SYNOPSIS

SPONSOR Vertex Pharmaceuticals Incorporated 130 Waverly Street Cambridge, Massachusetts 02139-4242 USA	~~*(For Regulatory Authority Use Only)*~~
NAME OF FINISHED PRODUCT VX-509 tablets	
NAME OF ACTIVE INGREDIENT VX-509	

TITLE OF STUDY

A 12-week, Double-blind, Randomized, Parallel-Group, Placebo-Controlled Study of 4 Doses of VX-509 in Subjects With Active Rheumatoid Arthritis

INVESTIGATORS AND STUDY CENTERS

Lead Investigator

[redacted], US

Study Centers

This study was conducted at 54 sites in Belgium, Croatia, Germany, Hungary, Poland, Puerto Rico, Romania, Russia, Serbia, and the United States (US).

PUBLICATION REFERENCE

Fleischmann R, Spencer-Green GT, Fan F, Frankovic B, Luo X, Hoock T, et al. Dose ranging study of VX-509, an oral selective JAK3 inhibitor, as monotherapy in patients with active rheumatoid arthritis (RA). Arthritis Rheum. 2011;63(12):4042.

STUDY PERIOD	**PHASE OF DEVELOPMENT**
24 February 2010 11 July 2011	2a

OBJECTIVES

Primary Objective

- To assess the clinical response of 4 doses of VX-509 compared to placebo in subjects with active rheumatoid arthritis (RA) as defined by 2 endpoints: the American College of Rheumatology defined 20% response based on C-reactive protein (ACR20-CRP) at Week 12 and the change from baseline using Disease Activity Score 28 based on CRP (DAS28-CRP) improvement at Week 12
- To evaluate the safety and tolerability of VX-509 compared to placebo when administered for 12 weeks to subjects with active RA

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Secondary Objectives

- To assess the clinical response of 4 doses of VX-509 compared to placebo in subjects with active RA using the following:
  - ACR-CRP-defined 50% and 70% responses (ACR50,70-CRP) at Week 12
  - European League Against Rheumatism (EULAR) response at Week 12
- To assess the improvement in individual components of the ACR response of 4 doses of VX-509 compared to placebo at Week 12
- To determine the pharmacokinetics (PK) of VX-509 when administered to subjects with active RA for 12 weeks
- To assess the phosphorylated signal transducer and activator of transcription (P-STAT) biomarker responses in blood and inflammatory protein/proteomic biomarker responses in plasma
- To assess the magnitude of improvement in quality of life (Short Form-36 [SF-36])

METHODOLOGY

This was a multicenter, double-blind, parallel-group, randomized, placebo-controlled study of 4 dosing regimens of VX-509 administered to subjects with active RA. Following a 3-week Screening Period, subjects with active RA and disease duration of at least 6 months, who had failed at least 1 previous disease-modifying antirheumatic drug (DMARD), were randomly assigned in a 1:1:1:1:1 ratio to 1 of the following 5 treatment groups: VX-509 25 mg, 50 mg, 100 mg, or 150 mg or matching placebo tablets twice a day (bid) for 12 weeks. Subjects returned to the clinic for safety, efficacy, PK, and pharmacodynamic (PD; biomarker) evaluations at Weeks 1, 2, 4, 6, 8, and 12. Follow-up evaluations were performed 4 weeks after the last dose of study drug.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED)

A total of approximately 200 subjects were planned for enrollment with 40 subjects in each of the 5 treatment groups. Forty-five clinical sites participated.

A total of 206 subjects were randomized and 204 subjects received at least 1 dose of VX-509: 41 subjects received 25 mg bid, 41 subjects received 50 mg bid, 40 subjects received 100 mg bid, and 41 subjects received 150 mg bid. Forty-one subjects received at least 1 dose of VX-509-matched placebo. A total of 164 subjects completed dosing with the study drug.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male or female subjects aged 18 to 75 years (inclusive) with RA as defined by the ACR-revised criteria with disease duration of at least 6 months and who had failed at least 1 nonbiologic DMARD, including methotrexate, were eligible for enrollment. Additionally, subjects could have had previously failed no more than 1 biologic DMARD and must have discontinued treatment for reasons other than inadequate response (e.g., adverse events [AEs] or intolerance).

Entry criteria included a swollen joint count of ≥6 of 28 joints and a tender joint count of ≥6 of 28 joints as well as a CRP level ≥1.5 times the upper limit of normal (ULN) at screening.

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TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS

VX-509 was studied as bid doses of 25, 50, 100, and 150 mg for 12 weeks.

VX-509 tablets were administered orally as tablets containing 25 mg (batches: B090472 and B100183 [USA]) or 50 mg (batches: B090476 and B100118 [USA])

DURATION OF TREATMENT

The total duration of the study was approximately 19 weeks, including up to a 28-day Screening Period, a 12-week Treatment Period, and a 4-week Safety Follow-up Period after completion or discontinuation of treatment. The study ended when the last subject completed the 4-week Safety Follow-up Visit.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS

VX-509-matching placebo tablets (batches: B090494 and B100116 USA]) were administered orally, bid for 12 weeks.

CRITERIA FOR EVALUATION

- Safety: Safety was assessed from physical examinations, including vital signs; clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis testing); electrocardiogram (ECG); and lipid profile.
- Efficacy: Efficacy was assessed from tender joint count, swollen joint count, subject assessment of general health, subject assessment of disability (Health Assessment Questionnaire [HAQ]), subject assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, CRP, erythrocyte sedimentation rate (ESR), duration of morning stiffness, and quality-of-life assessments (SF-36).
- PK: VX-509 plasma concentrations were determined from blood samples collected throughout the study.
- PD: Response was assessed from blood samples collected throughout the study. PD assessments included Janus kinase (JAK) 3 activity (P-STAT5), JAK2 activity (P-STAT3), and concentrations of lymphocyte subsets (T cells: cluster of differentiation [CD] 3, CD4, CD8; natural killer [NK] cells: CD56; B cells: CD19).

STATISTICAL METHODS

Pharmacokinetics

Dataset preparation, exploration, and visualization for the PK analysis were performed using R® Version 2.13.0

The population PK analyses were performed using nonlinear mixed-effects modeling analysis in NONMEM Version 7.2 with the first-order conditional estimation and the INTERACTION option. Perl-speaks-NONMEM (PsN V3.4.2) was used to generate the bootstrap resampling analysis and the visual predictive check. Various compartmental models were constructed to assess the PK of VX-509 based on sparse samples collected during the study. The form of between-subject variability and residual error models were also evaluated.

The quality-of-fit of compartmental models were evaluated using a standard model discrimination process including statistical criteria (minimum value of objective function) and pertinent graphical representations of goodness-of-fit (e.g., fitted and observed concentrations versus time).

Covariates at baseline, such as body weight, age, sex, and creatinine clearance were evaluated as possible

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explanatory variables for the PK of VX-509. The most relevant covariates were formally evaluated within NONMEM using a stepwise forward additive approach, using a *P* value of 0.05 then a backward elimination using a *P* value of 0.01.

Pharmacodynamics

The listings describing the percent change from baseline of P-STAT5 and P-STAT3 activity were generated with R® Version 2.13.0 [redacted]

Individual percent change from baseline of P-STAT5 and P-STAT3 were summarized by dose level of VX-509 (0, 25, 50, 100, and 150 mg bid) and visit with descriptive statistics (arithmetic mean, arithmetic standard deviation [SD], arithmetic percent coefficient of variation, median, minimum, maximum, geometric mean, geometric mean percent coefficient of variation, and N), and by plotting individual percent change from baseline against dose for each visit.

A detailed analysis of lymphocyte subsets was performed to assess potential changes in CD19+ (B lymphocytes), CD3+ (T lymphocytes), CD4+ (helper T lymphocytes), CD8+ (cytotoxic T lymphocytes), and CD56+ (NK cells). Data were presented as absolute counts with descriptive statistics for the Full Analysis Set (FAS). In addition, the change from baseline is presented in absolute counts with descriptive statistics.

Pharmacokinetics/Pharmacodynamics

Dataset preparation, exploration, and visualization for the PK/PD analysis were performed using R Version 2.13.0 [redacted]

The population PK/PD analyses were performed using nonlinear material effect analysis in NONMEM Version 7.2 with the first-order conditional estimation and the INTERACTION option. Perl-speaks-NONMEM (PsN V3.4.2) was used to generate the bootstrap resampling analysis and the visual predictive check.

Similar to the population PK analysis, effects of VX-509 on biomarkers (P-STAT5 and P-STAT3) and clinical responses of primary and selected secondary variables (ACR20-CRP [nonresponder imputation; NRI], ACR50-CRP [NRI], and DAS28-CRP [observed]) were characterized using nonlinear mixed-effects modeling in NONMEM.

The percent change from baseline in P-STAT5 and P-STAT3 was modeled with the sigmoid maximum inhibitory effect (I_{max}) model function driven with the observed concentration of VX-509 incorporated with placebo effect.

For the PK/PD population modeling, individual ACR20-CRP and ACR50-CRP were characterized as binary responses (0 or 1) at each of the observed time points. The relationship between exposure to VX-509 and the binary response ACR20-CRP (similarly for ACR50-CRP) was expressed as a probability [$P(ACR20\text{-}CRP_{ij}=1)$] using a logistic regression model. A model was developed that considered the placebo effect and drug effect. The placebo effect may be a function of time. The drug effect is the drug action, which may be direct, indirect, effect site, and may also depend on time.

For the PK/PD modeling of DAS28-CRP change from baseline as continuous response variable, a model was developed that considered a placebo effect and drug effect, both potentially with time interactions.

Safety

All safety analyses were based on the Safety Analysis Set, which included all subjects who received at least 1 dose of study drug. AEs were coded according to MedDRA, Version 13.0. The number and percentage of subjects experiencing AEs were summarized. Clinical laboratory evaluations were summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum), including change from baseline. An Interim

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Analysis was performed after approximately 80% of subjects (approximately 160 subjects) had received 6 weeks of therapy with study drug. The analysis evaluated safety, efficacy, PK, and biomarkers. Only descriptive statistics were performed. In addition, a more detailed analysis of lymphocyte subsets was performed to assess potential changes in CD19+ (B lymphocytes), CD3+ (T lymphocytes), CD4+ (helper T lymphocytes), CD8+ (cytotoxic T lymphocytes), and CD56+ (NK cells). The number and percentage of subjects with clinically significant, on-treatment ECG shifts from baseline were presented. Clinically significant abnormal ECG findings were reported as AEs. Vital signs and physical examination findings were presented in subject data listings.

Efficacy

Primary efficacy variables: For the primary efficacy endpoint, ACR20-CRP response at Week 12, the following statistical analyses were performed in both the FAS and the Per Protocol Set (PPS), unless otherwise specified, using NRI:

- A 2-sided Fisher's exact test for comparisons of the response of each VX-509 treatment group relative to the placebo group.
- The Hochberg adjustment in *P* values for multiple comparisons of each Fisher's exact tests were carried out for the primary analysis in the FAS.
- Odds ratio and its exact 2-sided 95% confidence intervals (CIs) of achieving an ACR20-CRP response in each of VX-509 treatment groups relative to the placebo group.
- A 2-sided 95% CI for the difference in response rates between each treatment and the placebo group.
- A supportive statistical test using the Cochran-Mantel-Haenszel (CMH) method stratified by geographic region (US depot, United Kingdom [UK] depot, and Russia depot).
- A summary of the proportion of ACR20-CRP response by treatment groups and visits through Week 12 based on observed data.
- A chart and a line plot of the ACR20-CRP response proportion by percentage graphed as the observed data by treatment group and scheduled visits in the FAS.

For the change from baseline in DAS28-CRP at Week 12, the following statistical analyses were carried out in the FAS.

- The primary analysis, 2-sided 2-sample t-test for comparison of difference in mean change from baseline between each VX-509 treatment group and the placebo group.
- The Hochberg adjustment in *P* values for multiple comparisons of each t-test were carried out.
- The supportive test using an analysis of covariance model with change from baseline in DAS28-CRP score as the dependent variable, and treatment, geographic region (US depot, UK depot, and Russia depot), and baseline DAS28 score as independent variables.
- A summary of DAS28-CRP scores in descriptive statistics by treatment groups and visits through Week 12 based on observed data.
- A plot of the means of DAS28-CRP was plotted by treatment groups over the scheduled visits based on observed data.

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Secondary efficacy variables: The analyses of secondary efficacy endpoints, ACR50,70-CRP were performed based on the FAS and the PPS. The analyses of endpoints EULAR response based on DAS28-CRP as observed and with NRI, and remissions based on DAS28-CRP as observed and with NRI, were performed based on the FAS only.

- A 2-sided Fisher's exact test for comparisons of a response between each VX-509 treatment group and the placebo group.
- Odds ratio and its exact 2-sided 95% CIs of achieving a response in each of VX-509 treatment groups relative to the placebo group.
- A 2-sided 95% CI for the difference in a response rate between each treatment and the placebo groups.
- A supportive statistical test using the CMH method stratified by geographic region (US depot, UK depot, and Russia depot).
- A summary of the proportions of responses, ACR50,70-CRP and EULAR based on DAS28-CRP observed data by treatment groups and visits through Week 12.

For the change from baseline in scores at Week 12 of each domain, Physical Component Summary (PCS), Mental Component Summary (MCS), and Utility Index of SF-6D from SF-36 survey, the following statistical analyses were carried out in the FAS.

- A 2-sided 2-sample t-test for comparison of difference in mean change from baseline in scores of each SF-36 domain or summary between each VX-509 treatment group and the placebo group.
- The supportive test using an analysis of covariance model with change from baseline in the scores as the dependent variable, and treatment, geographic region (US depot, UK depot, and Russia depot), and baseline SF-36 score as independent variables.
- A summary of the change from baseline in each of the individual ACR components and the change from baseline in SF-36 scores in statistical descriptions using the observed data by treatment group and visits through Week 12 based on the FAS.

Ad hoc efficacy variables: Ad hoc analysis included analyses of ad hoc efficacy endpoints and analyses of primary, secondary, or ad hoc endpoints with imputation of missing values.

Ad hoc endpoints, the average of ACR20-CRP responses and the average of postbaseline DAS28-CRP scores, were summarized using descriptive statistics in the FAS.

The following statistical analyses were performed for ad hoc endpoints: early termination imputation ACR20-ESR, EULAR based on last observation carried forward (LOCF) DAS28-CRP, EULAR based on DAS28-ESR at Week 12, LOCF ACR20-CRP, LOCF ACR50,70-CRP, remission based on LOCF DAS28-CRP, remissions based on observed DAS28-CRP, NRI remission based on DAS28-ESR, and remission based on LOCF DAS28-ESR at Week 12. The analyses of LOCF ACR20-CRP and LOCF ACR50,70-CRP were carried out in both the FAS and the PPS. The analyses of EULAR responses and remission responses were performed in the FAS.

- A 2-sided Fisher's exact test for comparisons of a response between each VX-509 treatment group and the placebo group.
- Odds ratio and its exact 2-sided 95% CIs of achieving a response in each of VX-509 treatment groups relative to the placebo group.

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- A 2-sided 95% CI for the difference in a response rate between each treatment and the placebo groups.
- A supportive statistical test using the CMH method stratified by geographic region (US depot, UK depot, and Russia depot).
- A summary of the proportions of responses, ACR20-ESR, EULAR based on DAS28-ESR, and remission based on DAS28-ESR as the observed data by treatment group and visits through Week 12.

The following statistical analyses were performed for ad hoc endpoint DAS28-ESR, LOCF DAS28-CRP, and LOCF DAS28-ESR at Week 12:

- A 2-sided 2-sample t-test for comparison of difference in mean change from baseline between each VX-509 treatment group and the placebo group.
- The supportive test using an analysis of covariance model with change from baseline in DAS28 score as the dependent variable, and treatment, geographic region (US depot, UK depot, and Russia depot), and baseline DAS28 score as independent variables.
- A summary of the observed DAS28-ESR scores in descriptive statistics by treatment group and visits through Week 12.

SUMMARY-CONCLUSIONS

PHARMACOKINETIC RESULTS

Based on the analysis of 1072 PK samples from 161 treatment subjects, the PK of VX-509 was well characterized by a structural 1-compartment model with lagged first-order absorption. Between-subject variability was incorporated into the model with 2 correlated multiplicative random effects: a random effect on apparent clearance (CL/F), a shared random effect on apparent central volume (Vc/F), and a first-order absorption rate (ka). In the covariate analysis, the effects of the body weight on CL/F and Vc/F were found to be statistically significant and were included in the final population PK model. The estimates of the exponent of the power functions for body weight were 0.641 for CL/F and 0.991 for Vc/F. Typical CL/F values of VX-509 after oral administration were 8.3 L/h for a 55-kg subject, 10.4 L/h for a 75-kg subject, and 13.3 L/h for a 110-kg subject. Typical Vc/F values of VX-509 after oral administration were 73.2 L for a 55-kg subject, 99.5 L for a 75-kg subject, and 145.4 L for a 110-kg subject.

Exposure to VX-509 appeared to be dose-proportional in the dose range evaluated. For doses from 25 mg to 150 mg bid, the post hoc estimation of the maximum plasma concentration (C_{max}) at steady state ranged from 321 ng/mL to 1990 ng/mL, and the area under the concentration-time curve from time of dosing to 12 hours post dose (AUC_{0-12}) at steady state ranged from 2490 ng.h/mL to 15800 ng.h/mL. The median time to maximum plasma concentration at steady state ranged from 1.27 to 1.85 hours. The elimination half-life of VX-509 was slightly influenced by body weight; the predicted elimination half-life is 5.9 hours for a 55-kg subject and 7.6 h for a 110-kg subject.

PHARMACODYNAMIC RESULTS

Data for P-STAT3 and P-STAT5 were available for a subset of 41 subjects. For the percent change in P-STAT5 from baseline, data for 35 subjects could be analyzed. For the percent change in P-STAT3 from baseline, data for 31 subjects could be analyzed. VX-509 had a dose-related inhibitory effect on both P-STAT5 and P-STAT3, with a greater effect on P-STAT5 than on P-STAT3. This supports the greater specificity of VX-509 for inhibiting the JAK3/STAT5 pathway as opposed to the JAK2/STAT3 pathway.

PK/PD analyses are further detailed in the PK/PD section below.

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Median counts of CD56+ NK cells and CD8+ lymphocytes were reduced during treatment with VX-509 in a dose-dependent manner. The reductions in these populations were reversible, returning to baseline at the Follow-up Visit after dosing was completed at Week 12. CD19+ lymphocyte counts were increased during treatment with the 3 highest dose groups and returned towards baseline at the Follow-up Visit. No obvious dose dependency was observed. No notable trends were observed in CD3+ and CD4+ subsets.

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS

The population PK/PD models developed for both biomarkers suggest that inhibition of P-STAT5 and P-STAT3 by VX-509 is well described by the direct inhibitory concentration resulting in maximum drug induced response (E_{max})-type model. The inhibitory effect of VX-509 was much stronger for P-STAT5 compared to P-STAT3 (I_{max}: 92.0% decrease for P-STAT5 versus 20.1% decrease for P-STAT3). The estimated mean VX-509 half maximal (50%) inhibitory concentration (IC_{50}) for this 92.0% inhibition of P-STAT5 was 633 ng/mL, and estimated mean VX-509 IC_{50} for this 20.1% inhibition of P-STAT3 was 682 ng/mL.

Based on data from the placebo group, the models also suggest that in the absence of VX-509, the levels of P-STAT5 and P-STAT3 would increase slightly in patients with RA.

The plots of P-STAT5 and P-STAT3 level versus VX-509 concentrations revealed that the relationships of P-STAT5 and P-STAT3 levels to the VX-509 concentrations were similar on Day 1 and on Week 6 (including placebo data).

However, the PK/PD analyses of biomarkers P-STAT5 and P-STAT3 were based on limited amounts of data, and especially, only limited P-STAT3 response was observed (I_{max} of 20.1%). These model estimation results should be interpreted with caution.

Analysis of binary (ACR20-CRP and ACR50-CRP, NRI) clinical responses was performed using data from 202 subjects, and analysis of continuous clinical response (DAS28-CRP change from baseline, observed) was performed using data from 199 subjects. For the binary responses, nonlinear mixed-effect logistic regression models indicated that the probability of achieving ACR responses can be described by including placebo effect and VX-509 drug effect. In addition to the placebo effect, increased exposure to VX-509 resulted in increased probability of achieving ACR20-CRP and ACR50-CRP responses. DAS28-CRP tended to decrease with increased VX-509 exposure, with an E_{max} typical value estimate of -2.28 (95% CI: -2.86 to -1.70).

Population PK/PD models were also developed to characterize the relationship between VX-509 exposure and 3 important clinical responses: ACR20-CRP, ACR50-CRP, and DAS28-CRP. Both exposure-response and dose-response PK/PD models can describe the relationship of these efficacy endpoints with VX-509 exposure with minimal bias. The ACR20-CRP and ACR50-CRP response to VX-509 exposure can be described by an E_{max}-type model in addition to the time-dependent placebo effect. DAS28-CRP change from baseline can be described by placebo effect and exposure effect, both with time interactions.

EFFICACY RESULTS

The majority of subjects were female (81.4%) and Caucasian (96.1%). The mean (SD) age was 56.1 (9.88) years. On average, subjects had been diagnosed with RA for 92.67 months (7.7 years). At baseline, the population exhibited very active disease with mean (SD) tender joint count of 16.4 (5.91), swollen joint count of 12.9 (5.32), CRP of 23.69 (22.641) mg/L, ESR of 50.7 (25.37) mm/h, and HAQ of 1.6477 (0.58356).

The ACR20-CRP response rate and DAS28-CRP improvement were statistically superior to placebo for the 50-, 100-, and 150-mg bid VX-509 groups. ACR50-CRP and ACR70-CRP responses were statistically superior to placebo for the 100- and 150-mg bid VX-509 groups; the ACR50-CRP response was also statistically superior to placebo for the 50-mg bid VX-509 groups. Good EULAR response (based on DAS-CRP) was

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statistically superior to placebo for the 50-, 100-, and 150-mg bid VX-509 groups. DAS28-CRP remission was statistically superior to placebo for the 100- and 150-mg bid VX-509 groups.

There appeared to be dose-related changes from baseline in the individual ACR components through Week 12 in subjects receiving VX-509, with the largest changes seen in the 50-, 100-, and 150-mg bid groups.

Summary of the Efficacy Results at Week 12

Variable	**Placebo**	**25 mg**	**50 mg**	**100 mg**	**150 mg**
Primary					
ACR20-CRP response (%)	29.3	39.0	61.0	65.0	65.9
Odds ratio (95% CI)		1.5 (0.6, 4.3)	3.8 (1.4, 10.5)	4.5 (1.6, 12.7)	4.7 (1.7, 13.2)
P value[a]		0.485, 0.485	0.007, 0.015	0.002, 0.005	0.002, 0.007
DAS28-CRP					
Mean (SD) score CFB	-1.25 (1.294)	-1.75 (1.448)	-2.60 (1.086)	-2.70 (1.567)	-3.06 (1.164)
Difference of mean CFB (95%CI)		-0.50 (-1.19, 0.19)	-1.35 (-1.96, -0.75)	-1.45 (-2.19, -0.71)	-1.81 (-2.44, -1.18)
P value[b]		0.155, 0.155	<0.001, <0.001	<0.001, <0.001	<0.001, <0.001
Secondary					
ACR50-CRP response (%)	7.3	17.1	31.7	37.5	48.8
Odds ratio (95% CI)		2.6 (0.5, 16.7)	5.9 (1.4, 34.5)	7.6 (1.8, 44.0)	12.1 (3.0, 68.5)
P value[c]		0.312	0.011	0.001	<0.001
ACR70-CRP response (%)	2.4	7.3	12.2	17.5	22.0
Odds ratio (95% CI)		3.2 (0.2, 169.8)	5.6 (0.6, 269.2)	8.5 (1.0, 391.7)	11.3 (1.4, 505.1)
P value[c]		0.616	0.201	0.029	0.014
EULAR response					
Good response (%)	13.8	28.6	39.4	56.3	56.3
Odds ratio (95% CI)		2.5 (0.6, 12.2)	4.1 (1.0, 19.4)	8.0 (2.0, 37.8)	8.0 (2.0, 37.8)
P value[c]		0.226	0.044	0.001	0.001
DAS28-CRP rem (%)	10.3	14.3	18.2	43.8	45.5
Odds ratio (95% CI)		1.4 (0.3, 10.1)	1.9 (0.4, 13.0)	6.7 (1.5, 40.6)	7.2 (1.6, 43.2)
P value[c]		0.719	0.483	0.004	0.004

ACR20-CRP: ACR20 based on C-reactive protein; ACR50-CRP: ACR50 based on C-reactive protein; ACR70-CRP: ACR70 based on C-reactive protein; CFB: change from baseline; CI: confidence interval; DAS28-CRP: DAS28 based on C-reactive protein; EULAR: European League Against Rheumatism; rem: remission

[a] Fisher's exact test *P* value followed by Hochberg adjusted *P* value

[b] 2-sample t-test *P* value followed by Hochberg adjusted *P* value

[c] Fisher's exact test *P* value

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For SF-36 subject reported outcomes at Week 12, the following results were observed:

- The changes from baseline to Week 12 in PCS, bodily pain, and SF-6D were significantly different from placebo for the 50-, 100-, and 150-mg bid groups (PCS: $P = 0.013$, 0.003, and 0.005, respectively; bodily pain: $P = 0.023$, 0.005, and <0.001, respectively; SF-6D: $P = 0.017$, 0.024, and 0.002, respectively).
- The change from baseline to Week 12 in general health was significantly different from placebo for the 50- and 150-mg bid groups ($P = 0.039$ and 0.005, respectively).
- The changes from baseline to Week 12 in MCS, vitality, social functioning, and mental health were significantly different from placebo for 150-mg bid group ($P = 0.046$, 0.026, 0.016, and 0.011, respectively).
- The changes from baseline to Week 12 in physical functioning, role physical, and role emotional were not statistically superior to placebo for any of the treatment groups.

SAFETY RESULTS

VX-509 was generally well tolerated compared to placebo when administered for 12 weeks to subjects with RA.

- A total of 96 subjects (47.1%) reported at least 1 AE. The incidence of AEs was similar between the combined VX-509 groups (47.2%) and the placebo group (46.3%). Within the VX-509 groups, AE incidence was higher in the 100-mg bid group (62.5%) and the 150-mg bid group (53.7%) as compared to the lower dose groups (29.3% in the 25-mg bid group, 43.9% in the 50-mg bid group). A similar trend was observed for the incidence of drug-related AEs, AEs leading to discontinuation, serious adverse events (SAEs), and severe AEs.
- Overall, the most common AEs were associated with infections and infestations (17.1% in the placebo group and 12.2%, 12.2%, 25.0%, and 19.5% in the 25-, 50-, 100-, and 150-mg bid groups, respectively) and gastrointestinal disorders (14.2%). By preferred term, the most common AEs were nausea, headache, and alanine aminotransferase (ALT) increased. No single preferred term was reported in more than 5% of subjects.
- Nausea, hypercholesterolemia, increased aspartate aminotransferase (AST), peripheral edema, and constipation were reported only in the VX-509 groups, and hypercholesterolemia and increased AST occurred only in the 100- and 150-mg bid groups.
- Most AEs were mild to moderate in severity. Six subjects (1 subject in the placebo group, 1 subject in the 25-mg bid group, 2 subjects in the 100-mg bid group, and 2 subjects in the 150-mg bid group) had severe AEs. Three of the severe AEs reported in the VX-509 groups [redacted] were considered possibly related to study drug.
- Treatment-related AEs were reported for 9 subjects (22%) in the placebo group and 45 subjects (27.6%) in the VX-509 groups (12.2% of subjects in the 25-mg bid group, 14.6% of subjects in the 50-mg bid group, 42.5% of subjects in the 100-mg bid group, and 41.5% of subjects in the 150-mg bid group). The most common treatment-related AEs in the VX-509 groups were associated with elevated liver function parameters and serum lipids, gastrointestinal disorders, and infections.
- A total of 11 SAEs occurred in 9 (4.4%) subjects, including fatal events of pneumonia and subarachnoid

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hemorrhage [redacted] All but 1 SAE [redacted] was considered by the investigator to be unrelated or unlikely related to study drug. However, the sponsor (Vertex) considered the fatal event of pneumonia as possibly related to VX-509. There were 5 serious infections in 5 subjects: osteomyelitis, erysipelas, and pneumonia (fatal) [redacted] bronchitis and tuberculosis [redacted].

- Fifteen (7.4%) subjects (13 [8.0%] from the VX-509 treatment groups and 2 [4.9%] from the placebo group) discontinued study treatment due to AEs.
- Treatment with VX-509 was associated with dose-related increases (primarily Grade 1; <3 × ULN) in ALT, AST, gamma-glutamyl transferase, and lactic dehydrogenase levels. Four subjects in the VX-509 groups compared to none in the placebo group experienced a maximum ALT that was between 3 × and <5 × ULN. Median values in all dose groups remained within normal limits through Week 12 and demonstrated a return to baseline levels at 4 weeks following the completion of the treatment period. No subjects with increased ALT or AST experienced increased bilirubin levels.
- Dose-related increases in mean total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were also observed across all VX-509 treatment groups. Elevated levels trended back to baseline in all dose groups after the end of the treatment period.
- Dose-related decreases in total white blood cell (WBC), neutrophil, and lymphocyte counts were observed over time in the VX-509 treatment groups. None of the decreased WBC values was associated with serious infections. Results for red blood cell parameters did not suggest any treatment-related concerns.
    - Median decreases in WBC counts ranged from 0.635 to 1.223 x 10^9 cells/L in the VX-509 groups at Week 12; WBC counts were trending toward baseline levels at the Follow-up Visit.
    - Median decreases in absolute neutrophil counts ranged from 0.6 (25 mg bid) to 1.75 x 10^9 cells/L (150 mg bid) and were generally seen between 6 to 12 weeks following the initiation of treatment. At the Follow-up Visit, median values appeared to be returning to baseline in the 25- and 50-mg bid groups, but remained well below baseline levels in the 100- and 150-mg bid groups.
    - Median lymphocyte counts were essentially unchanged from baseline in the VX-509 25- and 50-mg bid groups, while median decreases of 0.20 and 0.30 x 10^9 cells/L were seen in the 100- and 150-mg bid groups, respectively, between 6 and 12 weeks after the initiation of treatment. At the Follow-up Visit, median lymphocyte counts had returned to baseline values.
    - Median counts of CD56+ NK cells and CD8+ lymphocytes were reduced during treatment with VX-509 in a dose-dependent manner. The reductions in these populations were reversible, returning to baseline at the Follow-up Visit after dosing was completed at Week 12. CD19+ lymphocyte counts were increased during treatment with the 3 highest dose groups and returned towards baseline at the Follow-up Visit. No obvious dose dependency was observed. No notable trends were observed in CD3+ and CD4+ subsets.
- Results of vital sign measurements, physical exams, and ECGs were not suggestive of any clinically relevant treatment- or dose-related trends.

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CONCLUSIONS

Efficacy

- After 12 weeks of treatment in subjects with active RA, the clinical responses (ACR20-CRP response rate and DAS28-CRP improvement) in the 50-, 100-, and 150-mg bid VX-509 groups were statistically superior to placebo.
- The ACR50-CRP response rate and good EULAR response in the 50-, 100-, and 150-mg bid VX-509 groups were statistically superior to placebo at Week 12.
- The ACR70-CRP response rate and DAS28-CRP remission in the 100- and 150-mg bid VX-509 groups were statistically superior to placebo at Week 12.
- The mean percent changes from baseline in ACR components were greatest in the 50-, 100-, and 150-mg bid VX-509 groups at Week 12.
- Treatment with VX-509 significantly improved many quality-of-life measures of the SF-36 survey in the 50-, 100-, and 150-mg bid VX-509 groups compared to placebo.

Safety

- VX-509 at doses of 25 to 150 mg bid for 12 weeks was generally well tolerated in subjects with RA. Overall treatment-emergent AE rates were equivalent. SAEs were reported in 2.4% of placebo and 4.9% of VX-509 subjects, and withdrawal for treatment-emergent AEs occurred in 4.9% of placebo and 8.0% of VX-509 subjects. Dose-related increases in AST/ALT, total/HDL/LDL cholesterol, and triglycerides were observed in VX-509 subjects.

Pharmacokinetics/Pharmacodynamics

- A 1-compartment model with first-order absorption following a lag time parameterized in terms of CL/F and Vc/F fitted the plasma concentrations of VX-509 with minimal bias.
- The covariate analysis revealed statistically significant effects of the body weight on CL/F and Vc/F. Exposure to VX-509 appeared to be dose proportional in the dose range considered.
- Exposure to VX-509 appeared to be dose proportional in the dose range considered. Mean C_{max} at steady state ranged from 321 ng/mL to 1990 ng/mL, AUC_{0-12} at steady state ranged from 2490 ng.h/mL to 15800 ng.h/mL. The median time to maximum plasma concentration at steady state ranged from 1.27 to 1.85 hours. The elimination half-life of VX-509 was slightly influenced by body weight; the predicted elimination half-life is 5.9 hours for a 55-kg subject and 7.6 h for a 110-kg subject.
- The PK/PD analysis of the biomarker data suggest that the inhibitory effect of VX-509 on the biomarker responses was much stronger for P-STAT5 compared to P-STAT3 (i.e., I_{max} 92.0% versus 20.1%). This supports the greater specificity of VX-509 for inhibiting the JAK3/STAT5 pathway as opposed to the JAK2/STAT3 pathway. The estimated mean VX-509 IC_{50} for this 92.0% inhibition of P-STAT5 was 633 ng/mL, and estimated mean VX-509 IC_{50} for this 20.1% inhibition of P-STAT3 was 682 ng/mL would represent steady-state trough (predose) plasma concentrations of VX-509 for dose levels slightly higher than 100 mg bid.
- Both exposure-response and dose-response PK/PD models can describe the relationship of efficacy endpoints of ACR20-CRP, ACR50-CRP, and DAS28-CRP with VX-509 exposure with minimal bias. The ACR20-CRP and ACR50-CRP response to VX-509 exposure can be described by an E_{max}-type model in addition to the time-dependent placebo effect. DAS28-CRP change from baseline can be described by

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placebo effect and exposure effect, both with time interactions.	
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