurate Clinical Research, Inc. Suite 135 7959 Fredricksburg Road SAN ANTONIO, TX 78229 United States

Investigator Name	Site Name/Post Office Address
Devinck, Mieke	AZ Sint Lucas AZ Sint Lucas VZW Sint-Lucaslaan, 29 ASSEBROEK, 8310 Belgium
Dobrovodsky, Pavol	REUMA-GLOBAL, s r.o. Reumatologicka ambulancia Starohajska 2 TRNAVA, 91701 Slovakia
Dore, Robin	Robin K. Dore MD, Inc Suite 201 12791 Newport Avenue TUSTIN, CA 92780 United States
Dudler, Jean	HFR Fribourg – Hôpital Cantonal Service de Rhumatologie Chemin des Pensionnats 2-6 FRIBOURG, 1708 Switzerland
Edwards, Christopher	Southampton General Hospital NHS Foundation Trust Southampton Centre for Biomedical Research Tremona Road, Shirley SOUTHAMPTON, SO16 6YD United Kingdom
Edwards, William	Low Country Rheumatology, PA 2860 Tricom Street CHARLESTON, SC 29406 United States
Fasching, Peter	Wilhelminenspital der stadt Wien 5. Medizinische Abteilung Montleartstrasse 37 VIENNA, 1160 Austria

Investigator Name	Site Name/Post Office Address
Fenton, Ira	Deerbrook Medical Associates Suite 116 565 Lakeview Parkway VERNON HILLS, IL 60061 United States
Fernandez, Antonio	Hospital Regional Universitario de Malaga Unidad de Investigacion, Servicio de Reumatologia Pabellon Hospital Civil, 2a planta Plaza del Hospital Civil s/n MALAGA, 29009 Spain
Fischer, Peter	Mansfield Health Center 200 Copeland Drive MANSFIELD, MA 02048 United States
Fitzgerald, Oliver	St. Vincent's University Hospital Elm Park DUBLIN 4, D04 T6F4 Ireland
Fleischmann, Roy	Metroplex Clinical Research Center Suite 810 8144 Walnut Hill Lane DALLAS, TX 75231 United States
Fung, H.S. Eugene	Arthritis and Osteoporosis Clinic Suite 101 611 W. Hwy 6 WACO, TX 76710 United States
Garcia Garcia, Conrado	Unidad de Investigacion de las Enfermedades Reumatologicas S.A. de C.V. Av 20 Noviembre No. 82, Pisco 4, Col. Centro, Delegacion Cuauhtemoc MEXICO D.F., C.P. 06090 Mexico

Investigator Name	Site Name/Post Office Address
George, Ronald	PMG Research of Wilmington LLC Wilmington Health, PLLC 1202 Medical Center Drive WILMINGTON, NC 28401 United States
Gnylorybov, Andriy	LLC "Revmocentr" Department of Clinical Research 5, Spaska Str. KIEV, 04070 Ukraine
Goldberger, Edward	Arthritis Assoc of NW Ohio Suite 200 3922 Woodley Road TOLEDO, OH 43606 United States
Gonzalez Ferrandez, Jose	Hospital General Universitario de Elche Consultas Reumatologia 116-119 Efficio UIAE, 1 Planta Cami de l'Almazara, 11 ELCHE, ALICANTE, 03203 Spain
Goupille, Philippe	CHRU de Tours - Hopital Trousseau Service de Rhumatologie Avenue de la Republique CHAMBRAY-LES-TOURS, 37170 France
Griffiths, Hedley	Barwon Rheumatology Service 156 Bellerine Street GEELONG, VIC 3220 Australia
Guillibert, Caroline	Hopital Saint Joseph Service DE Rhumatologie 26 Boulevard de Louvain MARSEILLE, 13008 France

Investigator Name	Site Name/Post Office Address
Hall, Stephen	Emeritus Research 291 Wattletree Road MALVERN EAST, VIC 3145 Australia
Halter, Dale	Houston Institute for Clinical Research Suite 720 7777 Southwest Freeway HOUSTON, TX 77074 United States
Hassan, Waji	Leicester Royal Infirmary, Univ Hosp of Leicester NHS Balmoral Building Infirmary Square LEICESTER, LE1 5WW United Kingdom
Hofman, Julio	Mautalen Salud e Investigacion Azcuenaga 1860 CABA, C1128AAF Argentina
Hozman, Robert	Clinical Investigation Specialists, Inc. Suite 111 4709 Golf Road SKOKIE, IL 60076 United States
Hsieh, Song-Chou	National Taiwan University Hospital No. 7, Chung Shan South Road TAIPEI CITY, 10002 Taiwan
Huang, Chung-Ming	China Medical University Hospital No. 2, Yuh-Der Road, North District TAICHUNG CITY, 40447 Taiwan
Huynh, Doquyen	Allergy and Rheumatology Medical Clinic Suite 420 9850 Genesee Avenue LA JOLLA, CA 92037 United States

Investigator Name	Site Name/Post Office Address
Janska, Lenka	Nemocnice Hospital Slany Revmatologicka ambulance Politickych veznu 576 SLANY, 27401 Czech Republic
Jarvinen, Pentti	Kiljava Medical Research Donnerinkatu 5 HYVINKAA, 05800 Finland
Jedrychowicz-Rosiak, Krystyna	Mazowieckie Centrum Badan Klinicznych ul. Daleka 11 lok. 2021/2022/2024 GRODZISK MAZOWIECKIE, 05-825 Poland
Jeka, Slawomir	NZOZ Nasz Lekarz Ul. Szczytna 20 TORUN, 87-100 Poland
Jimenez, Richard	Western Washington Arthritic Clinic Suite 211 1909 214th St SE BOTHELL, WA 98021 United States
Joseph, John	Trinity Universal Research Associates, Inc. Suite 1002008 East Hebron Parkway CARROLLTON, TX 75007 United States
Jover Jover, Juan	Hospital Universitario Clinico San Carlos Servicio de Reumatologia 4a planta C/ Prof Martin Lagos, s/n MADRID, 28040 Spain
Jovic, Darko	University Clinical Center of the Republic of Srpska Dvanaest beba bb BANJA LUKA, 78000 Bosnia And Herzegovina

Investigator Name	Site Name/Post Office Address
Jundt, Jeffrey	Arthritis Consultants, P.A. Suite 226 2301 South Clear Creek Road KILLEEN, TX 76549 United States
Kapil, Sanjiv	Omega Research Consultants, LLC 609 North Charles Richard Beall Boulevard DEBARY, FL 32713 United States
Kivitz, Alan	Altoona Center for Clinical Research 175 Meadowbrook Lane DUNCANSVILLE, PA 16635 United States
Kolba, Karen	Pacific Arthritis Center Medical Group Suite A 607 East Plaza Drive SANTA MARIA, CA 93454 United States
Krause, Andreas	Immanuel-Krankenhaus Berlin Abteilung Rheumatologie und klinische Immunologieklinik fur Innere MedizinStandort Berlin- Buch, Lindenberger Weg19 BERLIN, 13125 Germany
Kremer, Joel	The Center for Rheumatology Suite 101 1367 Washington Ave ALBANY, NY 12206 United States
Krivoruchko, Natalya	JSC National Scientific Medical Research Center 42 Abylai Khan avenue ASTANA, 010009 Kazakhstan
Kuropatkin, Gennadiy	Samara Regional Clinical Hospital n.a. V.D.Seredavin 159, Tashkentskaya str. SAMARA, 443095 Russian Federation

Investigator Name	Site Name/Post Office Address
Lee, Chang	Asan Medical Center 88 Olympic-ro 43-gil, Songpa-gu SEOUL, 05505 Korea, Republic Of
Lee, Eric	Inland Rheumatology Clinical Trials Inc. 1238 East Arrow Highway UPLAND, CA 91786 United States
Lee, Shin-Seok	Chonnam National University Hospital 42 Jebong-ro, dong-gu GWANGJU, 61469 Korea, Republic Of
Levin, Robert	Clinical Research of West Florida, Inc. 2147 Northeast Coachman Road CLEARWATER, FL 33765 United States
Licheva, Rodina	Diagnostic Consultative Centre17 Sofia EOOD DCC "XVII - Sofia" EOOD, 108, Evlogi Georgiev Blvd. SOFIA, 1505 Bulgaria
Luggen, Michael	Cinncinnati Rheumatic Disease Study Group, Inc. 2nd Floor 311 Straight Street CINCINNATI, OH 45219 United States
Lukacova, Olga	Narodny ustav reumatickych chorob Piestany Nabrezie I. Krasku 4 PIESTANY, 92112 Slovakia
Macejova, Zelmira	ARTROMAC n.o. Neurologicka a reumatologicka ambulancia Poliklinika Terasa Toryska ul. 1 KOSICE, 040 11 Slovakia

Investigator Name	Site Name/Post Office Address
Marinova, Natalia	DCC "Fokus-5 - LZIP" EOOD 15 Hristo Stanchev str. SOFIA, 1463 Bulgaria
Marusenko, Irina	Autonomous Public Health Care Institution Republican Clinical Hospital n.a. Baranov 9 Republic of Karelia Pirogova str. 3 PETROZAVODSK, 185019 Russian Federation
Mastrovic Radoncic, Ksenija	Klinicka bolnica Sveti Duh Sveti duh 64 ZAGREB, 10000 Croatia
McCarthy, Timothy	Manitoba Clinic 790 Sherbrook Street WINNIPEG, MB R3A 1M3 Canada
McKay, Neil	Western General Hospital 1st Floor, Clock Tower Building Crewe Road EDINBURGH, EH4 2XU United Kingdom
Megyaszai, Marta	Revita Reumatologiai Rendelo Margit krt. 50-52. BUDAPEST, 1027 Hungary
Metyas, Samy	Medvin Clinical Research Suite A 500 W. San Bernardino Road COVINA, CA 91722 United States
Micaelo, Manuela	Instituto Portugues De Reumatologia Rua da Beneficencia, n.7, LISBON, 1050-034 Portugal

Investigator Name	Site Name/Post Office Address
Mohan, Monika	Advanced Rheumatology, PC Suite 115 4202 Collins Rd. LANSING, MI 48910 United States
Myasoutova, Leysan	Kazan State Medical University 49, Butlerov street KAZAN, 420012 Russian Federation
Nadashkevich, Oleg	Lviv Municipal City Clinical Hospital #4 Rheumatology Department , State Institution "Lviv National Medical University n.a. D. Halytskyi," Department of Family Medicine and Dermatology, Venereology 3, Sventsitskoho Str., LVIV, 79010 Ukraine
Naik, Latha	Dr. Latha Naik Medical Professional Corporation 641.750 Spadina Cr. East SASKATOON, SK S7K 3H Canada
Nayiager, Savithree	St. Augustine's Medical Centre Chelmsford Medical Centre 2 Suite 22 107 Chelmsford Road BEREA, DURBAN, NL 4001 South Africa
Neal, Jeffrey	Bluegrass Community Research, Inc. 330 Waller Avenue LEXINGTON, KY 40504 United States
Nemec, Petr	Revmatologie, s.r.o. Poliklinika Lesna Halasovo Namesti 1 BRNO, 638 00 Czech Republic

Investigator Name	Site Name/Post Office Address
Novak, Srdjan	Klinicki bolnicki Centar Rijeka Kresimirova 42 RIJEKA, 51000 Croatia
Novosad, Libor	L.K.N. Arthrocentrum, s r.o Na Valech 148/1 HLUCIN, 748 01 Czech Republic
Ong, Voon	Royal Free London Foundation Trust Pond Street LONDON, NW3 2QG United Kingdom
Palmer, William	Westroads Clinical Research, Inc. 10170 Nicholas Street OMAHA, NE 68114 United States
Park, Sung Hwan	The Catholic University of Korea, Seoul St. Mary's Hospital 222 Banpo-Daero,Seocho-gu SEOUL, 06591 Korea, Republic Of
Park, Won	Inha University Hospital 27, Inhang-ro, Jung-gu INCHEON, 22332 Korea, Republic Of
Patel, Rakesh	PMG Research of Salisbury, LLC 410 Mocksville Avenue SALISBURY, NC 28144 United States
Pavlova, Dace	LTD M&M Centrs Gaujas Street 11-6 ADAZI, LV-2164 Latvia
Peric, Porin	Medicinski Center Kuna-Peric Crvenog kriza 35 ZAGREB, 10000 Croatia

Investigator Name	Site Name/Post Office Address
Peters, Eric	Arizona Arthritis & Rheumatology Research, PLLC Suite 100 5681 West Beverly Lane GLENDALE, AZ 85306 United States
Petre, Octavian	Spitalul Municipal Ploiesti Sectia Reumatologie, Str. Ana Ipatescu, nr 59, PLOIESTI, 100337 Romania
Petrov, Dmitry	Yaroslavi State Medical University 5, Revolyutsionnaya street YAROSLAVL, 150000 Russian Federation
Phillips, Christopher	Four Rivers Clinical Research, Inc. Suite 305 225 Medical Center Drive PADUCAH, KY 42003 United States
Pickrell, Paul	Tekton Research, Inc. Suite 110 4534 West Gate Boulevard AUSTIN, TX 78739 United States
Pimentel-Santos, Fernando	Centro Hospitalar de Lisboa Ocidental Rua da Junqueira, 126 LISBON, 1349-019 Portugal
Pombo, Manuel	Hospital Nuestra Senora de la Esperanza Servicio de Reumatologia Avenida das Burgas, 2, A Coruna SANTIAGO DE COMPOSTELA, 15705 Spain

Investigator Name	Site Name/Post Office Address
Porter, David	Porter Rheumatology Ltd The Collingwood Centre 105 Collingwood St NELSON, 7010 New Zealand
Pulai, Judit	Fejer Megyei Szent Gyorgy Egyetemi Oktato Korhaz Reumatologiai Osztaly Seregelyesi ut 3. SZEKESFEHERVAR, 8000 Hungary
Puolakka, Kari	South Karelia Central Hospital Outpatient Clinic of RheumatologyValto Kaekelaen katu 1 LAPPEENRANTA, 53130 Finland
Racewicz, Artur\	"Osteo-Medic" spolka cywilna Artur Racewicz Jerzy Supronik ul. Wiejska 81 BIALYSTOK, 15-351 Poland
Rahman, Proton	St. Clare's Mercy Hospital Rheumatology Unit 154 LeMarchant Rd. ST. JOHN'S NFLD, A1C 5B8 Canada
Raoof, Tooraj	T. Joseph Raoof, MD, Inc./Encino Research Center #340/380 16133 Ventura Blvd. ENCINO, CA 91436 United States
Ratnik, Karin	Paernu Hospital Ristiku 1 PAERNU, 80010 Estonia
Rell-Bakalarska, Maria	Rheuma Medicus Zaklad Opieki Zdrowotnej ul. Pruszkowska 6 WARSAW, 02-118 Poland

Investigator Name	Site Name/Post Office Address
Rubbert-Roth, Andrea	Uniklinik Koln Klinik I fur Innere Medizin, Immunologische Ambulanz Kerpener Str. 62 COLOGNE, 50937 Germany
Rybar, Ivan	Slovak research center Team Member Thermium s.r.o. Emila Bellusa 6 PIESTANY, 92101 Slovakia
Salih, Abdelrazig	Warrington & Halton Hospitals NHS Foundation Trust Warrington Hospital Lovely Lane WARRINGTON, WA5 1QG United Kingdom
Schechtman, Joy	SunValley Arthritis Center, Ltd. 6818 West Thunderbird Road PEORIA, AZ 85381 United States
Scoville, Craig	Institute of Arthritis Research 2220 East 25th Street IDAHO FALLS, ID 83404 United States
Shim, Seung Cheol	Chungnam National University Hospital 282, Munhwa-ro, Daejeon JUNG-GU, 35015 Korea, Republic Of
Sidiropoulos, Prodromos	General University Hospital of Heraklion Internal Medicine / Rheumatology, Voutes, HERAKLEIO, 71110 Greece
Sniuoliene, Ilona	Klaipeda University Hospital Reumatology Department Liepojos 41 KLAIPEDA, 92288 Lithuania

Investigator Name	Site Name/Post Office Address
Spargo, Catherine	Arthritis Clinical Research Trials Room 201, 2nd floor The Park, Park Road PINELANDS,CAPE TOWN, 7405 South Africa
Sternad, Patrizia	MVZ Rheumatologie Dr. Martin Welcker GmbH Bahnhofstr. 32 PLANEGG, 82152 Germany
Sudano, Dominick	University of Arizona Arthritis Center #8303 1501 N. Campbell Avenue TUCSON, AZ 85724-5093 United States
Suh, Chang-Hee	Ajou University Hospital 164 Worldcup-ro, Yeongtong-gu, Gyeonggi-do SUWON-SI, 16499 Korea, Republic Of
Swarup, Areena	Arizona Arthritis and Rheumatology Research, PLLC Suite 202 1500 S. Dobson Road MESA, AZ 85202 United States
Tahir, Hasan	Whipps Cross University Hospital Barts Health NHS Trust Whipps Cross Road, Leytonstone LONDON, E11 1NR United Kingdom
Tam, Lai Shan	Prince of Wales Hospital Department of Medicine and Therapeutics 30-32 Ngan Shing Street, New Territories SHA TIN, 999077 Hong Kong
Tarr, Gareth	Winelands Medical Research Centre 14A & B Oewer Park STELLENBOSCH, WC 7600 South Africa

Investigator Name	Site Name/Post Office Address
Tesser, John	Arizona Arthritis & Rheumatology Research, PLLC Suite 505 9305 West Thomas Road PHOENIX, AZ 85037 United States
Tomkova, Sona	Nemocnica Kosice Saca, a.s. Reumatologicka a osteologicka ambulancia 1. sukromna nemocnica Lucna 57 KOSICE-SACA, 040 15 Slovakia
Trapp, Robert	Springfield Clinic Dept Clinical Research Suite 100 1130 South 6th Street SPRINGFIELD, IL 62703 United States
Tsai, Chang-Youh	Taipei Veterans General Hospital No. 201, Sec. 2, Shih-Pai Road Beitou District TAIPEI, 11217 Taiwan
Valter, Ivo	Center of Clinical and Basic Research J.Parna 4 TALLINN, 10128 Estonia
Van den Bosch, Filip	University Hospital Ghent, UZ Ghent Poli Reumatologie Entrance 74 Building P6 second floor De Pintelaan, 185 GENT, 9000 Belgium
Van Mullem, Xavier	Rhumaconsult SPRL Boulevard Audent 33 CHARLEROI, 6000 Belgium

Investigator Name	Site Name/Post Office Address
Vasylets, Viktoriia	Multifield Medical Centre (University Clinic #1) of Odesa National Medical University, Rheumatology Department 9 Pastera Str. ODESA, 65026 Ukraine
Veldi, Tiina	East Tallinn Central Hospital Rheumatology department Parnu road 104 TALLINN, 11312 Estonia
Venalis, Algirdas	Vilnius University Hospital Santariskiu Clinic Santariskiu str. 2 VILNIUS, 08661 Lithuania
Vinogradova, Irina	Ulyanovsk Regional Clinical Hospital 7, 3-Internatsionala street ULYANOVSK, 432017 Russian Federation
Vitek, Petr	PV-MEDICAL s.r.o. Revmatologicka ambulance Stefanikova 477 ZLIN, 760 01 Czech Republic
Wells, Alvin	Rheumatology and Immunotherapy Ctr., LLC 4225 W. Oakwood Park Court FRANKLIN, WI 53132 United States
Weng, Meng-Yu	National Cheng Kung University Hospital No.138, Sheng - Li Road TAINAN, 70403 Taiwan
Wu, Chien-Sheng	Far Eastern Memorial Hospital No.21, Section.2 Nanya S. Road, Banqiao Dist NEW TAIPEI, 220 Taiwan

Investigator Name	Site Name/Post Office Address
Yoo, Dae Hyun	Hanyang University Seoul Hospital Rheumatology 222-1 Wangsimni-ro, Seongdong-gu SEOUL, 04763 Korea, Republic Of
Zagar, Karen	Arthritis Center, Inc. Suite 2 32615 US Highway 19 North PALM HARBOR, FL 34684 United States
Zahabi-Unwala, Fehmida	Trinity Universal Research Associates, INC Suite 412 6300 Stonewood Drive PLANO, TX 75024 United States
Zaidi, Farrukh	Suncoast Clinical Research, Inc. 5604 Gulf Drive NEW PORT RICHEY, FL 34652 United States
Zamani, Omid	Rheuma Zentrum Favoriten GmbH Quellenstrasse 181 VIENNA, 1100 Austria