1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of VX-509 using Magnetic Resonance Imaging and Arthroscopic Biopsies in Subjects with Active Rheumatoid Arthritis on Stable Disease-Modifying Antirheumatic Drugs

Vertex Study Number: VX12-509-103

IND Number: 104,083

EUDRACT Number: 2012-003439-41

Date of Protocol: 09 October 2012 (Version 3.0)

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Summary of Changes to the Protocol

The previous version of this protocol (Version 2.0, 05 September 2012) was amended to create the current version (Version 3.0, 09 October 2012).

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 05 July 2012	Original version
Version 2.0, 05 September 2012	First amendment
Version 3.0, 09 October 2012	Current version.

Changes in current version are summarized below.

Change and Rationale	**Affected Sections**
The inclusion criterion related to the age range of subjects was changed from ages 18 to 80 to ages 18 to 65, inclusive. As this will be the first study to evaluate the 300 mg qd dose of VX-509 a more conservative approach to subject selection was selected.	Sections 2 and 10.1 (inclusion #2)
The Rheumatoid Arthritis Quality of Life (RAQoL) Questionnaire was replaced with the 36-Item Short Form Health Survey (SF-36; 8 subscales and 2 summary measures). This was done as targeted enrollment will not provide the data necessary to make a meaningful statement on change from baseline with this parameter. Given the study size, the SF-36 will provide more value and will serve as the baseline for long-term open-label extension study VX12-509-104.	Sections 2, 3, 7.2, 8.2, 12.8.2, 13.3.3.2, and 16.12
Adjusted instructions about the joint numbers that need to be assessed during Magnetic Resonance Imaging (MRI); specified that at a minimum the wrist and the metacarpophalangeal [MCP] joints #2 to #5 must be assessed. This adjustment was made based on functional feasibility at the site. Further details will be provided in the Imaging Guideline.	Sections 2, 8.1, and 12.8.1
The following endpoints were added: • Secondary: Change from baseline in Health Assessment Questionnaire –Disability Index (HAQ-DI) at Week 12. • Other: Change from baseline in OMERACT RAMRIS joint space narrowing score at Weeks 6 and 12 These endpoints were left out in error as their analysis was already described in the protocol.	Sections 2, 8.2, and 8.3
Clarified when the baseline X-ray of hands and feet will be performed.	Sections 2, 3, and 10.1 (inclusion #4)
Clarified eligibility requirements related to the tuberculosis (TB) test to indicate that subjects will not be eligible if they have a history of TB, regardless of history of anti-mycobacterial treatment; or active TB as determined by X-ray, TB skin test **and** QuantiFeron® TB Gold Assay (QuantiFeron assay). Guidance was also added to indicate that if the subject has a hypersensitivity to skin test preparation associated with the TB skin test then the QuantiFeron alone is acceptable.	Section 10.2 (exclusion #5)

Change and Rationale	Affected Sections
Language specifying that the DMARD dose must remain the same throughout the study was clarified to allow investigators to make dose adjustments as necessary for safety and toxicity.	Sections 2 and 10.3
ECG assessment language was previously updated to indicate that ECG vendor service will provide the ECG machines to sites that need them for use during the study. This is no longer the case. ECG assessment language has also been revised to match current standards at Vertex.	Section 12.9.5
Details related to the type of scanner to be used for conducting MRI were removed. Further details will be provided in the Imaging Guideline.	Sections 2 and 12.8.1
Contraceptive requirements have been revised to match updated requirements for the VX-509 development program.	Sections 12.9.6 and 12.9.6.2
The model to be used for the analysis of ACR20-CRP response at Week 12 was updated; Prior anti-TNF use was added as a covariate in the models for change from baseline in DAS28-4(CRP) all 4 RAMRIS scores (synovitis score, osteitis score, erosion score, and joint space narrowing) at Week 12.	Sections 13.3.3.1.1, 13.3.3.1.2, and 13.3.3.1.3
Assay for circulating osteoclast precursors was removed as it is in the development state and its use for this study is not certain.	Sections 2, 8.3, 12.6.1, and 13.5
Added calculation of the Clinical Disease Activity Index (CDAI), which does not require information on an acute phase reactant laboratory test, to serve as the baseline for long-term, treat-to-target, open-label extension study VX12-509-104.	Sections 2, 8.3, 13.3.3.3, and 16.9
Clarified that DAS28-4(CRP) will be used in the planned analyses (Disease Activity Score 28 using CRP [4-component]; Modified the cut-off table for Disease Activity Scores and EULAR Response Criteria to harmonize them with current standards as reported on the DAS-score website. http://www.das-score.nl/das28/en/difference-between-the-das-and-das28/importance-of-das28-and-tight-control/eular-response-criteria.html	Sections 2, 5, 8.2, 8.3, 9.2.1, 9.2.5, 13.3.2.3, 13.3.3.1, 13.3.3.1.2, 13.3.3.2, 13.3.3.4, 13.3.4.7, and 16.8

Typographical and administrative changes were also made to improve the clarity of the document.

2 PROTOCOL SYNOPSIS

Title A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of VX-509 using Magnetic Resonance Imaging and Arthroscopic Biopsies in Subjects with Active Rheumatoid Arthritis on Stable Disease-Modifying Antirheumatic Drugs

Clinical Phase 2b

Objectives

Primary Objectives

During 12 weeks of treatment in subjects with active rheumatoid arthritis (RA) on stable disease-modifying antirheumatic drug (DMARD) therapy:

- To evaluate the efficacy of VX-509 across a range of doses
- To evaluate the early effect of VX-509 administration on joint structures as assessed by magnetic resonance imaging (MRI)

Secondary Objectives

During 12 weeks of treatment in subjects with active RA on stable DMARD therapy:

- To evaluate major arthritis improvement with VX-509 administration across a range of doses
- To evaluate changes in RA physical function
- To evaluate changes in physical and mental health-related quality of life
- To investigate the pharmacokinetics (PK) of VX-509 and its metabolite in plasma
- To evaluate the safety of VX-509

Other Objectives

During 12 weeks of treatment in subjects with active RA on stable DMARD therapy:

- To evaluate the predictive value of MRI response for other efficacy parameters
- To evaluate change in health-related quality of life
- To investigate biomarkers reflecting bone turnover and inflammation during VX-509 administration
- To determine the PK/pharmacodynamic (PD) relationships between plasma exposure to VX-509 and its metabolite, and efficacy, safety, and plasma biomarkers

After 4 weeks of treatment in subjects with active RA on stable DMARD therapy (Synovial Biopsy Subset only):

- To investigate the immunomodulatory and anti-resorptive effects in the joint of VX-509 administration

- To determine the PK/PD relationships between plasma exposure to VX-509 and its metabolite, and biomarkers in the joint

Endpoints

Primary Endpoints

- Proportion of subjects who achieve ≥20% improvement in disease severity according to the American College of Rheumatology criteria (ACR20), using C-reactive protein (CRP) (ACR20-CRP) at Week 12.
- Change from baseline in Disease Activity Score 28 using CRP (4-component) (DAS28-4[CRP]) at Week 12.
- Change from baseline in Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) synovitis score in designated hand (minimal assessed joints: wrist, metacarpophalangeal [MCP] joints #2 to #5) at Week 12.
- Change from baseline in OMERACT RAMRIS bone marrow edema (osteitis) in designated hand (minimal assessed joints: wrist, MCPs #2 to #5) at Week 12.
- Change from baseline in OMERACT RAMRIS erosion score in designated hand (minimal assessed joints: wrist, MCP #2 to #5) at Week 12.

Secondary Endpoints

- Proportion of subjects who achieve ACR50-CRP and ACR70-CRP responses at Week 12.
- Proportion of subjects with DAS28-4(CRP) <2.6, and those who achieve a remission, moderate response or good response according to the European League Against Rheumatism (EULAR) response criteria at Week 12.
- ACR hybrid scores at Week 12.
- Change from baseline in Health Assessment Questionnaire –Disability Index (HAQ-DI) at Week 12.
- Change from baseline in the Physical Function subscale of the 36-item Short Form (SF-36) at Week 12
- Change from baseline in the Physical Component and Mental Health Components of the SF-36 at Week 12
- Change from baseline in OMERACT RAMRIS synovitis, bone marrow edema (osteitis), erosion scores at Week 6.
- PK parameters of VX-509 and its metabolite in plasma (maximum observed concentration [C_{max}] and area under the concentration versus time curve [AUC]).
- Safety and tolerability as indicated by adverse events, laboratory tests, electrocardiograms (ECGs) and vital signs.

Other Endpoints

- Predictive value of RAMRIS responses at Weeks 6 and 12 on DAS28-4(CRP) and ACR20-CRP at Week 12.
- Change from baseline in OMERACT RAMRIS joint space narrowing score at Weeks 6 and 12.
- Change from baseline in the Clinical Disease Activity Index (CDAI), CDAI moderate and low disease activity, and CDAI remission at Week 12.
- Change from baseline in the remaining 7 subscales of the SF-36 at Week 12.
- Change from baseline in blood biomarkers including markers of bone turnover, cytokines, and other biomarkers.
- Proportion of subjects who achieve ACR20, ACR50, and ACR70 assessed using erythrocyte sedimentation rate (ACR20-ESR, ACR50-ESR, and ACR70-ESR) responses, at Weeks 6 and 12.
- PK/PD relationship for plasma PK parameters and arthritis efficacy including RAMRIS, safety and plasma biomarkers.

Synovial Biopsy Subset only:

- Change from baseline at Week 4 in synovial biomarkers including histologic evidence of Janus Kinase (JAK3) activation, of osteoclast recruitment, level of monocellular infiltrate, and other biomarkers.
- PK/PD relationship for plasma PK parameters and synovial biomarkers.

Number of Subjects Approximately 40 subjects.

Study Population

- Must sign and date an informed consent document.
- Male and female subjects between the ages of 18 and 65 years, inclusive, on the day the informed consent is signed.
- Diagnosed with RA as defined by the 1987 ACR revised criteria and RA duration at screening of at least 24 weeks.
- Seropositivity based on either a positive rheumatoid factor or anti-cyclic citrullinated peptide antibody at screening **OR** known erosive disease based on previous X-ray report (available and filed) or erosions detected on baseline hand and foot X-ray.
- Subjects must have palpable 2+ synovitis of the wrist or ≥2 MCPs, defined as loss of bony contours with palpable joint effusion and/or swelling, in the MRI-designated hand (the hand being used in MRI assessments).
- Subjects must be receiving stable therapy with 1 of the following DMARDs: methotrexate, sulfasalazine, leflunomide, anti-malarial drug, or penicillamine. Stable therapy with 1 anti-malarial drug may be continued alone or with 1 of the other DMARDs listed above. Stable therapy is defined as initiation of the DMARD at least 16 weeks before screening and no change for the 8 weeks immediately before screening. The DMARD dose must remain the same throughout the study. Any increase, decrease, or change in the DMARD dose is prohibited during a subject's participation in the study, except for a dose

reduction that is mandated for toxicity. The required dose ranges for each of these DMARDS are summarized in Section 10.3.

- Subject must have a swollen joint count of ≥6 out of 66 assessed joints and a tender joint count of ≥8 out of 68 assessed joints at screening and Day 1. Joints in which there has been a total joint replacement will be excluded from the joint counts.
- Baseline CRP level ≥1.2 × ULN or Westergren erythrocyte sedimentation rate ≥1.2 × upper limit of normal at screening.
- Subjects in the Synovial Biopsy Subset must additionally have palpable 2+ synovitis, defined as loss of bony contours with palpable joint effusion and/or swelling, of the knee or the wrist in the non-MRI-designated hand (the wrist not being used in MRI assessments) to be biopsied; this joint may not have received a total joint replacement.
- Subject must be willing and able to comply with scheduled visits, treatment plan, lifestyle guidelines, concomitant medication guidelines, laboratory tests, vaccination rules, contraceptive guidelines, and other study procedures.

Investigational Drug

Active substance: VX-509

Activity: azaindole-based selective inhibitor of JAK3

Strength, Form, and Route of Administration: VX-509 (50 mg) tablets for oral administration

Study Design

This is a Phase 2, randomized, placebo-controlled, double-blind, dose-ranging, multicenter study of VX-509 in subjects with moderate to severe RA who are seropositive or have demonstrated erosive disease, and an inadequate response to a DMARD.

Schedule of Study Visits

The following study visits will be scheduled:

- Screening Visit;
- Treatment Period: Day 1 (baseline, first day of study drug administration, up to 4 weeks after the Screening Visit); visits on Weeks 2, 4 (only for subjects in the Synovial Biopsy Subset), 6, 8, and 12; and
- Safety Follow-up Visit 28 days after the last dose of study drug.

Pharmacokinetic Assessments

For **all subjects**, blood samples for determination of concentrations of VX-509 will be collected at the following time points:

- **Day 1:** Blood samples will be collected before the first study drug dose, at 0.5 to 2 hours postdose, and at 4 to 6 hours postdose for determination of VX-509. Guidelines for administration of study drug and food/drink restrictions on this day are provided in Section 11.2.
- **Weeks 6 and 12 Visits:** Two blood samples at least 2 hours apart will be collected for determination of VX-509 (no required relationship to dosing time).

For subjects in the Synovial Biopsy Subset only: In addition to the PK samples drawn at Day 1, Weeks 6 and 12 Visits for all subjects, this subset will also have a blood sample collected at Week 4 Visit for determination of VX-509 (no required relationship to dosing time) immediately before the synovial biopsy and within 60 minutes before collection of the synovial fluid PK sample.

Efficacy Assessments

Hand MRI

MRI-designated hand and wrist (the hand being used in MRI assessments) will be acquired using an MRI scanner as specified in the imaging guidelines.

Other Efficacy Assessments

- Tender/swollen joint counts
- Erythrocyte sedimentation rate
- C-reactive protein
- Physician Global Assessment of Disease Activity
- Subject Global Assessment of Disease Activity
- Subject assessment of pain (Visual Analog Scale)
- Subject assessment of general health (Visual Analog Scale)
- Subject assessment of disability (Health Assessment Questionnaire – Disability Index)
- Subject assessment of health-related quality of life (SF-36; 8 subscales and 2 summary measures)

Other Assessments

Arthroscopic Synovial Biopsies (Synovial Biopsy Subset only)

A subset of approximately 6 (no more than 10) subjects will undergo arthroscopic synovial biopsy before the first dose on Day 1 (baseline) and at Week 4 (Synovial Biopsy Subset). Subjects in the Synovial Biopsy Subset will only be randomized to the 200 mg qd dose of VX-509 (Arm C). During this procedure, a sample of synovial fluid and biopsies of synovial tissue will be collected for analysis.

Measurement of Biomarkers in Blood (all subjects)

Blood Biomarker Sample A will be stored by Vertex and used for potential exploratory biomarkers including measures of inflammation or response.

Blood Biomarker Sample B will be aliquoted as necessary and used to monitor the following biomarkers:

- **Osteoclast activation/bone turnover –** receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL), osteocalcin, osteoprotegrin (OPG), and C-terminal type I collagen crosslinks.
- **Inflammation** – tumor necrosis factor-α, interleukin-1β (IL-1β), IL-6, IL-15, IL-21 and macrophage colony-stimulating factor.

Flow Cytometry Sample

- **Lymphocyte subsets** – T cells (CD3, CD4, CD8), B cells (CD19), natural killer cells (CD56+, CD16+, and CD3-), and CD25+ T-cell subsets

Additionally other exploratory biomarkers including measures of inflammation or response may also be assessed.

Measurement of Biomarkers and PK in Synovial Fluid (Synovial Biopsy Subset only)

Synovial fluid will be collected as summarized in Section 12.5. The following assessments will be performed on synovial fluid samples (if possible, in descending order of priority):

- **Cell count and differential** - total white count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils (absolute and percent) and red blood cells, will be the first priority.
- **PK assessment -** assessment of VX-509 concentration in synovial fluid.
- **Frozen SF sample -** the remaining synovial fluid will be centrifuged, and the supernatant will be frozen and stored for exploratory assessment. This will be the final priority.

Additionally other exploratory biomarkers including measures of inflammation or response may also be assessed.

Measurement of Biomarkers in Synovial Tissue (Synovial Biopsy Subset only)

Synovial tissue will be collected as summarized in Section 12.5. The following assessments will be performed on synovial tissue samples (if possible, in descending order of priority):

Immunohistochemistry/Histochemistry

- CD68+, CD3+, CD20+, and CD138+ (hematoxylin and eosin)
- Staining for phosphorylated signal transducers and activators of transcription-5 (P-STAT5) (biomarker of JAK3 activation) and P-STAT3 (biomarker of JAK2 activation)
- Markers of bone homeostasis - CD14+, RANK+, RANKL, and OPG

Synovial RNA

- B cell marker, T cell marker, IL-15, IL-21, RANKL, OPG, retinoic acid receptor gamma, and T-box transcription factor

Synovial Protein

- P-STAT5, P-STAT3, P-STAT1, and P-STAT2

Additionally other exploratory biomarkers including measures of inflammation or response may be assessed.

Pharmacogenomics

A single blood sample (**DNA Sample A**) will be collected on Day 1 for potential exploratory evaluation of correlations between DNA markers with PK, PD, treatment benefit, and adverse events, except for subjects who do not choose to participate in this assessment.

A second blood sample (**DNA Sample B**) will be collected on Day 1 for potential exploratory evaluation of correlations between DNA markers with health and disease, especially RA, except for subjects who do not choose to participate in this assessment.

Blood samples (**RNA Sample**) will also be collected on Day 1 and Weeks 2, 4, 6, 12, and at the Safety Follow-up Visit, except for subjects who do not choose to participate in this assessment. These samples will be used for potential exploratory evaluation of correlations between RNA markers with PK, PD, treatment benefit, and adverse events.

3 SCHEDULE OF ASSESSMENTS

Table 3-1 Schedule of Assessments: Screening Visit

	Screening	
Assessment/Event	**Screening Visit Day –28 to –1**	**Day -7 to before the first dose on Day 1[a]**
Informed consent	X	
Assignment of screening number via IVRS/IWRS	X	
Verification of inclusion/exclusion criteria	X	
Demographics	X	
Medical history, including allergies and vaccination history	X	
Rheumatoid arthritis history	X	
Prior medications (60 days) and prior RA medications (lifetime)	X	
Social history (smoking, alcohol)	X	
Height, weight, and BMI	X	
Vital Signs	X	
Physical examination	X	
12-lead ECG	X	
Chest X-ray [b]	X	
Adverse events and concomitant medications	X	X
Serum chemistry	X	
Hematology	X	
Coagulation	X	
Urinalysis	X	
CRP and WESR	X	
Rheumatoid factor and anti-CCP antibodies	X	
Fasting lipid profile [c]	X	
Serology [d]	X	
Tuberculin skin test (purified protein derivative) [e]	X	
QuantiFERON® TB Gold Assay	X	
Serum FSH (postmenopausal females age 45 to 55 years only)	X	
Serum β-HCG pregnancy test (females of child-bearing potential only)	X	
MRI on designated hand		X [f]
Baseline X-ray of hands and feet		X [f]
Tender/swollen joint counts	X	
Physician Global Assessment of Disease Activity	X	
Subject Global Assessment of Disease Activity	X	
Subject assessment of pain (VAS)	X	
Subject assessment of general health (VAS)	X	
Subject assessment of disability (Health Assessment Questionnaire – Disability Index [HAQ-DI])	X	

Table 3-1 Schedule of Assessments: Screening Visit

	Screening	
Assessment/Event	**Screening Visit Day –28 to –1**	**Day -7 to before the first dose on Day 1[a]**
Subject assessment of health-related quality of life (Short Form Health Survey [SF-36])	X	

anti-CCP: anti-cyclic citrullinated peptide; β-HCG: β-human chorionic gonadotropin; BMI: body mass index; CRP: C-reactive protein; ECG: electrocardiogram; FSH: follicle stimulating hormone; IVRS/IWRS: Interactive Voice Response System/Interactive Web Response System; MRI: magnetic resonance imaging; RA: rheumatoid arthritis; WESR: Westergren erythrocyte sedimentation rate; VAS: Visual Analog Scale.

[a] The baseline arthroscopy procedure for the Synovial Biopsy Subset may be performed from Day -4 to before the first dose on Day 1; the arthroscopy procedure is summarized on Day 1 in Table 3-2.

[b] Not necessary if a recent chest X-ray is available (within 12 weeks of screening).

[c] Subjects must abstain from all food and drink (except water) at least 8 hours before blood draws for the fasting lipid profile.

[d] Hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus (HIV) 1 antibody, HIV 2 antibody.

[e] A 5 tu purified protein derivative (PPD) skin test will be positive if ≥10 mm at 48 to 72 hours.

[f] These procedures are performed after study eligibility is confirmed (other than Day 1 tender and swollen joint counts). Hand/foot X-ray should be performed earlier, if required to confirm eligibility (Section 10.1, inclusion criteria #4).

Table 3-2 Schedule of Assessments: Treatment Period and Follow-up

Assessment/Event	Day 1 (Base-line)[a]	Week 2 ± 3 days	Week 4 (Synovial Biopsy Subset only) ± 3 days	Week 6 (MRI) ± 3 days	Week 8 ± 7 days	Week 12 (MRI) or Early Treatment Termination ± 7 days[b]	Safety Follow-up Visit 28 ± 7 days after last dose
Outpatient visit	X	X	X	X	X	X	X
Randomization and assignment of IVRS/IWRS subject ID number	X						
Verification of inclusion/exclusion criteria	X						
Study drug administration [c]	X	Continuous until Week 12 or Early Treatment Termination					
Pill counts		X		X	X	X	
Weight, BMI	X			X		X	X
Physical examination [d]						X	X
Vital signs	X	X	X	X	X	X	X
12-lead ECG	X			X		X	
Adverse events and concomitant medications	X	X	X	X	X	X	X
Safety and Efficacy Laboratory Assessments							
Serum chemistry	X	X		X	X	X	X
Hematology	X	X		X	X	X	X
Coagulation						X	
CRP and WESR	X	X	X	X	X	X	X
Rheumatoid factor and anti-CCP Antibodies	X					X	
Fasting lipid profile [e]	X[f]	X		X		X[f]	X
Erythropoietin	X	X		X		X	X
Iron studies	X						
Urine pregnancy test (females of child-bearing potential only)	X					X	
Urinalysis						X	
Pharmacokinetic, Pharmacodynamic and Biomarker Laboratory Assessments							
Plasma VX-509 PK	X[g]			X[h]		X[h]	
Blood Biomarker Sample A	X	X		X		X	X
Blood Biomarker Sample B	X	X		X		X	X
Flow cytometry sample	X	X		X		X	X
Synovial Biopsy Subset only							
Diagnostic arthroscopy [i]	X[j]		X				

Table 3-2 Schedule of Assessments: Treatment Period and Follow-up

Assessment/Event	Day 1 (Base-line)[a]	Week 2 ± 3 days	Week 4 (Synovial Biopsy Subset only) ± 3 days	Week 6 (MRI) ± 3 days	Week 8 ± 7 days	Week 12 (MRI) or Early Treatment Termination ± 7 days[b]	Safety Follow-up Visit 28 ± 7 days after last dose
Blood Biomarker Sample B			X				
Plasma VX-509 PK (**in addition** to samples collected on all subjects)			X[k]				
Synovial Fluid (SF) samples (Synovial Biopsy Subset only; as fluid volume permits; allocated in descending order of priority):							
SF Cell count/differential sample	X		X				
SF VX-509 PK sample	X		X				
Frozen SF sample	X		X				
Synovial Tissue (ST) samples (Synovial Biopsy Subset only; allocated in descending order of priority):							
ST Immunohistochemistry/ histopathology sample	X		X				
ST RNA sample	X		X				
ST Protein extraction sample	X		X				
Pharmacogenomic Assessments							
DNA Sample A (optional)	X						
DNA Sample B (optional)	X						
RNA Sample (optional)	X	X	X	X		X	X
Efficacy Assessments							
MRI on designated hand				X		X[b]	
Tender/swollen joint counts	X	X		X	X	X	X
Physician Global Assessment of Disease Activity	X	X		X	X	X	X
Subject Global Assessment of Disease Activity	X	X		X	X	X	X
Subject assessment of pain (VAS)	X	X		X	X	X	X
Subject assessment of general health (VAS)	X	X		X	X	X	X
Subject assessment of disability (Health Assessment Questionnaire – Disability Index [HAQ-DI])	X	X		X	X	X	X
Subject assessment of health-related quality of life (Short Form Health Survey [SF-36])	X			X		X	X

anti-CCP: anti-cyclic citrullinated peptide; BMI: body mass index; CRP: C-reactive protein; ECG: electrocardiogram; IVRS/IWRS: Interactive Voice Response System/Interactive Web Response System; JAK: Janus kinase; MRI: magnetic resonance imaging; PK: pharmacokinetic; RA: rheumatoid arthritis; SF: synovial fluid; ST: synovial tissue; WESR: Westergren erythrocyte sedimentation rate.

[a] Baseline is the most recent evaluation before the first dose of study drug on Day 1.

[b] Subjects who discontinue treatment early will be asked to return to the clinical research unit to complete the procedures specified for Week 12/Early Treatment Termination. If the subject discontinues before completing 3 weeks of treatment, the MRI will not be repeated.

[c] Subjects will receive their respective oral dose of VX-509 or placebo for 12 weeks. VX-509 should be administered at approximately the same time every day, throughout the study.

[d] A complete physical examination will be performed at the time points indicated. For all other scheduled visits, a symptom-directed physical examination assessment may be performed if indicated.

[e] Subjects must abstain from all food and drink (except water) at least 8 hours before blood draws for the fasting lipid profile.

[f] Leptin and lipoprotein (a) will be assessed as part of the fasting lipid testing at this visit.

[g] Blood samples will be collected before the first study drug dose, at 0.5 to 2 hours postdose, and at 4 to 6 hours postdose for determination of VX-509. Subjects should be restricted from food and drink intake (except water) at least 8 hours before dosing and until 2 hours after dosing (Section 11.2). Record the date and time of administration of the first dose of study drug.

[h] Two blood samples at least 2 hours apart will be collected for determination of VX-509 (no required relationship to dosing time). Record the date and time of administration of the most recent study drug dose before the PK sample.

[i] Arthroscopic synovial biopsies will only be performed in a subset of subjects at selected study sites (the Synovial Biopsy Subset). The arthroscopy at Week 4 should be obtained from the same joint as the arthroscopy performed before the first dose on Day 1 (baseline). The arthroscopic procedure at each visit will be conducted only after all other scheduled assessments are completed.

[j] For subjects in the Synovial Biopsy Subset only, the baseline arthroscopic procedure may be performed from Day -4 to before the first dose on Day 1.

[k] For subjects in the Synovial PK Subset only: In addition to the PK samples drawn for all subjects, this subset will also have a blood sample collected for determination of VX-509 (no required relationship to dosing time) immediately before the synovial biopsy and within 60 minutes before collection of the synovial fluid PK sample. Record the date and time of administration of the 2 most recent study drug doses before the PK sample.

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5 LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
ACR	American College of Rheumatology
ACR20-CRP (ACR50-CRP, ACR70-CRP)	≥20% (50%, 70%) improvement in disease severity according to the American College of Rheumatology criteria, using C-reactive protein
ACR20-ESR, ACR50-ESR, ACR70-ESR	ACR20, ACR50, ACR70 assessed using erythrocyte sedimentation rate
AE	adverse event
ALT	alanine aminotransferase
anti-CCP	anti-cyclic citrullinated peptide
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration versus time curve
AUC_{0-12}	AUC from the time of dosing to 12 hours
AUC_{0-24}	AUC from the time of dosing to 24 hours
$AUC_{0-\tau}$	AUC during a dosing interval
bid	twice per day
BMI	body mass index
bpm	beats per minute
CD	cell of differentiation
CI	confidence interval
C_{max}	maximum observed concentration
C_{min}	minimum observed plasma concentration
CPAP	clinical pharmacology analysis plan
CRP	C-reactive protein
CTCAE	Cancer Institute Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAS28-4(CRP)	Disease Activity Score 28 using CRP (4-component)
DMARD	disease-modifying antirheumatic drug
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation	Definition
EENT	eyes/ears/nose/throat
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACS	fluorescent activated cell sorter
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GPS	Global Patient Safety
HAQ-DI	Health Assessment Questionnaire – Disability Index
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IA	interim analysis
IC_{50}	concentration resulting in 50% of maximum inhibition
ICH	International Conference on Harmonization
ID	identification
IL	interleukin
IRB	institutional review board
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
JAK	Janus kinase
LC/MS/MS	liquid chromatography with tandem mass spectroscropy
LDL	low density lipoprotein
max	maximum value
MCP	metacarpophalangeal
M-CSF	macrophage colony-stimulating factor
MedDRA	Medical Dictional for Regulatory Activities
min	minimum value
MRI	magnetic resonance imaging
MTX	methotrexate
NOAEL	no observable adverse effect level
NSAID	nonsteroidal anti-inflammatory drugs
OMERACT	Outcome Measures in Rheumatology Clinical Trials
OPG	osteoprotegrin
PD	pharmacodynamic(s)

Abbreviation	Definition
PK	pharmacokinetic(s)
PIP	proximal interphalangeal
PPD	purified protein derivative
prn	as needed
P-STAT	phosphorylated signal transducers and activators of transcription
q12h	every 12 hours
qd	once daily
QTc	QT interval corrected
RA	rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
SCID	severe combined immunodeficiency
SD	standard deviation
SF-36	36-item Short Form
SP	sulfapyridine
STAT	signal transducers and activators of transcription
STIR	short tau inversion-recovery
SUSAR	suspected, unexpected, serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
TIBC	total iron-binding capacity
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-α
ULN	upper limit of normal
vdHmTSS	Van der Heijde Modified Total Sharp Score
WESR	Westergren erythrocyte sedimentation rate
WHO-DD	World Health Organization-Drug Dictionary

6 INTRODUCTION

6.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology that affects 0.5% to 1% of adults in the developed nations.[1] RA often causes destruction of joint cartilage and erosion of adjacent bone, resulting in deformity, loss of function, and subsequent joint replacement. Many patients with RA suffer progressive disability over time[2,3], pain[4], work loss[5], substantial health care costs[6], and premature mortality.[7]

Although joint pain and inflammation are the primary clinical manifestation of the disease, RA is a systemic illness that can involve virtually any organ system in the body. The hallmark of the disease is synovitis, in which the synovial membrane is characterized by hyperplasia, increased vascularity, and infiltration of inflammatory cells that contribute to the formation of a destructive pannus.[8] Increased levels of proteolytic enzymes are produced, leading to destruction of cartilage matrix molecules and progressive joint damage.

RA therapy focuses on reducing symptoms and delaying progression of structural disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may reduce the symptoms of pain, swelling, and stiffness, but do not alter the natural course of the disease. Disease-modifying antirheumatic drugs (DMARDs) have the potential to slow the progression of joint damage and time to disability and thus alter the natural history of RA.

The most widely used DMARD is methotrexate (MTX). Methotrexate inhibits dihydrofolic acid reductase, interfering with DNA synthesis and cellular replication.[9] Although many RA patients initially respond, a substantial number ultimately have an inadequate response, necessitating the addition of other DMARDs.[10,11,12,13] The progression of structural damage may continue on MTX alone.[14] Newer biologic DMARDs such as tumor necrosis factor-α (TNF-α) inhibitor agents are effective in many cases, including the associated joint damage[15], although a proportion of patients do not respond or become refractory to these compounds. These newer agents have been associated with serious infections, and their long-term safety continues to be monitored.[16,17] Analysis of synovial tissue can be used to evaluate response to different agents, with change in macrophage infiltrate, levels of interleukin-6, (IL-6)/tumor necrosis factor alpha (TNF-α) predictive of effective treatments.[18] Decrease in the resorptive potential of the synovium can be demonstrated by decreased expression of osteoprotegrin (OPG), receptor activator of nuclear factor kappa-B (RANK) and receptor activator of nuclear factor kappa-B ligand (RANKL) (particularly near the pannus-bone interface) in the synovium.[19,20]

6.2 Magnetic Resonance Imaging

The Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS), developed initially by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) international working group in 1998, assesses synovitis, bone marrow edema (osteitis) and erosions of the wrist and metacarpophalangeal (MCP) joints.[21] Magnetic resonance imaging (MRI) is sensitive and rapidly responsive to change. Although not predictive at the individual subject level, MRI is effective in predicting structural disease response to therapeutic

interventions for groups, and can be used to guide dose selection for larger radiographic progression studies.

In a 20-subject cohort of early RA patients, an attempt to induce remission with MTX or MTX with infliximab showed no difference in van der Heijde Modified Total Sharp Scores (vdHmTSS) after 1 year (change of 10 vs. 12, respectively). However, MRI in the infliximab group showed improvement in bone marrow edema (osteitis) ($P<0.05$) by Weeks 4 and 14, which was predictive for no new MRI erosions in the infliximab group at 1 year ($P = 0.0125$ vs. MTX alone).[22] Even in treated subjects in clinical remission or with low clinical disease activity, MRI progression occurs, and baseline bone marrow edema (osteitis) was predictive for new erosions by MRI over the ensuing year.[23] In a Phase 2 study of golimumab and MTX, compared to MTX ('GO-BEFORE'), the concurrent MRI data in a subset of 318 subjects at Weeks 12 and 24 showed significantly lower RAMRIS erosion scores with golimumab ($P = 0.016$ and $P = 0.010$ vs. MTX alone at Weeks 12 and 24, respectively). In comparison, X-rays in the MRI cohort were underpowered at Week 28, but the full 637-subject X-ray data showed significant vdHmTSS benefit at that time point.[24] Highlighting the independent processes of synovitis and bone resorption in RA[15], the anti-RANKL monoclonal antibody denosumab showed decreased erosion progression at month 6 by both MRI ($P = 0.007$ vs. placebo) and X-ray ($P = 0.019$), without alterations in synovitis.[25]

6.3 Janus Kinases

Cytokines play pivotal roles in inflammation, and targeting either cytokines or their receptors are effective approaches to treating RA. Type 1 and 2 cytokine receptors associate with Janus kinases (JAKs) to affect intracellular signaling.[26] These structurally unique tyrosine protein kinases play an essential role in immune cell development and function. One JAK, JAK3, has particularly selective functions. JAK3 is an integral part of the signaling pathway used by γ chain cytokine receptors (the interleukin-2 family: IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-21).[26,27,28] Upon stimulation of the cytokine receptor by ligand (cytokine) binding, the receptors oligomerize, facilitating tyrosine phosphorylation of JAK3 and subsequent signal transduction via the signal transducers and activators of transcription (STAT). Expression of JAK3 is confined to the lymphohematopoietic system, while the other members of the JAK family (JAK1, JAK2, and tyrosine kinase 2) are more broadly expressed.[27,29,30] Mutations of the interleukin receptor γ chain underlie X-linked severe combined immunodeficiency (SCID), indicative of its critical role in the development and function of lymphocytes, and mutations of the downstream JAK3 are responsible for some cases of autosomal recessive SCID.[28]

6.4 VX-509

VX-509 is a potent small-molecule inhibitor of JAK3 in development as a potential treatment for subjects with active RA and other autoimmune diseases**.** In Phase 2a Study VX09-509-101 (Study 101), VX-509 demonstrated significant activity in reducing signs and symptoms of RA over 12 weeks in subjects not receiving concurrent DMARDs.[31,32] Additionally, other generalized JAK inhibitors are in development for RA.[33] Findings from these studies resulted in rapid, statistically significant reductions in the signs and symptoms

of RA; however, the effect on progression of erosive disease at 24 weeks in a study with a placebo control arm for 3 months was uncertain ($P<0.05$ with significant contribution by outliers).[34, 35]

The VX-509 Investigator's Brochure provides specific details about the completed nonclinical and clinical VX-509 studies and a full description of safety findings.[36] No safety issues have been identified in studies in RA patients and normal healthy volunteers that would preclude the dosing regimens proposed for the present study; however, this study is the first study in RA subjects receiving a DMARD to evaluate concurrent treatment with VX-509 300 mg daily (qd) for 12 weeks.

6.5 Rationale for the Present Study

The current study is designed to evaluate the safety and efficacy across doses of VX-509, including MRI imaging, in subjects with active RA who have had an inadequate response to DMARD. Information on early MRI response with the evaluated VX-509 doses in this trial will be utilized to help select appropriate dose(s) for a subsequent pivotal trial evaluating radiographic progression. Evaluation of synovial tissue pre- and post-VX-509 administration in a subset of the study subjects will provide further information concerning the JAK3-based mechanism of action of VX-509, within the target tissue, and concerning any alteration in the osteoclastogenic/resorptive synovial environment following VX-509 administration.

7 STUDY OBJECTIVES

7.1 Primary Objectives

During 12 weeks of treatment in subjects with active RA on stable DMARD therapy:

- To evaluate the efficacy of VX-509 across a range of doses
- To evaluate the early effect of VX-509 administration on joint structures as assessed by MRI

7.2 Secondary Objectives

During 12 weeks of treatment in subjects with active RA on stable DMARD therapy:

- To evaluate major arthritis improvement with VX-509 administration across a range of doses
- To evaluate changes in RA physical function
- To evaluate changes in physical and mental health-related quality of life
- To investigate the pharmacokinetics (PK) of VX-509 and its metabolite in plasma
- To evaluate the safety of VX-509

7.3 Other Objectives

During 12 weeks of treatment in subjects with active RA on stable DMARD therapy:

- To evaluate the predictive value of MRI response for other efficacy parameters
- To evaluate change in health-related quality of life
- To investigate biomarkers reflecting bone turnover and inflammation during VX-509 administration
- To determine the PK/pharmacodynamic (PD) relationships between plasma exposure to VX-509 and its metabolite and efficacy, safety, and plasma biomarkers

After 4 weeks of treatment in subjects with active RA on stable DMARD therapy (Synovial Biopsy Subset only):

- To investigate the immunomodulatory and anti-resorptive effects in the joint of VX-509 administration
- To determine the PK/pharmacodynamic (PD) relationships between plasma exposure to VX-509 and its metabolite and biomarkers in the joint

8 STUDY ENDPOINTS

8.1 Primary Endpoints

- Proportion of subjects who achieve ≥20% improvement in disease severity according to the American College of Rheumatology criteria (ACR20), using C-reactive protein (CRP) (ACR20-CRP) at Week 12.
- Change from baseline in Disease Activity Score 28 using CRP (4-component) (DAS28-4[CRP]) at Week 12.
- Change from baseline in Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) synovitis score in designated hand (minimal assessed joints: wrist, MCP joints #2 to #5) at Week 12.
- Change from baseline in OMERACT RAMRIS bone marrow edema (osteitis) in designated hand (minimal assessed joints: wrist, MCP joints #2 to #5) at Week 12.
- Change from baseline in OMERACT RAMRIS erosion score in designated hand (minimal assessed joints: wrist, MCP joints #2 to #5) at Week 12.

8.2 Secondary Endpoints

- Proportion of subjects who achieve ACR50-CRP and ACR70-CRP responses at Week 12.
- Proportion of subjects with DAS28-4(CRP) <2.6, and those who achieve a remission, moderate response or good response according to the European League Against Rheumatism (EULAR) response criteria at Week 12.
- ACR hybrid scores at Week 12.

- Change from baseline in Health Assessment Questionnaire –Disability Index (HAQ-DI) at Week 12.
- Change from baseline in the Physical Function subscale of the 36-item Short Form (SF-36) at Week 12
- Change from baseline in the Physical Component and Mental Health Components of the SF-36 at Week 12
- Change from baseline in OMERACT RAMRIS synovitis, bone marrow edema (osteitis), erosion scores at Week 6.
- PK parameters of VX-509 and its metabolite in plasma (maximum observed concentration [C_{max}] and area under the concentration versus time curve [AUC]).
- Safety and tolerability as indicated by adverse events, laboratory tests, electrocardiograms (ECGs) and vital signs.

8.3 Other Endpoints

- Predictive value of RAMRIS responses at Weeks 6 and 12 on DAS28-4(CRP) and ACR20-CRP at Week 12.
- Change from baseline in OMERACT RAMRIS joint space narrowing score at Weeks 6 and 12.
- Change from baseline in the Clinical Disease Activity Index (CDAI), CDAI moderate and low disease activity, and CDAI remission at Week 12.
- Change from baseline in the remaining 7 subscales of the SF-36 at Week 12.
- Change from baseline in blood biomarkers including markers of bone turnover, cytokines, and other biomarkers.
- Proportion of subjects who achieve ACR20, ACR50, and ACR70 assessed using erythrocyte sedimentation rate (ACR20-ESR, ACR50-ESR, and ACR70-ESR) responses, at Weeks 6 and 12.
- PK/PD relationship for plasma PK parameters and arthritis efficacy including RAMRIS, safety and plasma biomarkers.

Synovial Biopsy Subset only:

- Change from baseline at Week 4 in synovial biomarkers including histologic evidence of JAK3 activation, of osteoclast recruitment, level of monocellular infiltrate, and other biomarkers.
- PK/PD relationship for plasma PK parameters and synovial biomarkers.

9 STUDY DESIGN

9.1 Overview of Study Design

This is a Phase 2, randomized, placebo-controlled, double-blind, dose-ranging, multicenter study of VX-509 in subjects with moderate to severe RA who are seropositive or have demonstrated erosive disease, and an inadequate response to a DMARD.

Subjects who have been on a stable dose of DMARD (Section 10.3) must have a swollen joint count of ≥6 out of 66 assessed joints and a tender joint count of ≥8 out of 68 assessed joints, and a CRP level ≥1.2 × the upper limit of normal (ULN) or Westergren erythrocyte sedimentation rate ≥1.2 × ULN to qualify for the trial. MRI of the most swollen hand (2+ synovitis of wrist or ≥2 MCPs) at baseline will be performed before dosing and at Weeks 6 and 12. A subset of approximately 6 (no more than 10) subjects will undergo arthroscopic synovial biopsies before the first dose at baseline (Day 1) and at Week 4 (Synovial Biopsy Subset).

Subjects will be randomized with stratification based on prior use of biological response modifiers (including a tumor necrosis factor [TNF] inhibitor). VX-509 will be coadministered with DMARD for a planned duration of 12 weeks. Approximately 40 subjects will be randomized to 1 of 4 dosing regimens at a 1:1:1:1 ratio. VX-509-matched placebo tablets will be used to maintain the double-blind. As an exception, the subjects in the Synovial Biopsy Subset will only be randomized to the 200 mg qd dose of VX-509 (Arm C). Subjects in the Synovial biopsy Subset will know that they are not receiving placebo, but not the dose they are receiving.

Arm A. Placebo (N = 10)

Arm B. 100 mg VX-509 qd (N = 10)

Arm C. 200 mg VX-509 qd (N = 10)

Arm D. 300 mg VX-509 qd (N = 10)

The protocol has optional interim analyses (IA) for the purpose of selecting appropriate dose(s) for a subsequent pivotal trial (Section 13.3.4.7). No changes in study design or conduct will be made based on the results of an IA.

9.1.1 Screening

Procedures to be performed during the Screening Visit are listed in Table 3-1.

The Screening Visit will occur within 28 days before administration of study drug to confirm that subjects meet the selection criteria. The investigator (or an appropriate authorized designee at the investigator site) will obtain written informed consent from each subject before conducting any study related assessments or procedures.

Subjects who fail screening initially may be rescreened 1 additional time within 30 days of the initial Screening Visit. Subjects who fail screening because of abnormal safety laboratory results or CRP/WESR are not required to complete the entire Screening Visit for their rescreening, and may rescreen by testing just those laboratory abnormalities.

9.1.2 Treatment Period

Procedures to be performed during the Treatment Period are listed in Table 3-2.

After verifying subjects are eligible according to the inclusion and exclusion criteria on Day 1, subjects will be randomized to the dosing groups described in Section 9.1.

Dosing details are given in Section 11.2.

9.1.3 Safety Follow-up

All subjects will have a Safety Follow-up Visit 28 (± 7) days following the last dose of study drug, and the procedures as listed in Table 3-2 will be completed.

9.1.4 Early Discontinuation

Subjects who prematurely discontinue treatment in this study for any reason will be asked to return to the clinical research unit for the Week 12/Early Termination of Study Treatment Visit (Table 3-2). If the subject discontinues before completing 3 weeks of treatment, the MRI will not be repeated.

Stable background NSAIDs and low dose corticosteroid treatment are allowed in this study. Analgesics, both narcotic and non-narcotic, are allowed during the trial with the exception of the period before joint assessments (Section 10.3). It is anticipated that these factors will serve to limit withdrawals for inadequate control of disease activity over 12 weeks. If the investigator determines that the only mechanism to control disease activity in this period would be to perform an arthrocentesis with or without an intraarticular injection, this proposal (as opposed to early treatment discontinuation) should be discussed first with the medical monitor.

Discontinuation of study drug administration will be considered for subjects with, but not limited to, the occurrence of 1 or more of the abnormalities listed below:

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels and/or alkaline phosphatase levels that increase ≥3 × ULN (see Section 12.9.3)
- Lymphocytes <0.5 K/µL
- Absolute neutrophils <1.0 K/µL
- Platelets <100 K/µL
- Hemoglobin ≤8 g/dL

Subjects who prematurely discontinue treatment in this study for any reason will complete the Week 12/Early Treatment Termination assessments. Subjects who withdraw will be asked to return to the site, if they consent, for the Safety Follow-up Visit at 28 (± 7) days after their last dose of study drug. The assessments to be conducted during the Safety Follow-up Visit are listed in Table 3-2.

9.2 Rationale for Study Design and Study Drug Regimens

9.2.1 Study Design

The study is designed to evaluate early response to VX-509 administration, including local synovial and bone response assessment by MRI imaging and synovial biopsy (Section 6.5). The double-blind placebo-controlled design will allow comparison to variability in efficacy parameters for control subjects. No blinded joint assessor is utilized in the trial due to the small subject numbers and partial unblinding of all arthroscopy subjects, who are randomized to the 200 mg qd dose of VX-509 (Arm C) to avoid the variability inherent with dose-ranging. Due to the increased assay sensitivity of joint MRI, and blinded reading by 2 central readers, there is improved study power to detect RAMRIS differences and the validity of MRI data is maintained. As a sensitivity analysis, the ACR20-CRP and DAS28-4(CRP) efficacy parameters will be re-evaluated without inclusion of the arthroscopy subjects.

9.2.2 Study Drug Dose and Duration

VX-509 doses between 100 mg qd and 200 mg qd are currently being evaluated in Study VX11-509-102 (Study 102), a Phase 2b study for RA subjects receiving background MTX. In Phase 2a Study 101, total daily doses of 100, 200, and 300 mg were shown to be safe and efficacious when administered using twice per day (bid) regimen (50, 100, or 150 mg bid).[31,32] This study is the first clinical study conducted with VX-509 in subjects with RA to evaluate concurrent treatment with VX-509 300 mg qd and a DMARD for 12 weeks.

9.2.3 Rationale for Dosing Regimen

In Study VX10-509-004 (Study 004), VX-509 doses of 150 mg every 12 hours (q12h) and 300 mg qd were administered to healthy subjects in a crossover design.[37] The results indicated that the qd and bid dosing regimens resulted in a similar total daily exposure (AUC from the time of dosing to 24 hours [AUC_{0-24}]) to VX-509 (Table 9-1).

Table 9-1 Total Daily Exposure to VX-509 in Study VX10-509-004

	AUC_{0-24h} (hr•µg/mL)		
Dose Regimen	**Mean (SD)**	**C_{max} (µg/mL)**	**C_{min} (µg/mL)**
150 mg q12h	24.0 (5.15)[a]	1.95	0.349
300 mg qd	24.0 (5.32)	3.67	0.109

Source: Study VX10-509-004.[37]

AUC_{0-24h}: area under the concentration versus time curve from the time of dosing to 24 hours; bid: twice per day; C_{max}: maximum observed plasma concentration; C_{min}: minimum observed plasma concentration; q12h: every 12 hours; qd: once daily.

[a] Value is 2 × AUC_{0-12h} for 150 mg q12h.

Based on a review of clinical studies involving other JAK3 inhibitors with a mechanism of action similar to that of VX-509, using a simulation from the PK profile of CP-690,550 (JAK1/JAK3 inhibitor), it is apparent that clinical improvement in RA only requires intermittent inhibition of JAK3 greater than 50% (concentration resulting in 50% of maximum inhibition [IC_{50}] of approximately 24 ng/mL) for about 4 to 6 hours in every 12 hour period.[38,39,40] The VX-509 dosing levels of 100 mg qd and above yield

approximately 6 hours of >50% inhibition (VX10-509-004; simulated data not shown). Considering VX-509 has a moderate half-life of approximately 8 hours, once daily dosing is feasible and was selected for this study.

9.2.4 Safety Margin

Estimated daily exposure based on doses from Study 004[37] (healthy subjects) and Study 101[31] (RA subjects) is summarized in Table 9-2. Using these projections, the estimated safety margin at the clinical dose of 300 mg/day based on exposures observed at the no observable adverse effect level (NOAEL) in rats and dogs during chronic toxicity studies is approximately 2.7- and 3.5-fold, respectively (Table 9-3).

Table 9-2 Estimated Daily Exposure to VX-509 in Study VX12-509-103, from Study VX10-509-004 and Study VX09-509-101 Data

Dose	$AUC_{0\text{-}24h}$ (µg•hr/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)
100 mg qd	9.46[a]	1.22[b]	0.036[b]
200 mg qd	19.9[a]	2.45[b]	0.073[b]
300 mg qd	33.4[a]	3.67[c]	0.109[c]
100 mg bid	19.9[a]	1.21[d]	0.477[d]

Sources: Study VX-509-101;[31,41] Study VX10-509-004.[37]

$AUC_{0\text{-}24h}$: area under the concentration versus time curve from the time of dosing to 24 hours; bid: twice per day; C_{max}: maximum observed plasma concentration; C_{min}: minimum observed plasma concentration; qd: once daily.

[a] Values obtained by 2 × $AUC_{0\text{-}12h}$ of corresponding daily equivalent bid dose (e.g., 50 mg bid for 100 mg qd) for RA subjects in Study 101.[31, 41]

[b] Values obtained by applying fraction of dose (one third; two third) to the observed 300 mg qd value from healthy subjects in Study 004.[37]

[c] Observed value from healthy subjects in Study 004.[37]

[d] Observed value from RA subjects in Study 101.[31]

Table 9-3 Estimated Chronic Non-Clinical Safety Margin over Estimated Clinical Exposure at VX-509 Dose of 300 mg/day

Observations at NOAEL	Observed (Rat/Dog) $AUC_{0\text{-}24h}$ (µg•hr/mL)	Estimated $AUC_{0\text{-}24h}$ (µg•hr/mL) at Clinical Dose of 300 mg qd[a]	Estimated Safety Margin at Clinical Dose of 300 mg qd
Male rats	89.5	33.4	2.68
Female rats (NOAEL based on uterine atrophy finding)	7.83	33.4	0.23 (2.68) [b]
Male dogs	102	33.4	3.05
Female dogs	117	33.4	3.50

Sources: VX-509 Investigator's Brochure[36], Study VX-509-101;[31,42]
$AUC_{0\text{-}24h}$: area under the concentration versus time curve from the time of dosing to 24 hours; C_{max}: maximum observed plasma concentration; NOAEL: no observable adverse effect level; qd: once daily.

[a] In Study VX09-509-101, estimated $AUC_{0\text{-}24h}$ for 300 mg qd was 33.4 µg•hr/mL (Table 9-2).

[b] Uterine and mammary gland atrophy are considered to be rat species-specific findings.[36] Based on the male rat NOAEL (60 mg/kg/day), the safety margin for female rats would also be 2.68.

9.2.5 Previous Clinical Findings

In 3 Phase 1 studies, VX-509 was administered as single doses from 10 to 900 mg, and as multiple daily doses of 25 to 600 mg for 7 or 14 days (Study VX08-509-001, Study VX08-509-002, and Study VX10-509-004).[37,43,44] Overall, the results demonstrated that VX-509 was safe and well-tolerated with administration of multiple doses of up to 600 mg daily for 14 days in normal healthy volunteers. One subject receiving a single 900 mg dose of VX-509 developed symptoms of nausea, vomiting, headache, and tremor. This subject was found to have a higher plasma VX-509 exposure (173 µg•hr/mL), which exceeded the exposure level at the NOAEL in all nonclinical species.

Data from a 12-week Phase 2a study (Study 101) of VX-509 administration in 204 RA subjects demonstrated that ACR20-CRP responses at Week 12 were achieved in 29%, 39%, 61%, 65% and 66% of the placebo, 25-, 50-, 100- and 150-mg bid VX-509 groups, respectively ($P \leq 0.007$ for the 3 highest doses).[31] Statistically significant improvement was also seen for the 3 highest doses in DAS28-4(CRP) at Week 12 ($P < 0.001$).

The most frequent adverse events (AEs) were infections, seen in approximately 17% of both placebo and VX-509 subjects, although more frequently in higher VX-509 dose groups. There were 11 treatment-emergent serious adverse events (SAEs) seen in 9 subjects (10 SAEs in 8 VX-509 subjects) and SAEs were more frequent in the higher VX-509 dose groups. There were 5 SAEs in the infections and infestations system organ class, all in subjects receiving VX-509, including bronchitis, erysipelas, pneumonia, tuberculosis, and osteomyelitis. There were 2 fatal SAEs of subarachnoid hemorrhage and pneumonia in VX-509 subjects.

Primarily Grade 1 increases ALT or AST values, and increases in both low density lipoprotein (LDL)- and high density lipoprotein (HDL)-cholesterol were observed in subjects who received higher doses of VX-509. For further information refer to the VX-509 Investigator's Brochure.[35]

9.2.6 Drug-Drug Interaction Potential with Required DMARDs and Corticosteroids

Drug-drug interaction studies of VX-509 with the DMARDs required in the current study have not been conducted. In Study 102, the potential interactions of VX-509 and MTX will be explored, but these data are not yet available.

VX-509 is mainly metabolized in the liver through oxidation by cytochrome P450 34A CYP3A4, and subsequent glucuronidation, sulfate conjugation, and hydrolysis. Only approximately 1% of VX-509 is renally excreted unchanged in urine in humans. The protein binding of VX-509 is approximately 81% to 91%.[36]

VX-509 may slightly increase the level of corticosteroid exposure in subjects, therefore close monitoring of steroid side effects is recommended. If necessary, adjustments should be made as detailed in Section 10.3.

For MTX, 80% to 90% of MTX is excreted unchanged renally.[9] Therefore, drug-drug interaction between VX-509 and MTX are unlikely as VX-509 is not expected to interfere with the renal clearance of MTX.

For leflunomide, its definitive metabolic pathway has not been established. Most likely, leflunomide is metabolized via CYP1A2.[45,46] The active metabolite of leflunomide, M1, is most likely metabolized through CYP2A6.[47] Therefore, drug-drug interaction between VX-509 and leflunomide is unlikely as VX-509 is not expected to interfere with CYP1A2 and CYP2A6 on which leflunomide and M1 metabolism depend.

Penicillamine, a chelating agent, appears in the plasma as free penicillamine, penicillamine disulfide, and cysteine-penicillamine disulfide, and is mainly excreted renally as disulfide.[48] It may interact with food, antacids, and iron, which may interfere with the formation of chelating compounds, and is therefore best dosed while fasting. Drug-drug interaction of VX-509 and penicillamine coadministration is unlikely, if VX-509 and penicillamine are not taken simulataneously.

Sulfasalazine, a probiotic agent, is absorbed quickly and almost completely.[49] Sulfasalazine is metabolized via intestinal bacteria to its active metabolites, sulfapyridine (SP) and 5-aminosalicylic acid (5-ASA). Absorbed SP and 5-ASA and their metabolites are primarily eliminated in the urine either as free metabolites or as glucouronide conjugates. Drug-drug interaction of VX-509 and sulfasalazine coadministration is unlikely.

9.2.7 Other Considerations

VX-509 was shown to be teratogenic in rat and rabbit embryo-fetal studies in doses equal to or above human equivalent doses which will be investigated in the current study (the VX-509 Investigator's Brochure provides specific details about the nonclinical findings).[36] The effect of VX-509 on oral contraceptives has not been studied. Subjects will be required to use appropriate contraception as detailed in Section 12.9.6.1.

9.2.8 Overall Risk Benefit Estimation

Taking the risk/benefit factors together, these results support the selection of the doses used in this study (placebo, 100 mg, 200 mg, and 300 mg VX-509 qd). The doses are anticipated to be within the therapeutic window and will have adequate safety margins.

9.2.9 Rationale for Study Assessments

The study assessments for the primary and secondary endpoints (i.e., ACR, DAS, and EULAR) for this protocol are validated and accepted for use in clinical studies in RA to assess efficacy.

MRI of an inflamed joint is a sensitive measure of change, and MRI at Week 4 has shown significant improvement in bone marrow edema (osteitis) with TNF inhibition, as compared to placebo plus background DMARD.[22] MRI evaluations at Weeks 6 and 12 will be utilized to evaluate early change in synovitis and osteitis, a predictor of therapeutic inhibition of radiographic structural damage.

10 SELECTION OF STUDY POPULATION

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

10.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible for this study:

1. Must sign and date an informed consent document.
2. Male and female subjects between the ages of 18 and 65 years, inclusive, on the day the informed consent is signed.
3. Diagnosed with RA as defined by the 1987 ACR revised criteria and RA duration at screening of at least 24 weeks.
4. Seropositivity based on either a positive rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP) antibody at screening **OR** known erosive disease based on previous X-ray report (available and filed) or erosions detected on baseline hand and foot X-ray.
5. Subjects must have palpable 2+ synovitis of the wrist or ≥2 MCPs, defined as loss of bony contours with palpable joint effusion and/or swelling, in the MRI-designated hand (the hand being used in MRI assessments).
6. Subjects must be receiving stable therapy with 1 of the following DMARDs: methotrexate, sulfasalazine, leflunomide, anti-malarial drug, or penicillamine. Stable therapy with 1 anti-malarial drug may be continued alone or with 1 of the other DMARDs listed above. Stable therapy is defined as initiation of the DMARD at least 16 weeks before screening and no change for the 8 weeks immediately before screening. The DMARD dose must remain the same throughout the study. Any increase, decrease, or change in the DMARD dose is prohibited during a subject's participation in the study,

except for a dose reduction that is mandated for toxicity. The required dose ranges for each of these DMARDS are summarized in Section 10.3.

7. Subject must have a swollen joint count of ≥6 out of 66 assessed joints and a tender joint count of ≥8 out of 68 assessed joints at screening and Day 1. Joints in which there has been a total joint replacement will be excluded from the joint counts.
8. Baseline CRP level ≥1.2 × ULN or Westergren erythrocyte sedimentation rate ≥1.2 × ULN at screening.
9. Subjects in the synovial biopsy subset must additionally have palpable 2+ synovitis, defined as loss of bony contours with palpable joint effusion and/or swelling, of the knee or the wrist in the non-MRI-designated hand (the wrist not being used in MRI assessments) to be biopsied; this joint must not have received a total joint replacement.
10. Subject must be willing and able to comply with scheduled visits, treatment plan, lifestyle guidelines, concomitant medication guidelines, laboratory tests, vaccination rules, contraceptive guidelines, and other study procedures.

10.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will **not** be eligible for this study:

1. Inflammatory and rheumatological disorders other than RA, where arthritis may be a prominent feature, such as systemic lupus erythematosus, mixed connective tissue disease, scleroderma, poly/dermatomyositis, or gout; secondary Sjogren's syndrome or interstitial lung disease are allowed.
2. History of any illness that might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This may include, but is not limited to, history of cardiovascular or central nervous system disease, history or presence of clinically significant abnormalities on physical exam, ECG or laboratory examination, or history of clinically significant psychiatric or mental disease.
3. History of cancer, except squamous or basal cell cancers of the skin or in situ cancer of the cervix.
4. History of hematologic disorders including neutropenia and thrombocytopenia other than Felty's syndrome.
5. History of tuberculosis (TB), regardless of history of anti-mycobacterial treatment; or active TB as determined by X-ray, TB skin test and QuantiFeron® TB Gold Assay (QuantiFeron assay). If the subject has a hypersensitivity to skin test preparation associated with the TB skin test then the QuantiFeron alone is acceptable.
6. Acute or chronic active infection requiring systemic antimicrobial treatment with the exception of onychomycosis receiving antifungal medication, or acne and rosacea receiving low-dose antibiotics.
7. History of febrile illness within 5 days before the first dose of study drug.
8. History of previous osteomyelitis, infected joint or joint prosthesis.

9. Subjects who are at high risk of developing an infection due to a compromised immune system including poorly controlled diabetes.
10. Weight <45 kg at screening.
11. A 12-lead ECG demonstrating QT interval corrected (QTc) >450 msec at the screening Visit. If QTc exceeds 450 msec, the ECG should be repeated 2 more times, and the average of the 3 QTc values used to determine the subject's eligibility. Subjects should also be excluded if any other clinically significant interval (e.g., PR prolongation), morphologic (e.g., T-wave inversion), or conduction abnormalities are observed.
12. Planned surgery during the study.
13. Metal implant or other contra-indication to MRI scanning.
14. History of alcohol or drug abuse, or excessive alcohol consumption as determined by the investigator, during the previous 12 months before screening.
15. For female subjects: Pregnant or nursing; or planning to become pregnant during the study or within 90 days following the last VX-509 dose; or female subjects of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from at least 14 days before the first dose of study drug and for 90 days following the last dose of study drug.
16. For male subjects: Subject has a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days following the last VX-509 dose; or male subjects who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from at least 14 days before the first dose of study drug and for 90 days following the last dose of study drug.
17. Subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, other staff, or a relative of study personnel directly involved with the conduct of the study.
18. Requirement for more than 1 NSAID after signing informed consent at screening (additional aspirin [second NSAID] ≤325 mg/day is allowed). The dose of any ongoing NSAID must be stable for at least 28 days before Day 1.
19. Systemic corticosteroid treatment (prednisone or equivalent) >10 mg/day. The dose of any ongoing systemic corticosteroid must be stable for at least 28 days before Day 1 (Section 16.13).
20. Allergy to gadolinium.
21. Prior treatment with a JAK inhibitor.
22. Other DMARDs (biologic/non-biologic) beyond the required DMARD for study entry must have been discontinued for specified minimum periods before screening (see Section 16.2). Subjects with prior treatment with rituximab/ocrelizumab (or other depleting monoclonal antibody) must show demonstrated recovery of any cytopenia(s).
23. Intraarticular corticosteroids in any joint within 4 weeks before screening, or within 12 weeks before screening for the MRI-designated hand or joint planned for arthroscopy.

24. Treatment with an investigational drug within 60 days or 5 half-lives preceding the first dose of study drug, whichever is longer.
25. Subjects who require concomitant use of any moderate or strong inhibitors or inducers of CYP3A or P-gp or who require CYP3A substrates with serious associated side effects at high exposure (Section 10.3; partial lists in Section 16.3).
26. Have received a live or live attenuated vaccination in the 4 weeks before study Day 1.
27. Positive urine or serum pregnancy test.
28. Hemoglobin <11 g/dL for females or <12 g/dL for males at screening.
29. Absolute neutrophil count <1.5 K/μL at screening.
30. Platelet count <120 K/μL at screening.
31. ALT or AST ≥1.5 × the ULN at screening.
32. Creatinine clearance <30 mL/min at screening
33. Positive hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus 1 and 2 antibodies at screening.
34. Other clinically significant out-of-range laboratory results in hematology, serum chemistry, coagulation studies, or urinalysis at the screening as judged by the investigator.

10.3 Prior and Concomitant Medications and Other Study Restrictions

All medications (including herbal medicines and supplements) administered from 60 days before the Screening Visit through the Safety Follow-up Visit will be recorded in the source documents and on the electronic case report form (eCRF).

Subjects will be questioned at each study visit regarding use of medications during the period since the last visit. All medications used during the period will be recorded in the eCRF.

NSAIDs: Subjects may continue treatment with one NSAID (additional aspirin [second NSAID] ≤325 mg/day is allowed) at a dose that is stable for at least 28 days before Day 1, which must remain the same throughout the study. Any increase, decrease, or change in the dose of the one NSAID (not including aspirin) is prohibited during a subject's participation in the study, except for a dose reduction that is mandated for NSAID toxicity. NSAIDs are not stopped for the analgesic holiday before joint count assessments.

Systemic Corticosteroids: Subjects may continue treatment with prednisone ≤10 mg/day (or equivalent; Section 16.13), which must be a stable dose for at least 28 days before Day 1. Any increase, decrease, or change in the dose of systemic corticosteroid is prohibited during a subject's participation in the study, except for a dose reduction that is mandated for corticosteroid toxicity. Intraarticular corticosteroids are prohibited in any joint within 4 weeks before screening, and within 12 weeks before screening for the MRI-designated hand or joint planned for arthroscopy. Intraarticular corticosteroid injections are prohibited throughout the study (see Section 10.2), although this option may be discussed with the medical monitor if required to prevent early discontinuation (Section 9.1.4).

Live, Attenuated Vaccinations: Subjects who receive study drug should not receive any type of live or attenuated live vaccinations in the 4 weeks before study Day 1, during the study, or within 4 weeks after the final dose of study drug.

Drug-Drug Interactions: Any moderate or strong CYP3A or P-gp inhibitors or inducers as well as CYP3A sensitive substrates will be prohibited during the study; a partial list of prohibited medications is provided in Section 16.3.

Preliminary analysis of the PK data from a drug-drug interaction study of VX-509 and midazolam shows a strong inhibition of the CYP3A isozyme by VX-509 and its metabolite, M3. A mean 13-fold increase in overall midazolam exposure (AUC_{last}) and 3-fold mean increase in peak midazolam exposure (C_{max}) were observed when VX-509 was coadministered with midazolam, a drug which is extensively metabolized by CYP3A (CYP3A substrate). Therefore, a subject's exposure to medications that are metabolized extensively via CYP3A may increase significantly when coadministered with VX-509. As a result of this finding:

- Avoid concomitant use of VX-509 with sensitive CYP3A medications with serious side effects at high exposure (i.e. narrow therapeutic window, prolonged QTc).
- Use caution with administration of other CYP3A-metabolized medications, and/or consider use of alternative medications if appropriate.
- Discuss any questions regarding concomitant medications, and/or study eligibility, with the Study Medical Monitor.
- Remind patients to inform the investigator of all medications they are taking, including prescription and non-prescription medications or herbal remedies.

Non-narcotic Analgesic Medications (other than NSAIDs): Subjects are permitted to use acetaminophen/ paracetamol as a supplemental analgesic medication during the study. The dose should not exceed 4 g/day. These medications must not be taken during the full 24 hour day before, and on the day of each joint assessment until the joint counts are completed, including the assessment on Day 1 dosing.

Narcotic Analgesic Medications: Subjects are permitted to take tramadol, codeine, oxycodone, or codeine/oxycodone based combination analgesics on an as needed (prn) basis if prescribed by a physician for their RA. Subjects are not permitted to use other opiates. These medications must not be taken during the full 24 hour day before, and on the day of each joint assessment until the joint counts are completed, including the assessment on Day 1 before dosing.

DMARDs: For study eligibility (Section 10.1), subjects must be receiving stable therapy with 1 of the following DMARDs: methotrexate, sulfasalazine, leflunomide, anti-malarial drug, or penicillamine. Stable therapy with 1 anti-malarial drug may be continued alone or with 1 of the other DMARDs. Stable therapy is defined as initiation of the DMARD/anti-malarial drug at least 16 weeks before screening and no change for the 8 weeks immediately before screening. The DMARD/anti-malarial dose must remain the same throughout the study. Any increase, decrease, or change in the DMARD/anti-malarial dose is prohibited

during a subject's participation in the study, except for a dose reduction that is mandated for toxicity. The required dose ranges for each of these DMARDS are provided below:

Methotrexate and Folate/Folinic acid: If a concomitant medication at screening, methotrexate at doses of 15 to 25 mg per week (oral, intramuscular) may be continued at a stable dose throughout the trial, coadministered with folic or folinic acid ≥5 mg/week. For subjects with documented toxicity at a methotrexate dose of 15 mg/week, a stable methotrexate dose of ≥7.5 mg/week is acceptable. Subjects who discontinued methotrexate before study entry must have at least a 45-day washout period before screening (Section 16.2).

Sulfasalazine: If a concomitant medication at screening, sulfasalazine at doses of 1 to 2 g/day may be continued at a stable dose throughout the study. Subjects who discontinued sulfasalazine before study entry must have at least a 45-day washout period before screening (Section 16.2).

Leflunomide: If a concomitant medication at screening, leflunomide at doses of 10 to 20 mg/day may be continued at a stable dose throughout the study. Subjects who discontinued leflunomide before study entry must have received cholestyramine and have at least a 28-day washout period before screening (Section 16.2).

Penicillamine: If a concomitant medication at screening, penicillamine at doses of 250 to 750 mg/day may be continued at a stable dose throughout the study. Subjects who discontinued penicillamine before study entry must have at least a 60-day washout period before screening (Section 16.2).

Anti-Malarials: If a concomitant medication at screening, hydroxychloroquine at doses of ≤200 mg bid (or equivalent dose chloroquine) may be continued at a stable dose throughout the study. Subjects who discontinued an anti-malarial drug before study entry must have at least a 28-day washout period before screening (Section 16.2).

Prohibited Non-Biologic DMARD Medications: All other non-biologic DMARDs (gold, azathioprine, mycophenolyate, others) are prohibited from screening until the Safety Follow-up Visit or early discontinuation. Refer to Section 16.2 for the non-biologic DMARD washout periods before screening which are required for study eligibility.

Prohibited Biologic DMARD Medications Including TNF Inhibitors: All biologic DMARDs are prohibited from screening until the Safety Follow-up Visit or early discontinuation. Refer to Section 16.2 for the biologic DMARD washout periods before screening which are required for study eligibility.

Any other medication that might interfere with study evaluations is prohibited. In case of uncertainty, the investigator or designee should contact the Vertex/CRO medical monitor. Subjects are not permitted to participate in investigations of other medications during this study.

10.4 Removal of Subjects in the Study

See Section 9.1.4 for specific rules about consideration for discontinuation related to safety monitoring.

In addition, subjects may withdraw at any time at their own request, and subjects may be withdrawn at any time at the discretion of the investigator or Vertex for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final Safety Follow-up Visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Subjects who prematurely discontinue treatment in this study for any reason will complete the Week 12/Early Treatment Termination assessments. Subjects who withdraw will be asked to return to the site, if they consent, for the Safety Follow-up Visit at 28 (± 7) days after their last dose of study drug. The assessments to be conducted during the Safety Follow-up Visit are listed in Table 3-2.

10.5 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study will not be replaced.

11 STUDY DRUG ADMINISTRATION AND MANAGEMENT

11.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

11.2 Administration

VX-509 tablets or VX-509-matching placebo tablets will be administered orally for each treatment arm described in Section 9.1. VX-509-matching placebo tablets contain the same excipients as VX-509 tablets (microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, sodium lauryl sulfate, magnesium stearate).[36]

Subjects will be dispensed drug on Day 1 and will be provided additional drug at subsequent visits as needed.

The investigator or designee should explain the correct use of the study drug to each subject. Subjects should be instructed how to replace any lost or missed doses of VX-509 (or placebo).

Subjects should be instructed to always consult with the investigator before replacing any lost or missed doses of VX-509 or placebo.

In order to maintain the blind in the study, each subject in each cohort will receive the same number of tablets at each dosing occasion. Six tablets will be administered at each dosing occasion for each treatment arm for 12 weeks:

Arm A	Placebo	6 × VX-509-matched placebo tablets
Arm B	100 mg VX-509 qd	2 × 50-mg tablets and 4 × VX-509-matched placebo tablets
Arm C	200 mg VX-509 qd	4 × 50-mg tablets and 2 × VX-509-matched placebo tablets
Arm D	300 mg VX-509 qd	6 × 50-mg tablets

VX-509 should be administered at approximately the same time every day, throughout the study. No restriction is placed for ingestion of food, except on Day 1 when the PK samples are taken after dose.

On Day 1, the first VX‑509 dose should be administered at the study site, after the predose PK blood sample is taken. Subjects will be instructed to stay at the study site for a minimum of 4 to 6 hours after administration of the morning dose of study drug until all required clinical assessments are obtained (Section 12.4.1). Subjects should be restricted from food and drink intake (except water) at least 8 hours before dosing and until 2 hours after dosing.

11.3 Dose Modification for Toxicity

Modifications of the study drug dose are prohibited. The exception will be the synovial biopsy subjects, who will be allowed to make dose reductions after discussion with the Vertex medical monitor.

If study drug dosing must be interrupted due to an adverse event or laboratory abnormality, the subject may be restarted or terminated from the study after discussion with the Vertex medical monitor. Specific instructions for interruption for elevated liver function tests are provided in Section 12.9.3.

11.4 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a unique screening number by the study site before evaluation of inclusion and exclusion criteria at screening. Subjects who satisfy inclusion and exclusion criteria will receive a unique subject number on Day 1, before the first dose, according to a predetermined randomization schedule.

Personnel at the study site will contact the interactive voice/web response system (IVRS/IWRS) for subject enrollment and randomized treatment assignment. The IVRS/IWRS will assign subjects at a ratio of 1:1:1:1 to 1 of the 4 treatment groups, with stratification based on previous use of any biologic response modifier drug (including anti-TNF) for RA. The subjects who additionally undergo synovial biopsy will be an exception and will only be randomized to Arm C.

The randomly assigned subject number in the IVRS/IWRS will be used to identify the individual subject for the duration of the study. Appropriate study drug will be dispensed for each subject based on the randomization information from IVRS/IWRS.

11.5 Packaging and Labeling

Study drug will be supplied by Vertex. VX-509 will be provided as 50-mg tablets. VX-509-matched placebo tablets will be the same size but will not contain any active drug. These tablets will be packaged into weekly blister cards. Study drug labeling will be in compliance with applicable local and national regulations.

Additional details regarding packaging, labeling, and dispensing for VX-509 and placebo will be included in the Pharmacy Manual.

11.6 Study Drug Supply, Storage, and Handling

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements.

Detailed instructions regarding the storage and handling of VX-509 and placebo will be provided in the Pharmacy Manual.

11.7 Compliance

On Day 1, the dose will be administered under the direct supervision of the investigator or designee.

For study drug doses administered during the outpatient periods of the study, drug accountability will be assessed at each visit by counting returned dosage units. Subjects will be instructed to bring all used and unused study medication supplies, including empty blister packs, to each visit. Discrepancies will be discussed with the subject and recorded in the source documents.

If subjects demonstrate continued non-compliance of study drug dosing despite educational efforts, the investigator should contact the medical monitor to discuss discontinuation of the subject from the study.

11.8 Drug Accountability

Study drug may be dispensed only under the supervision of the investigator or authorized designee and only to study subjects. The pharmacist or designated site staff will maintain information regarding the dates and amounts of (1) study drug received; (2) study drug dispensed to subjects; and (3) study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the study site. These materials will be retained at the study site according to instructions provided by Vertex, or its designee, until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

11.9 Disposal, Return, or Retention of Unused Drug

The site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. At the end of the study, Vertex will provide instructions as to the disposition or return of any unused investigational product. If the site has a drug destruction policy in place and drug destruction capabilities, Vertex may authorize destruction at the study site. In such cases, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations,

institutional policies, and any special instructions provided by Vertex. Adequate documentation of study drug destruction must be provided.

11.10 Blinding and Unblinding

This will be a double-blind, placebo-controlled study. As an exception, the subjects in the Synovial Biopsy Subset will only be randomized to the 200 mg qd dose of VX-509 (Arm C). Subjects in the Synovial Biopsy Subset will know that they are not receiving placebo, but not the dose they are receiving.

11.10.1 Blinding

Blinding of all data will be maintained until the study database is locked. The packaging and labeling of study drug will be performed in a way that ensures dose levels are blinded. Investigators and site personnel will be blinded to drug concentrations during VX-509 dosing.

All study personnel will be blinded to subject treatment assignments except for the following individuals: an unblinded Vertex statistician who is not a member of the study execution team, Vertex Global Patient Safety and Regulatory Affairs representatives when required to satisfy regulatory reporting requirements, and Vertex bioanalytical scientist(s) or designee (as specimens from subjects randomized to placebo will not be routinely analyzed for PK).

11.10.2 Unblinding

The following are the limited circumstances where unblinding may be performed.

11.10.2.1 Unblinding: PK/PD Analyses

The Vertex clinical pharmacologist or designated clinical pharmacology vendor may request unblinded VX-509 and biomarkers data with masked subject identification numbers and true treatment assignments (Section 13.4).

A limited internal Vertex clinical pharmacology team will be unblended to subject randomization data for purposes of performing the PK analysis. However, other Vertex staff, clinical site staff, and subjects will remain blinded through study Data Lock.

11.10.2.2 Unblinding: Interim Analyses

An unblinded Biostatistician may perform an IA as described in Section 13.3.4.7. The unblinded Biostatistician may request unblinded interim data with true subject identification (ID) numbers and true treatment assignments, as will be specified in an Interim Analysis Statistical Analysis Plan.

11.10.2.3 Unblinding: Final Analysis

The Vertex study biostatistician or designee may request blinded final data after Week 12 with true subject ID numbers and dummy treatment assignments. Details will be provided in the Statistical Analysis Plan (SAP). The Vertex study biostatistician or designee may request unblinded final data after data lock with true subject ID numbers and true treatment assignments. Details will be provided in the SAP.

11.10.2.4 Unblinding: Drug Supply Quality Control at Study Sites and Depots

The Vertex Quality Assurance group or its designee will perform quality control/assurance inspections at study sites and drug supply depots. For those Vertex representatives who need access to unblinded data to perform this audit, they may request to be unblinded to true subject identification numbers and true treatment assignments.

11.10.3 Unblinding: Medical Emergencies or Urgent Clinical Situations

At the initiation of the study, each clinical study site will be instructed on the method for breaking the blind. The unblinding method will be either a manual or an electronic process.

Unblinding of individual subject treatment by the investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, the investigator must first attempt to contact the study medical monitor (see relevant telephone numbers provided in a separate contact information document), to discuss and agree to the need for unblinding. In situations in which the investigator has attempted and failed to contact the medical monitor, investigators should use their best judgment, based on the nature and urgency of the clinical situation, and proceed with unblinding.

Detailed instructions for unblinding in the case of medical emergencies will be provided in the study manual.

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor and study team should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (reason, date, etc.) should be clearly recorded in the subject’s study file. In addition, the investigator should consider whether the clinical event that prompted unblinding should be considered a serious adverse event (SAE), according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex Global Patient Safety or its designee.

Vertex Global Patient Safety or its designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Vertex Global Patient Safety may, for matters relating to safety concerns, unblind individual subjects at any time.

12 ASSESSMENTS

12.1 Timing of Assessments

The timing of assessments is shown in Table 3-1 and Table 3-2.

12.2 Subject and Disease Characteristics

Subject and disease characteristics will include the following: demographics, medical history (including allergies and vaccination history), RA medical history [(including RA duration and past RA therapies based on subject recall (no external documentation required)], height, weight, body mass index (BMI), and social characteristics (smoking and alcohol history).

12.3 Baseline X-rays

Baseline chest X-ray (posteroanterior and lateral view) will be performed at screening, unless available from a recent (within 12 weeks) X-ray. Chest X-ray may be performed on the same day as the hand and foot X-ray; however the screening Chest X-ray must be read before the hand and foot X-ray are performed.

Baseline X-rays of hands (posteroanterior view) and feet (anteroposterior view) will be performed by digital or single emulsion radiographs using a calibrated X-ray unit, according to the protocol Radiograph Manual. If single emulsion radiographs are performed, they will be subsequently digitized for blinded reading. The central reading facility (single reader) will review X-rays for correct technique and request repeat films if required, before the reading.

12.4 Pharmacokinetics

For the evaluation of plasma and synovial fluid concentrations of VX-509, samples will be collected according to the schedule of assessments detailed in Table 3-2.

12.4.1 Blood Sampling

For **all subjects**, blood samples for determination of concentrations of VX-509 will be collected at the following time points:

- **Day 1:** Blood samples will be collected before the first study drug dose, at 0.5 to 2 hours postdose, and at 4 to 6 hours postdose for determination of VX-509. Guidelines for administration of study drug and food/drink restrictions on this day are provided in Section 11.2.
- **Weeks 6 and 12 Visits:** Two blood samples at least 2 hours apart will be collected for determination of VX-509 (no required relationship to dosing time).

For subjects in the Synovial Biopsy Subset only - In addition to the PK samples drawn at Day 1, Weeks 6 and 12 for all subjects, this subset will also have a blood sample collected at Week 4 for determination of VX-509 (no required relationship to dosing time) immediately before the synovial biopsy and within 60 minutes before collection of the synovial fluid PK sample.

Approximately 4 mL of whole blood will be collected via direct venipuncture or by an indwelling catheter at each blood draw.

When an ECG coincides with a PK blood sampling time point, the ECG must be performed before blood sampling (Section 12.9.5).

The following should be recorded accurately in the CRF documentation: date and time (24-hour clock time) of administration of the study drug dose before PK sample collection (Day 1, Weeks 6 and 12); date and time of administration of the 2 most recent study drug doses before the PK sample (Week 4 for Synovial Biopsy Subset); and the date and time of each of PK blood sample.

12.4.2 Processing and Handling of PK Samples

Full instructions for PK sample collection from blood and synovial fluid, as well sample processing, handling, storage, and shipment will be included in the Study Reference Manual.

12.4.3 Bioanalysis of PK Samples

Plasma concentrations of VX-509 and its metabolite will be determined using validated liquid chromatography with tandem mass spectroscopy (LC/MS/MS) methods by Vertex or a qualified vendor under the supervision of Vertex. A description of the assay and validation data will be provided in separate reports.

Concentrations of VX-509 and its metabolite in synovial fluid will be determined using exploratory liquid chromatography with tandem mass spectroscopy (LC/MS/MS) methods, if successfully developed, by Vertex or a qualified vendor under the supervision of Vertex. A description of the assay will be provided in separate reports.

12.5 Arthroscopic Synovial Biopsies (Synovial Biopsy Subset only)

Arthroscopic synovial biopsies will be performed in a subset subjects at selected study sites (Synovial Biopsy Subset, Section 9.1). The subjects in the Synovial Biopsy Subset will only be randomized to the 200 mg qd dose of VX-509 (Arm C). Subjects at the selected arthroscopy sites should be offered participation in the study, regardless of their additional consent for the arthroscopy procedure, to prevent any sense of coercion. The institutional informed consent for the surgical procedure must be obtained before the first arthroscopy.

The arthroscopic procedure will be performed using sterile technique and local anesthetic, using a diagnostic arthroscope and secondary biopsy probe. The subject may receive a systemic agent for anxiety or muscle relaxation before the procedure.

An index joint of a knee or the non-MRI-designated wrist will be selected, with ≥2+ palpable synovitis defined as defined as loss of bony contours with palpable joint effusion and/or swelling. This joint must not have undergone a total joint replacement. The arthroscopy at Week 4 should be obtained from the same joint as the arthroscopy performed before the first dose on Day 1 (baseline). The baseline arthroscopic procedure may be performed from Day -4 to before the first dose on Day 1. The arthroscopic procedure at each visit will be conducted only after all other scheduled assessments are completed. The site staff will record the date and actual initiation time of the arthroscopic procedure on the eCRF using a standard 24-hour clock time. The site staff will ask the subject about their 2 most recent doses of study drug before the arthroscopic procedure and record the date and time of both doses in the source documentation.

Collection of Synovial Fluid: Upon initial introduction of the arthroscope into the joint space, 2 samples of synovial fluid will be collected for analysis of cell counts (first priority), of VX-509 concentration/PK (second priority), and the remainder of the fluid spun, decanted from the pellet, and frozen for potential analysis (Section 12.6.2). Full instructions for synovial fluid sample collection as well as processing, handling, storage, and shipment will be included in the Study Reference Manual.

Collection of Synovial Tissue: Synovial tissue will be obtained by shaver. For the knee, the biopsied quadrant would be suprapatellar pouch or medial/lateral gutter regions; for the wrist, the general joint should be biopsied. The biopsy at Week 4 should be obtained from the same region as the biopsy before the first dose on Day 1 (baseline). The location of the biopsy will be recorded in the procedure notes. The level of synovitis will be visually recorded. The

sample of synovial tissue will be collected in prefilled screw top vials for immunohistochemistry/histology (first priority), RNA (second priority) and protein (final priority). Full instructions for the collection of synovial samples as well as processing, handling, storage, and shipment will be included in the Study Reference Manual.

12.6 Biomarkers

12.6.1 Measurement of Biomarkers in Blood (all subjects)

At each time point indicated in Table 3-2, 3 whole blood samples of approximately 8 mL each will be collected via direct venipuncture or by an indwelling catheter.

Blood Biomarker Sample A will be stored by Vertex and used for potential exploratory biomarkers including measures of inflammation or response.

Blood Biomarker Sample B will be aliquoted as necessary and used to monitor the following biomarkers:

- **Osteoclast activation/bone turnover –** RANKL, osteocalcin, osteoprotegrin, and C-terminal type I collagen crosslinks
- **Inflammation** – TNF-α, IL-1β, IL-6, IL-15, IL-21 and macrophage colony-stimulating factor (M-CSF)

Flow Cytometry Sample:

- **Lymphocyte subsets** - T cells (CD3, CD4, CD8), B cells (CD19), natural killer cells (CD56+, CD16+, and CD3-), and CD25+ T-cell subsets

Additionally other exploratory biomarkers including measures of inflammation or response may also be assessed.

12.6.2 Measurement of Biomarkers in Synovial Fluid (Synovial Biopsy Subset only)

Synovial fluid will be collected as summarized in Section 12.5. The following assessments will be performed on synovial fluid samples (if possible, in descending order of priority):

- **Cell count and differential** - Total white count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils (absolute and percent) and red blood cells, will be the first priority.
- **PK assessment -** assessment of VX-509 concentration in synovial fluid.
- **Frozen synovial fluid sample -** the remaining synovial fluid will be centrifuged, and the supernatant will be frozen and stored for exploratory assessment. This will be the final priority.

Additionally other exploratory biomarkers including measures of inflammation or response may also be assessed.

12.6.3 Measurement of Biomarkers in Synovial Tissue (Synovial Biopsy Subset only)

Synovial tissue will be collected as summarized in Section 12.5. The following assessments will be performed on synovial tissue samples (if possible, in descending order of priority):

Immunohistochemistry/Histochemistry:

- CD68+, CD3+, CD20+, and CD138+ (hematoxylin and eosin)
- Staining for phosphorylated signal transducers and activators of transcription-5 (P-STAT5) (biomarker of JAK3 activation) and P-STAT3 (biomarker of JAK2 activation)
- Markers of bone homeostasis: CD14+, RANK+, RANKL, and OPG

Synovial RNA:

- B cell marker, T cell marker, IL-15, IL-21, RANKL, OPG, Retinoic acid receptor gamma, and T-box transcription factor

Synovial Protein:

- P-STAT5, P-STAT3, P-STAT1, and P-STAT2

Additionally other exploratory biomarkers including measures of inflammation or response may be assessed.

12.7 Pharmacogenomics

A single blood sample (**DNA Sample A**) will be collected on Day 1 for potential exploratory evaluation of correlations between DNA markers with PK, PD, treatment benefit, and adverse events, except for subjects who do not choose to participate in this assessment.

A second blood sample (**DNA Sample B**) will be collected on Day 1 for potential exploratory evaluation of correlations between DNA markers with health and disease, especially RA, except for subjects who do not choose to participate in this assessment.

Specimens collected for DNA assessment will be identified by the unique subject number. Subjects' name, initials, or birth date will not be associated with the respective specimen. Samples will be stored for at least 2 years and up to 15 years post-study completion by the Sponsor (or designee).

Blood samples (**RNA Sample**) will also be collected on Day 1 and Weeks 2, 4, 6, 12, and at the Safety Follow-up Visit, except for subjects who do not choose to participate in this assessment. These samples will be used for potential exploratory evaluation of correlations between RNA markers with PK, PD, treatment benefit, and adverse events.

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for pharmacogenomics analysis will be provided in a separate document.

12.8 Efficacy Assessments

12.8.1 Hand Magnetic Resonance Imaging

MRI-designated hand and wrist (the hand being used in the MRI assessments) will be acquired using an MRI scanner as specified in the imaging guidelines.

OMERACT RAMRIS scores for synovitis, bone marrow edema (osteitis), erosions, and joint space narrowing[50] will be read by 2 independent readers, who are blinded to dose assignment and to chronology of each time point. If the scores of the 2 independent readers exceed a pre-defined difference, a consensus adjudication session with both readers will occur to reach a consensus score for the designated cases.

12.8.2 Other Efficacy Assessments

The following assessments will be performed for the evaluation of efficacy:

- Tender/Swollen Joint Counts (restrictions related to analgesic medications taken in the period before each joint assessment are described in Section 10.3)
- Erythrocyte sedimentation rate
- C-reactive protein
- Physician Global Assessment of Disease Activity (Section 16.4)
- Subject Global Assessment of Disease Activity (Section 16.5)
- Subject assessment of pain (Visual Analog Scale, Section 16.6)
- Subject assessment of general health (Visual Analog Scale, Section 16.7)
- Subject assessment of disability (Health Assessment Questionnaire – Disability Index [HAQ-DI], Section 16.11
- Subject assessment of physical function and health-related quality of life (SF-36 Section 16.12)

12.9 Safety

Safety evaluations will include clinical laboratory assessments, clinical evaluation of vital signs, ECGs, physical examinations, and reporting of adverse events.

Medical history and physical examinations information will be collected during the course of the study and will be captured in the source documentation. Physical examinations post baseline will not be captured for inclusion into the study database. However, any untoward findings identified on physical examinations conducted after the administration of the first dose of study medication will be captured as an AE if those findings meet the definition of an AE. Demographic data collected at screening will be included in the study database.

12.9.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH-GCP guidelines. Section 14.1 outlines the definitions, collection periods, criteria, and procedures for

documenting, grading, and reporting adverse events. A separate document that details AE case report form completion guidelines for investigators as well as training will be provided.

12.9.2 Clinical Laboratory Assessments

Blood and urine samples for the procedures described in Table 12-1 will be analyzed at a local or central laboratory. Subjects must abstain from all food and drink (except water) at least 8 hours before blood draws for the fasting lipid profile. Laboratory test results that are abnormal and considered by the investigator to be clinically significant must be reported as adverse events.

Table 12-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis
Glucose Blood urea nitrogen Creatinine Creatine kinase Sodium Potassium Calcium Chloride Magnesium Inorganic phosphate Total and indirect bilirubin Alkaline phosphatase Aspartate transaminase Alanine transaminase Lactate dehydrogenase Total protein Albumin Uric acid Iron Studies **(baseline only)** Serum iron Ferritin Total iron-binding capacity	Hemoglobin Red blood cell count Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Reticulocyte count White blood cell count Differential (absolute and percent): Eosinophils Basophils Neutrophils Lymphocytes Monocytes	Leukocytes Nitrite Urobilinogen Protein pH Blood Specific gravity Ketones Bilirubin Glucose Microscopy: * Casts Bacteria Red blood cells White blood cells * If gross urinalysis is positive for leukocytes, erythrocytes, nitrite, protein, or bilirubin, microscopic examination of urine will be performed.

Additional Evaluations

Coagulation studies: Activated partial thromboplastin time; prothrombin time; and International Normalized Ratio.

Inflammation tests: C-reactive protein, and Westergren erythrocyte sedimentation rate

Fasting lipid profile: Total Cholesterol**,** HDL-C**,** LDL-C, LDL-C/HDL-C ratio, triglycerides. Leptin and lipoprotein (a) will be assessed as part of this profile only on Day 1 and at the Week 12/Early Discontinuation Visit.

Erythropoietin

Serology: Hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus 1 antibody, and human immunodeficiency virus 2 antibody.

Tuberculin skin testing: A 5 tu purified protein derivative (PPD) skin test will be positive if ≥10 mm at 48 to 72 hours.

QuantiFeron® TB Gold Assay: Serum incubation and enzyme-linked immunosorbent assay (ELISA) testing for latent tuberculosis.

Serum follicle stimulating hormone (FSH) test: Serum FSH concentrations for 45- to 55-year-old postmenopausal females only (Screening Visit only). Levels must be within the laboratory's postmenopausal range for subjects to be eligible for the study.

Pregnancy β-human chorionic gonadotropin (β-HCG) testing: for females of child-bearing potential. Serum samples will be obtained during the Screening Visit and analyzed at the central lab. The urine pregnancy test before dosing on Day 1 will be performed at the site.

Additional clinical laboratory evaluations may be performed at other times if judged to be clinically appropriate.

12.9.3 Liver Function Test Monitoring and Management

Study drug administration must be interrupted immediately and the medical monitor notified in subjects with elevations of ALT or AST >3 × ULN. Study drug should be permanently discontinued in subjects who experience either:

- ALT or AST >5 × ULN, or
- Total bilirubin >2 × ULN (or clinical jaundice) in association with an ALT, or AST >3 × ULN, with exception of subjects with Gilbert's Syndrome.

All subjects with transaminase elevations >3 × ULN should be followed closely, with repeat testing within 48 to 72 hours of the initial findings to check for progression or improvement. An investigation into potential causes should be conducted as outlined in the study manual.

Subjects in whom study drug was interrupted (not permanently discontinued) may resume dosing, following consultation with the medical monitor, if ALT and AST levels have improved within 3 weeks after study drug interruption. If AST and ALT values have not improved within 3 weeks of interruption of study drug, study drug must be permanently discontinued and the subject withdrawn from the study.

Following resumption of study drug, liver function tests should be monitored closely, with weekly testing for the first 2 weeks, and according to the study schedule thereafter.

12.9.4 Physical Examination, Weight/Height, and Vital Signs

A physical examination with review of all body systems, weight (with height at screening), and vital signs assessment will be performed at select study visits, as listed in Table 3-1 and Table 3-2. For all other scheduled visits, a symptom-directed physical examination assessment may be performed if indicated.

A physical examination includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin;

musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in physical examinations should be reported as adverse events.

Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, and respiratory rate. These will be assessed following a 5-minute rest in the supine position. Additional vital sign assessments may be performed if clinically indicated, in the opinion of the investigator.

12.9.5 Electrocardiograms

Standard 12-lead Electrocardiograms (ECGs) will be performed using a machine with printout at the time points indicated in Table 3-1and Table 3-2.

Additional 12-lead ECGs should be performed at any other time if clinically indicated.

The performance of all ECGs must adhere to the following guidelines:

- The subject will be instructed to rest in the supine position for at least 5 minutes before having an ECG performed.
- The ECG will be performed before any other procedures that may affect heart rate (e.g., blood draws).

The ECG traces will be manually read at the site at the Screening and Follow up Visits. The ECG machine will compute the PR, QT, and QTc intervals, QRS duration, and heart rate. RR intervals may be computed on site, or calculated later during analysis if this function is not available on site. A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Any clinically significant ECG abnormalities at screening will exclude the subject's participation in the study. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTc is increased by >45 msec from the baseline or an absolute QTc value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (>45 msec from baseline or ≥500 msec), a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

12.9.6 Contraception and Pregnancy

Embryo/fetal development studies in rats and rabbits performed with VX-509 showed evidence of fetal soft tissue and skeletal variations only in the rat, at high doses that were toxic to the mother, and were considered AEs on fetal growth and development (teratogenesis). The effects of VX-509 on conception, pregnancy, and lactation in humans are not known. Female subjects should not be exposed to VX-509 if breastfeeding or attempting to conceive.

Due to the potential for VX-509 presence in sperm, male subjects receiving VX-509 in a clinical study should not expose their partner if she pregnant, breastfeeding, or attempting to conceive VX-509 in a clinical study should not expose their partner if she pregnant, breastfeeding or attempting to conceive.

12.9.6.1 Contraception

At this stage in the development of VX-509, participation in this study (VX12-509-201) requires a commitment from the research subject and his/her partner to use 2 methods of birth control. Contraception for the couple is waived if the female partner is of non-childbearing potential (defined below) or in the rare case where the male partner is of non-childbearing potential (s/p orchiectomy).

Female Subjects of Non-Childbearing Potential:

To be considered of non-childbearing potential, the female subject must be:

- Postmenopausal: amenorrheic for at least 2 years and have a serum FSH level at screening within the laboratory's reference range for postmenopausal females; the FSH requirement is waived after age 60.
- Documented hysterectomy, or a bilateral oophorectomy/salpingo-oophorectomy.
- All other female subjects (including subjects with tubal ligations and subjects that do not have a documented hysterectomy) will be considered of childbearing potential.

Acceptable Contraceptive Methods:

Acceptable contraceptive methods for the **male** include the following:

- True abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomy 6 months or greater before the first dose of study drug, with a negative post-vasectomy semen analysis for sperm.
- Condom with spermicide (either as a single product if commercially available and/or allowed according to local regulations; otherwise condom and spermicide as separate products). This method should be in successful use at least 28 days before the first dose of study drug.
- Acceptable contraceptive methods for the **female** include the following:
- True abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Bilateral tubal ligation performed at least 6 months before the first dose of study drug.
- Oral, transdermal, injectable or implantable hormonal birth control method successfully used for at least 28 days before the first dose of study drug.

- An intrauterine device (hormone-releasing or non-hormone-releasing) in place for at least 90 days before the Screening Visit.
- Barrier contraception such as diaphragm, cervical cap, female condom or contraceptive sponge, with spermicide. This method should be in successful use at least 28 days before the first dose of study drug.
    - *Note: Female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.*
- All contraceptive methods must be utilized throughout the study and for 90 days following the last dose of study drug.

In addition, male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days following the last dose of study drug.

12.9.6.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug.

If a subject or the female partner of a male subject becomes pregnant while participating in the study, study treatment must be permanently discontinued immediately. The investigator must notify the medical monitor and Vertex Global Patient Safety within 1 business day of the site's knowledge of the subject's (or partner's) pregnancy, by utilizing the Initial Pregnancy Notification Report Form.

If confirmed to be on active drug, the subject or partner will be followed until end of pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained from at least 1 parent. A separate informed consent form will be provided to explain these follow-up activities. Pregnancy itself does not constitute an adverse event.

13 STATISTICAL AND ANALYTICAL PLANS

Analysis of all data, including safety, PK profiles, efficacy, and synovial biopsies will be performed by Vertex or designee. The results of all parts of the study will be reported in the clinical study report. A detailed analysis plan for the analysis of safety data and efficacy data will be presented in a statistical analysis plan (SAP), and a detailed analysis plan for PK profiles will be presented in a clinical pharmacology analysis plan (CPAP) before the database is locked for analysis.

As synovial biopsy subjects will only be randomized to the 200 mg qd VX-509 dose (Arm C), potential bias is introduced related to patient selection, subjective assessments, and other subject interactions. To minimize the impact of this potential bias, subjects in the Synovial Biopsy Subset will know that they are not receiving placebo, but not the VX-509 dose they are receiving. Centrally blinded MRI reading limits the potential impact on RAMRIS scores.

13.1 Sample Size and Power

Due to the small sample size of this trial, the study is not powered for demonstration of the significant changes in the treatment arm(s) as compared to placebo. Assuming that the true ACR20-CRP rates at Week 12 are 25%, 38%, 60%, and 65% for the 4 treatment groups, respectively (placebo, 100 mg, 200 mg, and 300 mg VX-509 qd), the study has approximately 25% power to demonstrate a significant difference between placebo and the 300 mg (highest) VX-509 dose.

The study will be utilized to evaluate early effects on the level of synovitis and bone marrow edema (osteitis) by MRI, and the dose-ranging information on RAMRIS scores will be utilized at end of Phase 2 to select the pivotal VX-509 dose(s) for study in Phase 3 clinical studies.

A published 24 week study evaluating golimumab 100 mg with or without concurrent methotrexate (MTX) in early RA subjects who were MTX-naïve showed mean baseline (interquartile range; minimum and maximum from any arm) RAMRIS scores of 8.8 to 10.3 (4.0 to 14.5), 8.4 to 11.5 (1.5 to 17.8), and 17.7 to 25 (8.8 to 27.0) for synovitis, bone marrow edema, and erosion, respectively.[24] Mean (standard deviation [SD]) change from baseline in placebo arm RAMRIS scores (N = ~60) were 0.14 (2.98), 0.56 (3.97), and 0.24 (3.38) for synovitis, bone marrow edema, and erosion, respectively. Changes from baseline for subjects receiving golimumab 100 mg therapy alone (N = ~60) were -1.76 (2.76), -2.04 (5.69), and 0.51 (3.09) for synovitis, bone marrow edema, and erosion, respectively. Changes from baseline for subjects receiving golimumab 100 mg therapy with MTX (N = ~62) were -2.18 (3.26), -1.22 (4.88), and 0.00 (0.83) for synovitis, bone marrow edema, and erosion, respectively. Using the golimumab + MTX scores, a trial would be 80% powered with 30, 100, and 1650 subjects per arm for synovitis, bone marrow edema, and erosion RAMRIS scores, respectively.

13.2 Analysis Sets

The Randomized Set is defined as all subjects who received a subject ID number and randomization with treatment assignment from the IVRS/IWRS.

The Full Analysis Set (FAS) is defined as all randomized subjects who received at least 1 dose of study drug. The FAS is an intention-to-treat efficacy analyses set in which subjects will be analyzed according to their randomized treatment group.

The Safety Set is defined as all randomized subjects who received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the actual treatment they received on Day 1.

The MRI Set is defined as all subjects in the FAS Set who had at least 1 post-baseline MRI assessment.

The PK Set is defined as all subjects in the Safety Set who had at least 1 post-baseline PK sample assessment.

The Synovial Biopsy Subset is defined as all patients in the Safety Set who had at least 1 post-baseline synovial biopsy performed.

13.3 Statistical Analysis

The Vertex Biometrics Department or its designee will analyze the efficacy, safety, and tolerability data. Methodological and related details will be provided in the SAP for this study, which will be finalized before clinical database lock.

13.3.1 General Considerations

Continuous data will be summarized by treatment group using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). For each continuous variable, if the measurements in the eCRF data are integers, then the corresponding mean and median will be presented to 1 decimal place and the SD to 2 decimal places; if the measurements are obtained to 1 decimal place, then the mean and median will be presented to 2 decimal places and the SD to 3 decimal places and so forth. Minimum and maximum will be displayed as reported in the eCRF data.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified.

Summaries of continuous and categorical data will be presented, as appropriate, by treatment group, for all treatment groups combined, and scheduled time points. The scheduled time points are presented in the assessment schedule in Table 3-1 and Table 3-2.

All subject data, including those derived, will be presented in the subject data listings; listings will display all subjects who were enrolled, regardless of whether or not they received study drug.

Unscheduled Visits: If a subject's unscheduled visit falls within the allowed visit window, then the unscheduled assessment will be subject to selection methods defined under the visit windows. All other unscheduled assessments will be included in subject data listings only.

Data handling conventions: For visit level summaries, the visit windows will be used to identify observations to be included in each visit summary.

13.3.2 Background Characteristics

13.3.2.1 Subject Sets

Subject numbers will be summarized by study arm, showing the number and percentage of subjects in the following defined subject sets, as appropriate: Randomized Set, FAS, Safety Set, MRI Set, PK Set and Synovial Biopsy Set.

13.3.2.2 Subject Disposition

Subject disposition data will be summarized for the FAS and Safety set (if different from the FAS), showing the number and percentage of subjects in the following categories, as appropriate:

- Completed 12 weeks of dosing
- Prematurely discontinued dosing and the reasons for discontinuation

- Completed the Safety Follow-up Visit
- Prematurely discontinued the study between end-of-dosing and the Safety Follow-up Visit and the reasons for discontinuation

13.3.2.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by FAS. Demographics will include age, gender, race, weight, height, BMI, region (United States, Other). Baseline characteristics will include duration of RA, DAS28-4(CRP), tender joint count, swollen joint count, CRP, ESR, rheumatoid factor (RF) (negative/positive), anti-CCP antibody status (negative/positive), RF and CCP status (RF+/CCP+, RF+/CCP-, RF-/CCP+, RF-/CCP-), current smoking status, HAQ-DI, subject assessment of pain, subject global assessment, physician global assessment, prior biologic response modifier (including anti-TNF) use (yes/No), previous number of DMARDs used (biologic + nonbiologic), baseline erosion status (yes/No), baseline vdHmTSS, and baseline RAMRIS scores (synovitis score, bone marrow edema (osteitis), erosion score, joint space narrowing score).

Continuous variables will be summarized by descriptive summary statistics and categorical variables will be summarized by counts in each category. For the RF and CCP status summary, if there is missing information, it will be considered as negative status. Duration of RA is defined as number of months between date of RA diagnosis and date of randomization. If day of diagnosis is missing, 15th day of the month will be used for duration calculation. If month is missing, July 1st of the diagnosis year will be imputed for the duration calculation.

Medical history will be presented in a subject data listing for condition/diagnosis and each medical history condition will be recorded as ongoing or not on the date of informed consent.

No statistical tests will be carried out to evaluate any baseline imbalance between dose groups.

13.3.2.4 Tuberculosis Screening

A PPD skin test and a serum QuantiFERON assay will be conducted at Screening to test for tuberculosis.

The administration and results (negative or if + mm induration) of the PPD skin test will be presented in subject data listing. The administration and results (value and positive or negative) of the QuantiFERON assay will be presented in subject data listing.

13.3.2.5 Chest X-ray

A chest X-ray (postanterior and lateral view) will be performed at screening, unless available from a recent (within 12 weeks) X-ray. All chest X-ray results, including the X-ray date, will be presented in a subject data listing.

13.3.2.6 Prior and Concomitant Medications

Medications taken 60 days before the Screening Visit and up to the Safety Follow-up Visit will be summarized by preferred term using the World Health Organization-Drug Dictionary (WHO-DD) for the FAS set as frequency tables in 2 parts:

Prior medication: medication that started before the first dose of study drug, regardless of when dosing of the medication ended.

Concomitant medication: medication received at or after the first dose of study drug, or medication that was received before initial dosing and continued after initial dosing of study drug, or with missing stop date.

Medication that started before the first dose of study drug and continued after the first dose of study drug will be summarized as prior medication and separately as concomitant medication. Medications with a missing start date will be considered to have a start date before the first dose of study drug.

Concomitant medication as defined above will also be summarized by preferred term using the World Health Organization-Drug Dictionary (WHO-DD) for the FAS set using Anatomical Therapeutic Chemical (ATC) level 1 and level 2 coding. In some drug categories, additional lower level ATC coding will also be displayed (NSAIDs, systemic corticosteroids, DMARDs, proton pump inhibitors, anti-infective agents, narcotic analgesics).

13.3.2.7 Study Drug Exposure

Exposure to study drug (i.e., duration of treatment) will be summarized in terms of the duration of subject treatment (in days). Duration of treatment (computed as date of the last dose of study drug minus date of the first dose of study drug plus 1) will be summarized using descriptive statistics. Study drug exposure with the relevant information will be presented in an individual subject data listing for all enrolled subjects.

Exposure summaries will be based on the Safety set.

13.3.2.8 Study Drug Compliance

The number of tablets planned is calculated based on the treatment duration for each visit interval. Compliance based on the study medication pill counts will be presented in a listing for the Safety Set. Compliance summaries will be tabulated.

13.3.2.9 Baseline Hand and Foot X-RAY

The central reading facility (single reader) will read hand and foot X-rays for the baseline vdHmTSS. The vdHmTSS score will be divided by the calculated duration of RA (in years) at study entry, to estimate the annual progression rate for erosions in each subject before study participation. The definition of no erosions at baseline will be an average vdHmTSS erosion subscore ≤ 1.

13.3.3 Efficacy Analysis

The primary efficacy analysis will assess the clinical response to 3 dose regimens of VX-509 administered comparing to placebo at Week 12 in subjects with active RA on stable DMARD therapy. All efficacy analyses will utilize the FAS or MRI Set or Synovial biopsy Subset, as applicable.

13.3.3.1 Analysis of Primary Variables

Clinical response will be measured by: proportion of subjects who achieve an ACR20-CRP response at Week 12, change from baseline in the DAS28-4(CRP) score at Week 12 and change from baseline of RAMIS scores. ACR responses for primary and secondary efficacy will be calculated using nonresponder imputation, where missing responses for any reason will be considered nonresponders.

13.3.3.1.1 ACR20-CRP Response

The response rate of ACR20-CRP at Week 12 will be summarized by the randomized treatment group and 95% confidence interval (CI) for each treatment group comparing to placebo will use the M&N method, a score-based interval.[51] Cochran-Armitage trend test will be performed at Week 12.

13.3.3.1.2 Change from Baseline in DAS28-4(CRP)

For the change from baseline in DAS28-4(CRP) at Week 12, the linear mixed effect model for repeated measures will be applied. It includes treatment dose group (placebo, 100 mg, 200 mg, 300 mg VX-509) and visit as fixed effects, and subject as random effect, with adjustment of baseline DAS28-4(CRP) and prior anti-TNF use as covariates. The difference in DAS28-4(CRP) at Week 12 compared to placebo for each treatment group will be estimated. The corresponding 95% CI of the difference from placebo will be provided. A dose-response trend test will be performed at Week 12.

13.3.3.1.3 Change from Baseline in RAMRIS Scores

The revised OMERACT 5 RAMRIS will be used to score the designated hand and wrist for MRI scans in this study. [52] Two independent readers who are blind to dose assignment will score the MRIs and will subsequently reconcile any disparity by an adjudication meeting. The interreader and intrareader reliability coefficients based on RAMRIS scores at Week 12 will be calculated for RAMRIS synovitis, edema (osteitis), erosion and joint space narrowing scores. The definition of no progression of erosions from baseline at Week 12 (or end of study) will be an average change in RAMRIS erosion score ≤ 0.

Change from baseline for all 4 RAMRIS scores (synovitis score, osteitis score, erosion score, and joint space narrowing) at Week 12 will be analyzed separately. A similar linear mixed effect model for repeated measures will be applied. It includes treatment dose group (placebo, 100 mg, 200 mg, 300 mg VX-509) and visit as fixed effects, and subject as random effect, with adjustment of baseline RAMRIS score and prior anti-TNF use as covariates. The difference for these three scores at Week 12 compared to placebo for each treatment group will be estimated. The corresponding 95% CI of the difference from placebo will be provided.

13.3.3.2 Analysis of Secondary Efficacy Variables

ACR50-CRP, ACR70-CRP response at Week 12

The response rate of the ACR50-CRP is defined as the subjects achieving an ACR50-CRP response divided by the total number of subjects included in the FAS, with a similar

definition for the ACR70-CRP. Non-responder imputation will be applied. The response rate at Week 12 will be summarized by the randomized treatment group and the 95% CI of the response rate difference for each treatment group compared to placebo will be calculated using the M&N method, a score-based interval.[53]

Remission based on DAS28-4(CRP) at Week 12

Remission as defined by DAS score is DAS28-4(CRP) score lower than 2.6. The DAS remission rate will be assessed at Week 12. Non-responder imputation will be applied. The response rate at Week 12 will be summarized by the randomized treatment group and the 95% CI of the response rate difference for each treatment group compared to placebo will be calculated using the M&N method.[53]

ACR Hybrid Scores at Week 12

The ACR hybrid score is designed to combine the ACR20, ACR50, and ACR70 response score with the mean % improvement in all of the 7 individual ACR components, and is a more sensitive measure of change.[54,55] The % improvement or worsening in each component is limited to 100%. If the mean % improvement is ≥20% in a subject who did not meet ACR20 criteria, the ACR hybrid score is limited to 19.99; similarly for ACR50 and ACR70. Conversely, if the mean % improvement is <20% in a subject who met ACR20 criteria, the ACR hybrid score is 20.00; similarly for ACR50 and ACR70.

For the change from baseline of ACR hybrid score, the linear mixed effect model for repeated measures will be applied. It includes treatment dose group and visit as fixed effects, subject as random effect, with adjustment of baseline ACR hybrid score and prior anti-TNF use as covariates. The difference of ACR hybrid score for each treatment group comparing to placebo at Week 12 will be estimated. The corresponding 95% CIs of the differences from placebo will be provided.

Change from Baseline in Physical Function at Week 12

Physical Function is assessed using the HAQ-DI and the Physical Function subscale of the SF-36. The following analyses apply to both. The linear mixed effect model for repeated measures will be applied. It includes treatment dose group and visit as fixed effects, subject as random effect, with adjustment of baseline scores and prior anti-TNF use as covariates. The difference of scores for each treatment group comparing to placebo at Week 12 will be estimated. The corresponding 95% CIs of the differences from placebo will be provided.

Change from Baseline in Physical Component Summary (PCS) score and Mental Component Summary (MCS) score from the SF-36, at Week 12

For the change from baseline for PCS score and MCS score at Week 12, the linear mixed effect model for repeated measures will be applied. It includes treatment dose group (placebo, 100 mg, 200 mg, 300 mg VX-509) as main effect, with adjustment of baseline scores and prior ant-TNF use as covariates. The difference of scores for each treatment group comparing to placebo at Week 12 will be estimated. The corresponding 95% CIs of the differences from placebo will be provided.

13.3.3.3 Analysis of Other Variables

Analyses of blood and synovial biomarkers are summarized in Section 13.5.

The relationship of change from baseline of RAMRIS scores at Weeks 6 and 12, change in disease activity by CDAI with ACR/EULAR or CDAI remission, and change from baseline of DAS 28-ESR and ACR20-ESR response at Weeks 6 and 12 will be explored.

To assess changes in health-related quality of life, each of the remaining 7 subscales of the SF-36 item scores will be analyzed.

13.3.3.4 Sensitivity Analyses

Due to the potential bias for the synovial biopsy subjects randomized only to 200 mg group, sensitivity analyses will be performed for the primary endpoints, ACR20-CRP and DAS28-4(CRP). The sensitivity analyses will exclude synovial biopsy subjects. Similar statistical methods will be applied for these sensitivity analyses.

13.3.4 Safety Analysis

The primary safety objective of the study is to evaluate the safety and tolerability of multiple doses of VX-509 when administered for 12 weeks in subjects with active RA on stable DMARD therapy. All safety analyses will be based on the Safety Set. All safety data will be presented in subject data listings.

Safety and tolerability are part of the primary objectives of this study. Safety variables include (1) adverse events; (2) labs (biochemistry, hematology, fasting lipids); (3) ECG measurements; and (4) vital signs. Safety analyses will be based on the Safety Set.

For safety variables, baseline value will be the last non-missing measurement before the first dose of study drug.

13.3.4.1 Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 15.0 or higher). The number and percentage of subjects experiencing an adverse event will be summarized by the MedDRA system organ class and preferred term, as well as by treatment group. Adverse events will be classified as pre-treatment or treatment-emergent. Pre-treatment AEs will be defined as AEs that developed or worsened after informed consent up to the first dose of study drug. Treatment-emergent AEs (TEAEs) will be defined as AEs that developed or worsened at or after the first dose of study drug up to and including the Safety Follow-up Visit or 28 days after the last dose of study drug, whichever is later.

Adverse event overall summary tables will be presented for TEAEs only and will include the following:

- TEAE/ related TEAE
- TEAE leading to death/related TEAE leading to death
- Serious TEAE/related serious TEAE

- TEAE leading to treatment interruption/related TEAE leading to treatment interruption
- TEAE leading to treatment discontinuation/related TEAE leading to treatment discontinuation
- Severe/life threatening TEAEs.

The TEAE by severity summary will be presented by MedDRA system organ class and preferred term using frequency counts and percentages.

Some rules that will apply to the summarization of adverse events are:

- a subject with multiple occurrences of the same adverse event or a continuing adverse event will only be counted once
- only the maximum severity level will be presented in the severity summary
- only the aggregate of possibly related or related relationship levels will be presented in the relationship summary

Adverse events will be listed separately for those leading to death, serious SAEs, dose interruption, and permanent discontinuation.

Adverse events leading to death, SAEs, dose interruption, and permanent discontinuation will be listed separately. All adverse events through the Safety Follow-up Visit will be listed in an individual subject data listing, including pretreatment adverse events.

13.3.4.2 Clinical Laboratory

All statistical analyses of laboratory values will be performed using SI units for hematology, serum chemistry, iron studies/erythropoietin, and fasting lipid profile tests. Laboratory results in both SI and conventional units will be presented in subject data listings.

Statistical summaries of all laboratory values will be presented by treatment group at each assessment time point for each continuous chemistry, hematology, iron studies/ erythropoietin and fasting lipid profile laboratory measurement. Changes from baseline will also be summarized by visit and treatment group. The number and percentage of subjects with shift changes from baseline, based on the laboratory normal ranges and the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) toxicity grading scale, will be tabulated for continuous laboratory assessments.

Two subject data listings of lab toxicity values of Grade 3 or higher will be provided: one listing displaying all clinically significant laboratory tests listed for subjects with any lab toxicity values of Grade 3 or higher, and the other listing with laboratory tests listed for subjects with Grade 3 or higher toxicity for the lab tests.

Change from baseline plots will be presented by treatment group and scheduled visit for selected laboratory values. The selected tests are lymphocytes, neutrophils, hemoglobin, erythropoietin, AST, ALT, creatinine, CRP, LDL, HDL, LDL/HDL ratio, triglycerides, platelet count, and each of the lymphocyte subsets.

Urinalysis and coagulation results will not be summarized in tables but only listed in subject data listings.

Clinically significant abnormal laboratory findings will be reported as adverse events.

13.3.4.3 Electrocardiograms

A summary of raw values and change from baseline values will be provided by treatment group at each scheduled visit for the following ECG measurements: PR, QT, QRS, and QTc intervals and heart rate. In addition, the number and percentage of subjects by maximum on-treatment value of QT/QTc intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum on-treatment change from baseline value of QT/QTc intervals, categorized as ≤30 msec, >30 msec and ≤60 msec, and >60 msec. A listing of subjects with abnormal, clinically significant ECGs will also be provided.

13.3.4.4 Vital Signs

The following vital signs will be summarized by treatment group at each scheduled time point: systolic and diastolic blood pressure (mmHg), body temperature, pulse rate (beats per minute [bpm]), and respiratory rate (breaths per minute). Clinically significant abnormal findings in vital signs will be reported as adverse events.

13.3.4.5 Physical Examination

Physical examination results will be presented in individual subject data listings only. Clinically relevant results will be reported as adverse events.

13.3.4.6 Other Safety Analysis

Fasting Lipid Profile

Fasting lipid profile raw values and change from baseline for total cholesterol, LDL, HDL, LDL/HDL ratio, triglycerides, leptin and lipoprotein (a) will be summarized by treatment group at each scheduled visit using descriptive statistics. Normal ranges for these tests will be presented.

Dyslipidemia Adverse Events

All subjects with treatment-emergent adverse events related to lipid abnormalities characterized by the specific Custom MedDRA Query ‘dyslipidemia,’ which pools the relevant ATC codes, will be summarized.

13.3.4.7 Interim and Data Monitoring Committee Analyses

A maximum of 2 IAs may be performed by an unblinded biostatistician. The IAs are not required, however an IA including efficacy and MRI data may be performed to enable dose selection for Phase 3 studies with VX-509. One IA may be conducted when all subjects have completed Week 6. Another potential IA may be conducted when approximately 50% to 70% of subjects have completed Week 12. No changes in study design or conduct will be made based on the results of an IA, therefore no statistical penalty (e.g., alpha spending) will be considered for final analysis testing.

Proper IA sets will be defined for efficacy IAs. Efficacy analyses for the primary endpoints, such as ACR20-CRP, DAS28-4(CRP), RAMRIS scores will be analyzed by the unblinded statistician by the described methodology based on the available data at the interim. Blinding of the study team will be maintained.

There will be no Data Monitoring Committee for this 12-week, 40-subject study.

No member of the Vertex study team will be unblinded to IA information for the study. Any member of the Vertex study team who becomes unblinded during study conduct, regardless of reason for unblinding, will be replaced until after final (end-of-study) database lock with a function representative who is blinded and be instructed not to disclose any unblinded information outside the unblinded team.

13.4 Clinical Pharmacology Analysis

The PK and PD analyses will include the analysis of PK and exploration of exposure-response relationships, between PK parameters and efficacy, safety, and/or PD biomarkers. Details of the analysis will be described in the CPAP.

13.4.1 Pharmacokinetic Analysis

The PK of VX-509 and its metabolite will be described using summary statistics. Preliminary review and analyses of the drug concentrations may be done before database lock under the conditions of masked identifications of the subject concentrations. Listings of VX-509 plasma concentration data from this study will be reported in the Bioanalytical Report for this study.

A population PK analysis of plasma concentration versus time data of VX-509 will be performed using the nonlinear mixed effects modeling approach. The population PK analysis will be reported in stand-alone document. Individual empirical Bayesian estimates extracted from the final population PK model will be used to simulate full, steady-state VX-509 PK profiles, from which individual steady state PK parameters will be derived, e.g., minimum observed concentration (C_{min}), maximum observed concentration(C_{max}), and AUC during a dosing interval ($AUC_{0-\tau}$).

Details of the analyses will be provided in a CPAP.

13.4.2 Pharmacodynamic Analysis

PD analyses are covered under efficacy (Section 13.3.3), safety (Section 13.3.4), and biomarker analyses (Section 13.5).

13.4.3 Pharmacokinetic/Pharmacodynamic Analyses

Selected biomarker response, efficacy, and key safety endpoints to the exposure of VX-509 and its metabolite relationship will be explored.

In the synovial fluid concentration of VX-509 and its metabolite will be correlated to the synovial biomarker and selected efficacy endpoints.

13.5 Biomarker Analyses

Blood Biomarker Sample A (all subjects): Analysis of these samples is undefined and will be documented in a separate future exploratory analysis plan.

Blood Biomarker Sample B (all subjects): For biomarkers of osteoclast activation/bone turnover and inflammation, change from baseline by visit and treatment dose group will be summarized. The methodology will be summarized in the SAP.

Flow Cytometry Sample: For the following cell populations, change from baseline by visit and treatment dose group will be summarized: lymphocyte subsets. The methodology will be summarized in the SAP.

Correlations between these the above markers and efficacy measures will be assessed. This analysis will be descriptive and the methodology will be summarized in the SAP.

Synovial Fluid Samples (Synovial Biopsy Subset only): Change from baseline by visit and treatment dose group of synovial fluid cell count and differential will be summarized by descriptive statistics. The methodology will be summarized in the SAP.

Analysis of synovial fluid sample will be described in an exploratory analysis plan.

Synovial Tissue Samples (Synovial Biopsy Subset only): For biomarkers in synovial tissue, including those assessed with immunohistochemistry/histochemistry, RNA, and protein, change from baseline at Week 4 will be summarized by treatment group. In addition, the ratio of OPG to RANKL will be calculated and the change from baseline at Week 4 of the ratio will be determined. The methodology will be summarized in the SAP.

Additional Analyses: Additional biomarker analyses may include: changes in gene transcription markers (RNA; test optional) in blood cells, and nucleotide polymorphisms in genomic DNA (optional). The exploratory biomarkers may be used to identify markers of efficacy, adverse events, or to find optimal dose. The methodology will be summarized in an exploratory analysis plan or the SAP depending upon timing of experimental results.

14 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

14.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

14.1.1 Adverse Events

14.1.1.1 Definition of an Adverse Event

An adverse event is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after the informed consent form (ICF) is signed.

A subset of adverse events may meet serious criteria. The definition of an SAE as well as reporting procedures are detailed in Section 14.1.2 of the protocol. The definitions below apply to both adverse events and SAEs.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered adverse events unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).

Exacerbation or worsening of the disease under study, RA, should not be captured as an adverse event unless either the event is at least possibly related to the product or the event meets the definition of an SAE.

14.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs should be assessed and those deemed a clinically significant worsening from baseline documented as an adverse event. When possible, a clinical diagnosis for the study assessment should be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself should be listed as the adverse event (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has or requires 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant must be made by the investigator.

A laboratory abnormality judged to be Grade 4, in itself, may not constitute an SAE unless the clinical status of the subject indicates a life-threatening adverse event.

14.1.1.3 Documentation of Adverse Events

All adverse events will be collected from the time informed consent signed until the following time points:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects: through the Safety Follow-up Visit

All subjects will be queried, using nonleading questions, about the occurrence of adverse events at each study visit. When possible, a constellation of signs and/or symptoms should be identified as one overall event or diagnosis. All adverse events for enrolled subjects will be recorded in the eCRF and source documents. Adverse events for subjects who are screened but not subsequently enrolled in the study will be recorded only in the subject's source documents. Adverse events should be reported and documented in accordance with the eCRF Completion Guidelines document which will be provided separately, along with training. The following data should be documented for each adverse event:

- Description of the event
- Classification of “serious” or “not serious”
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant or other treatment given

14.1.1.4 Adverse Event Severity

The investigator must determine and record the severity of all serious and nonserious adverse events.

The CTCAE Version 4.0 (Cancer Therapy Evaluation Program website; available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm; accessed 25 January 2010) should be used for grading the severity of adverse events. Adverse events of CTCAE Grades 4 and 5 should be documented as “life-threatening” in the eCRF and source documents. In considering the severity of an adverse event in a pediatric subject, the investigator should consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. An adverse event that does not appear in the CTCAE should be determined according to the definitions in Table 14-1. Clinically significant laboratory tests should be recorded in the eCRF as adverse events.

Table 14-1 Grading of Adverse Event Severity

Classification	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death

14.1.1.5 Adverse Event Causality

Every effort should be made by the investigator to assess the relationship of the adverse event, if any, to the study drug(s). Causality should be classified using the categories presented in Table 14-2.

Table 14-2 Classifications for Adverse Event Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event re-appeared on re-exposure to the investigational study drug.
Possibly Related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely Related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not Related	The event is related to an etiology other than the investigational study drug (the alternative etiology must be documented in the study subject's medical record).

14.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the adverse event according to the categories shown in Table 14-3.

Table 14-3 Classifications for Study Drug Action Taken With Regard to an Adverse Event

Classification	Definition
Dose Not Changed	Study drug dose not changed in response to the adverse event.
Dose Reduced	Study drug dose reduced in response to an adverse event.
Drug Interrupted	Study drug administration interrupted in response to an adverse event.
Drug Withdrawn	Study drug administration permanently discontinued in response to an adverse event.
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as when the investigational treatment had been completed before the adverse event began and no opportunity to decide whether to continue, interrupt or withdraw treatment is possible.

14.1.1.7 Adverse Event Outcome

An adverse event should be followed until the investigator has determined and provided the final outcome. The outcome should be classified according to the categories shown in Table 14-4.

Table 14-4 Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an adverse event with no residual signs or symptoms
Recovered/ Resolved With Sequelae	Resolution of an adverse event with residual signs or symptoms
Not Recovered/ Not Resolved (Continuing)	Either incomplete improvement or no improvement of an adverse event, such that it remains ongoing
Fatal	Outcome of an adverse event is death. "Fatal" should be used when death is at least possibly related to the adverse event.
Unknown	Outcome of an adverse event is not known (e.g., a subject lost to follow-up)

14.1.1.8 Treatment Given

The investigator must ensure that adequate medical care is provided to subjects for any adverse events, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the adverse event. "Yes" is used if any treatment was given in response to an adverse event, and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an adverse event.

14.1.2 Serious Adverse Events

14.1.2.1 Definition of a Serious Adverse Event

An SAE is any adverse event that meets any of the following criteria:

- Fatal (death, regardless of cause, which occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization, with the exception of planned or elective hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly or birth defect.
- Important medical event, which, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home).

Clarification should be made between the terms "serious" and "severe," because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on subject/event outcome or action criteria described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

14.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Follow–up Visit, regardless of causality, must be reported by the investigator to Vertex Global Patient Safety (GPS). In addition, all SAEs, including those that result in death, that occur after the Safety Follow-up Visit, and are considered related to study drug(s) must be reported to Vertex GPS **within 24 hours**.

SAEs will be recorded on the Vertex Clinical Trials SAE Form using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the Clinical Trials SAE Form, relationship to study drug(s) will be assessed only as related or not related, and severity assessment will not be necessary. The investigator is required to follow all SAEs to resolution/stabilization and report the outcome of all events to Vertex Global Patient Safety using the Clinical Trials SAE Form.

14.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the Sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The Vertex Clinical Trial SAE Form should be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow up information as soon as it becomes available, to ensure timely reporting to Health Authorities.

The SAE Form should be faxed to Vertex Global Patient Safety using the bar-coded fax cover sheet provided by GPS:

SAE Contact Information

Vertex Global Patient Safety

Fax: 1-866-545-6600 (US)

1-630-477-0000 (non-US)

Telephone: 617-444-6677

Country-specific toll-free contact information for reporting SAEs will be provided in the study manual.

14.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, and participating investigators, in accordance with ICH Guidelines, and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to Central Ethics Committees (EC).

It is the responsibility of the investigator or designee to promptly notify the local institutional review board/independent ethics committee (IRB/EC) of all unexpected serious adverse drug reactions involving risk to human subjects.

14.2 Administrative Requirements

14.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and according to local applicable laws and regulations. The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/EC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards, if applicable), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the investigator or Vertex, as allowable by local applicable laws and regulations.

14.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject before study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP guidelines and all applicable laws and regulation and will be subject to approval by Vertex or its designee.

14.2.3 Investigator Compliance

No modifications to the protocol should be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/EC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact should be made before the implementation of any changes. Any departures from the protocol must be fully documented in the source documentation and in a protocol deviation log.

14.2.4 Access to Records

The investigator must make the office and/or hospital records of subjects enrolled in this study available for inspection by Vertex or its representative at the time of each monitoring visit. The records must also be available for inspection, verification, and copying, as required by applicable laws and regulations and by officials of the regulatory health authorities (FDA and others). The investigator must comply with applicable privacy and security laws for use and disclosure of information related to this research set forth in this protocol.

14.2.5 Subject Privacy

To maintain subject confidentiality, all eCRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers. As required by federal regulations, the investigator will allow Vertex and/or its representative's access to all pertinent medical records in order to allow for the verification of data gathered in the eCRFs and for the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation for inspection.

As applicable, in accordance with the Health Insurance Portability and Accountability Act of 1996 and associated privacy regulations, a subject authorization to use personally identifiable health information may be required from each subject before research activities. This authorization document must clearly specify which parties will have access to a subject's personal health information, for what purpose and for how long.

14.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP guidelines and/or applicable local regulatory requirement(s), whichever is longest. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Vertex must be notified in writing.

14.2.7 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigator, IRB/EC, or Vertex may terminate the study at a given center or all centers.

Conditions that may warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

- Written notification that includes the reason for the clinical study termination is required.

14.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. Diaries and subject-reported outcomes will be entered into an eCRF by trained data entry staff using a secure, validated, web-based EDC application. Vertex will have access to all data upon entry in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution. Any changes to study data will be made to the eCRF and documented in an audit trail, which will be maintained within the clinical database.

14.4 Monitoring

Monitoring and auditing procedures developed or approved by Vertex will be followed, in order to comply with ICH GCP guidelines. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex (site monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

14.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC application sufficient to permit site personnel to enter or correct information in the eCRFs on the subjects for which they are responsible.

An eCRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, other observations, and subject status.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. An explanation should be provided for all missing data.

The audit trail entry will show the user's identification information, and the date and time of any correction. The investigator must provide formal approval of all the information in the

eCRFs, including any changes made to the eCRFs, in order to endorse the final submitted data for the subjects for whom the investigator is responsible. This formal approval must be made via the EDC application.

Vertex will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a CD or other electronic media will be placed in the investigator's study file.

14.6 Publications and Clinical Study Report

14.6.1 Publication of Study Results

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere should be considered the confidential and proprietary property of Vertex. The investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary in order to evaluate that information. The investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and therefore may be disclosed as required to other clinical investigators, the US FDA, and to other government agencies. The investigator also understands that, in order to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between Vertex and the investigator and/or the investigator's institution.

14.6.2 Clinical Study Report

A clinical study report, written in accordance with the ICH E3 Guidelines, will be submitted in accordance with local regulations.

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16 APPENDICES

16.1 The American College of Rheumatology Revised Criteria for Rheumatoid Arthritis

Four or more criteria must have been present at the time of diagnosis of RA. Criteria 1 through 4 must have been present for at least 6 weeks. Subjects with 2 clinical diagnoses are not to be excluded.

CRITERION	DEFINITION
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left proximal interphalangeal joint (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and metatarsophalangeal (MTP) joints
3. Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in ≤5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

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16.2 Washout Periods for DMARDs

	Washout Periods Before Screening if DMARD Recently Discontinued
DMARD – 1 DMARD REQUIRED (Anti-malarial allowed alone or with 1 other DMARD)	
Leflunomide	28 days[a]
Methotrexate	45 days
Penicillamine	60 days
Sulfasalazine	45 days
Anti-malarial: Hydroxychloroquine/Chloroquine	28 days
NON-BIOLOGIC DMARD – MUST WASH OUT	
Azathioprine/ 6-mercaptopurine	45 days
Cyclophosphamide	60 days
Cyclosporine	60 days
Oral or injectable gold	60 days
Mycophenolate	60 days
BIOLOGIC DMARD – MUST WASH OUT	
Abatacept	60 days
Adalimumab	45 days
Anakinra	45 days
Certolizumab pegol	60 days
Etanercept	45 days
Golimumab	60 days
Infliximab	60 days
Rituximab/Ocrelizumab (any depleting monoclonal)	365 days[b]
Tocilizumab	60 days

[a] Subjects required to take cholestyramine for 3 days and then subsequently at least 28 days of the washout period.

[b] All cytopenias must have recovered.

16.3 Lists of Prohibited Medications and Medications to be used with Caution

Table 16-1 Potential for Significant Drug Interactions: CYP3A and P-gp Inhibitors and Inducers Not to be administered from 14 days before first dose of study drug until 7 days after last dose of study drug*

Activity	Medication	VX-509 Dose Adjustment
Strong CYP3A Inhibitors	Antibiotic: clarithromycin, telithromycin HIV: indinavir, lopinavir/ ritonavir, nelfinavir, ritonavir, saquinavir HCV: boceprevir, telaprevir Anti-fungal: itraconazole, ketoconazole, voriconazole, posaconazole Calcium channel blocker: mibefradil[b] Phenylpiperazine anti-depressant: nefazodone Vasopressin receptor antagonist: conivaptan grapefruit, grapefruit juice[a]	Prohibited
Moderate CYP3A Inhibitors	Antibiotic: ciprofloxacin, erythromycin HIV: Amprenavir, atazanavir, darunavir, fosamprenavir, ritonavir Anti-fungal: fluconazole Calcium channel blocker: diltiazem, verapamil Myeloproliferative: imatinib Substance P antagonist: aprepitant grapefruit, grapefruit juice[a]	Prohibited
Strong CYP3A Inducers	Cholesterol acyltransferase (ACAT) inhibitor: avasimibe[b] Anticonvulsant: carbamazepine, phenobarbital, phenytoin Anti-mycobacterial: rifabutin, rifampin St. John's wort[c]	VX-509 plasma concentrations will decrease more rapidly – not allowed in clinical trial
P-gp Inhibitors	Calcium channel blocker: verapamil Antibiotic: erythromycin Anti-fungal: itraconazole, ketaconazole Anti-arrhythmic: quinidine	Prohibited
P-gp Inducers	Anti-mycobacterial: rifampin St John's wort[c]	Prohibited

* Please be advised that this list is not exhaustive. For an up to date list of CYP3A4 inhibitor medications, please refer to the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

a The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low strength).

b Withdrawn from the United States market for safety reasons.

c Herbal product.

Table 16-2 Potential for Significant Drug Interactions: CYP3A Substrates Not to be administered from 14 days before first dose of study drug until 7 days after last dose of study drug*

Alpha 1-adrenoreceptor antagonist	
alfuzosin	
tamsulosin	
Analgesics	**alternative: dextromorphan (with caution)**
Alfentanil	
Buprenorphine	
Fentanyl	
Lidocaine (systemic)	
Methadone	
Anti-arrhythmics (all Class I and Class III, including but not limited to the following examples):	
Class I - quinidine, flecainide, propafenone	
Other - bepridil	
Antihistamines	**alternatives: loratadine, fexofenadine**
astemizole	
terfenadine	
Sedatives/anxiolytics	**alternatives (with caution)**: **alprazolam, diazepam,**
oral midazolam	**trazadone, midazolam IV**
estazolam	
triazolam	
Calcium channel blockers	**alternatives (with caution): amlodipine, diltiazem,**
felodipine	**nicardipine, nifedipine, verapamil**
nisoldipine	
GI/GERD treatments	**alternative: metoclopramide**
cisapride	
domperidone	
Lipid lowering agents	**alternatives: pravastatin, rosuvastatin**
lovastatin	**alternative (with caution): atorvastatin**
simvastatin	
Phosphodiesterase type-5 inhibitors	
sildenafil	
tadalafil	
vardenafil	
Migraine	**alternatives: sumatriptan, zolmitriptan, frovatriptan**
ergot derivatives (dihydroergotamine, ergotamine, ergonovine, methylergonovine)	
eletriptan	
Miscellaneous	
colchicine	
cyclosporine	
dronedarone	**alternative: cardioversion**
eplerenone	**alternative: spironolactone**
pimozide	**alternatives: other antipsychotics (some with caution)**
salmeterol	
sirolimus/tacrolimus	

Table 16-2 Potential for Significant Drug Interactions: CYP3A Substrates Not to be administered from 14 days before first dose of study drug until 7 days after last dose of study drug*

	telithromycin	**alternative: azithromycin; other antibiotics approved for CAP**

* Please be advised that this list is not exhaustive. For any drug that is metabolized by CYP3A and not on this table, please check with Medical Monitor for guidance on coadministration. Note that this may also include certain dietary supplements including androgenic supplements.

Table 16-3 Medications To Be Used With Caution: CYP3A Substrates Dose reduction or limits to dosing frequency may be required in the presence of study drug*

Analgesics
dextromorphan
Calcium channel blockers
diltiazem
nicardipine
nifedipine
verapamil
Sedatives/anxiolytics
diazepam
trazadone
midazolam IV
Lipid lowering agents
atorvastatin
Miscellaneous
bosentan
budesonide
buspirone
dexamethasone
fluticasone
imatinib
saxagliptin
terbinafine
warfarin
voriconazole
zolpidem

* Please be advised that this list is not exhaustive. For any drug that is metabolized by CYP3A but that is not on this table, please check with the Medical Monitor for guidance on coadministration. Note that this may also include certain dietary supplements including androgenic supplements.

16.4 Physician Global Assessment of Disease Activity

Physician Global Assessment of Disease Activity

- The subject's current disease activity is estimated by the physician.
- The physician should not view the patient’s assessment prior to performing this estimate.
- A zero (0) means no disease activity and a ten (10) means extreme disease activity.
- One number is circled.

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

16.5 Subject Global Assessment of Disease Activity Worksheet

Subject Global Assessment of Disease Activity

- The subject assesses overall arthritis activity
- A zero (0) means no disease activity and a ten (10) means extreme disease activity.
- One number is circled.

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

16.6 Subject Pain Visual Analog Scale

The length of the line is measured from the left (in mm) and the value (in mm) recorded in the subject's case report form.

Indicate the amount of pain you are currently experiencing by marking a vertical line at the appropriate position through the line below.

16.7 Subject General Health Visual Analog Scale

The length of the line is measured from the left (in mm) and the value (in mm) recorded in the subject's case report form.

Please indicate in general, how you would rate your health currently by marking a vertical line at the appropriate position through the line below.

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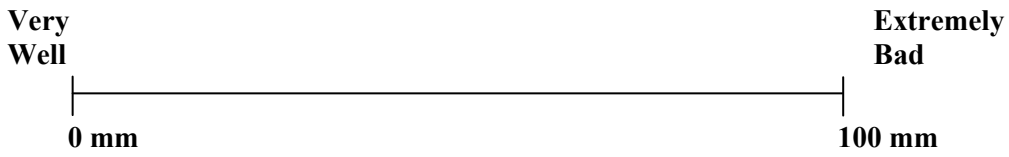

16.8 Disease Activity Scores and EULAR Response Criteria

The DAS28-4(CRP) (4-component) will be calculated using the following formula:

DAS28-4(CRP) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96

TJC28: 28 Tender joint count; SJC28: 28 Swollen joint count; CRP: C-reactive protein; GH: General Health on a 100mm Visual Analogue Scale (VAS).

Comparing the DAS28-4(CRP) from 1 subject on 2 different time points, it is possible to define improvement or response. The EULAR response criteria are defined as follows:

	DAS28-4(CRP) Improvement from Baseline		
Present DAS28-4(CRP)	**>1.2**	**>0.6** to **≤1.2**	**≤0.6**
≤3.2	good response	moderate response	no response
>3.2 to ≤5.1	moderate response	moderate response	no response
>5.1	moderate response	no response	no response

Further information on DAS28-4(CRP) can be found at http://www.das-score.nl

16.9 ACR/EULAR Definition of Remission, SDAI and CDAI

Subjects shall be considered to be in remission when either:

(1) scores on the tender joint count, swollen joint count, CRP (mg/dL), and subject global assessment (0-10 scale) are all ≤1

OR

(2) the score on the Simplified Disease Activity Index is ≤3.3

The Simplified Disease Activity Index will be calculated using the following formula:

Sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and CRP (mg/dL)

The Clinical Disease Activity Index (CDAI) will be calculated using the following formula:

Sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), and physician global assessment (0–10 scale)

CDAI (range 0-76)	
>22	severe disease
>10 - ≤22	moderate disease activity
>2.8 - ≤10	low disease activity
≤2.8	remission

Note: 28/28 joint counts are utilized for the DAS28-4(CRP) calculation and EULAR response criteria using DAS (Appendix 16.8 and for ACR/EULAR remission, SDAI and CDAI, while 48/46 joint counts are utilized for the ACR calculation (Appendix 16.10). ACR/EULAR publications note that disease activity can be missed with 28 joints and suggest addition of ankles and feet.

References:

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16.10 American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis

Required: ≥20% improvement in tender joint count

≥20% improvement in swollen joint count

And, at least 20% improvement in 3 of the following 5:

Subject pain assessment

Subject global assessment

Physician global assessment

Subject self-assessed disability

Acute-phase reactant (CRP or ESR)

	Disease Activity Measure	Method of Assessment
1.	Tender joint count	ACR tender joint count, an assessment of 28 joints or more. The joint count should be done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The information on various types of tenderness should then be collapsed into a single tender-versus-nontender dichotomy.
2.	Swollen joint count	ACR swollen joint count, an assessment of 28 or more joints. Joints are classified as either swollen or not swollen.
3.	Subject's assessment of pain	A horizontal pain VAS (0-100 mm) is used to assess the subject's current level of pain.
4.	Subject's global assessment of disease activity	The subject's overall assessment of their arthritis is documented on a 0-10 scale.
5.	Physician's global assessment of disease activity	The physician's assessment of the subject's disease activity is documented on a 0-10 scale
6.	Subject's assessment of physical function	The HAQ self-assessment instrument which measures physical function in RA subjects is acceptable, validated, has reliability, and has been proven in RA trials to be sensitive to change.
7.	Acute-phase reactant value	A Westergren erythrocyte sedimentation rate or C-reactive protein level

ACR = American College of Rheumatology

CRP = C-reactive protein

ESR = Erythrocyte sedimentation rate

RA = Rheumatoid Arthritis

HAQ = Health Assessment Questionnaire

Pain VAS = Pain Visual Analog Scale

Reference: Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R Jr, Paulus H, Strand V. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995; 38(6): 727-35.

16.11 Health Assessment Questionnaire – Disability Index [HAQ-DI]

HEALTH ASSESSMENT QUESTIONNAIRE

Name____________________________________ Date__________________________________

PATKEY#________
QUESTDAT_______

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_______

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

QUESTYPE_______

PMSVIS_________
RASTUDY________
QUESTNUM_______

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
DRESSING & GROOMING					
Are you able to:					
- Dress yourself, including tying shoelaces and doing buttons?	____	____	____	____	
- Shampoo your hair?	____	____	____	____	DRESSNEW______
ARISING					
Are you able to:					
- Stand up from a straight chair?	____	____	____	____	
- Get in and out of bed?	____	____	____	____	RISENEW_______
EATING					
Are you able to:					
- Cut your meat?	____	____	____	____	
- Lift a full cup or glass to your mouth?	____	____	____	____	
- Open a new milk carton?	____	____	____	____	EATNEW________
WALKING					
Are you able to:					
- Walk outdoors on flat ground?	____	____	____	____	
- Climb up five steps?	____	____	____	____	WALKNEW

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane
_____ Walker
_____ Crutches
_____ Wheelchair
_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
_____ Built up or special utensils
_____ Special or built up chair
_____ Other (Specify:_____________________)

DRSGASST_______
RISEASST_______

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

EATASST________
WALKASST_______

STANFORD-RA (MAY99 - Phase 31) – English, USA -1-

HAQ-DI - United States/English
f:\institut\cultadap\project\5000\study5000\questionnaire\original\forproject\haq-di_au1.0-eng-usori.doc-10/12/2006-co

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	____	____	____	____	
- Take a tub bath?	____	____	____	____	
- Get on and off the toilet?	____	____	____	____	HYGNNEW______
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	____	____	____	____	
- Bend down to pick up clothing from the floor?	____	____	____	____	REACHNEW______
GRIP					
Are you able to:					
- Open car doors?	____	____	____	____	
- Open jars which have been previously opened?	____	____	____	____	
- Turn faucets on and off?	____	____	____	____	GRIPNEW______
ACTIVITIES					
Are you able to:					
- Run errands and shop?	____	____	____	____	
- Get in and out of a car?	____	____	____	____	
- Do chores such as vacuuming or yardwork?	____	____	____	____	ACTIVNEW______

Please check any AIDS OR DEVICES that you usually use for any of these activities:

____Raised toilet seat ____Bathtub bar

____Bathtub seat ____Long-handled appliances for reach

____Jar opener (for jars previously opened) ____Long-handled appliances in bathroom

____Other (Specify: ____________________)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

____Hygiene ____Gripping and opening things

____Reach ____Errands and chores

HYGNASST______
RCHASST______
GRIPASST______
ACTVASST______

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A <u>VERTICAL</u> (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 ____ SEVERE PAIN 100

PAINSCAL______

STANFORD-RA (MAY99 - Phase 31) – English, USA -2- ©Stanford University

HAQ-DI - United States/English

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16.12 Version 2 of the SF-36 Health Survey (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

16.13 Steroid Equivalence Table

Substance*	**Representative Trade Names (not including topical, ophthalmologic or inhaled preparations)**	**Prednisone 10 mg/day Equivalence**
Prednisone	Apo-prednisone, Deltasone, Melicorten, Orasone, Panasol-S, Prednicen-M, Sterapred, Winpred, Decortin, Hostacortin	10 mg
Betamethasone	Alphatrex, Betacort, Betaderm, Betatrex, Betnesol, Benelan, Betamethasone Diproprionate, Celestone/Alphatrex, Beta-Val, Celestan, Maximate, Diprolene AF, Diprosone, Teladar/Diprolene	1.2 mg
Budesonide	Entocort	2.25 mg
Cloprednole	Synthesan	5 mg
Cortisone	Cortson CIBA, Cortone Acetate	50 mg
Deflazacort	Calcort	12 mg
Dexamethasone	Aeroseb-Dex, Dalalone, decadrone phosphate, Dexasone, Dexacen LA-8, Dexacen-4, Dexone, Hexadrol phosphate, Solurex, Decadron, Fortecortin, Auxiloson, Milicorten	1.5 mg
Fluocortolone	Ultralan	10 mg
Hydrocortisone	Cortef, Hydrocortisone, Hydrocortone, Solu-Cortef, Cortenema, Cortifoam, Colocort Rectal suspension, Hydrocortison Hoechst, Proctofoam-HC	40 mg
Methylprednisolone	Medrol, Depo-Medrol, Depo-Medrone, Duralone, Solu-Medrol, Medralone, Rep-Pred/A-Methaped, Medrate, Urbason	8 mg
Paramethasone	Monocortin	4 mg
Prednisolone	Delt-Cortef, Hydeltrasol, Hydeltra-TBA, Key-Pred 25, Predalone 50, Precor-25, Prelone, Solu-decortin-H, Detacortril, Orapred, Hostacortin_H, Ultracorten-H, Scherisolon	10 mg
Prednylidene	Decortilen	12 mg
Triamcinolone	Amcort, Aristocort, Atolone, Azmacort, Cenocort A-40, Cenocort Forte, Kenocort, Kenalog, Tac-40, Triam-A, Triamcinolone, Triam Forte, Triamolone, Tri-kort, Trilog, Trilone, Dephicort, Extracort, Triam-oral, Volon	8 mg

*Use only the corticosteroid drugs approved in the subject's country of residence