



Clinical trial results:

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

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-003439-41 |
| Trial protocol | LT EE DK NL |
| Global end of trial date | 09 January 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 28 June 2016 |
| First version publication date | 07 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX12-509-103 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01754935 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Vertex Pharmaceuticals Incorporated |
| Sponsor organisation address | 50 Northern Avenue, Boston, MA, United States, 02210-1862 |
| Public contact | Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com |
| Scientific contact | Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 April 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 January 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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 and to evaluate the early effect of VX-509 administration on joint structures as assessed by magnetic resonance imaging (MRI).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy:

Stable treatment with 1 of the following DMARDs: methotrexate, sulfasalazine, leflunomide, penicillamine, or antimalarial drug.

Evidence for comparator:

No active comparator.

| | |
|---|------------------|
| Actual start date of recruitment | 17 December 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Estonia: 2 |
| Country: Number of subjects enrolled | United States: 38 |
| Country: Number of subjects enrolled | Lithuania: 3 |
| Worldwide total number of subjects | 43 |
| EEA total number of subjects | 5 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|--|----|
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 40 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All 43 subjects were included in the Safety Set, and all 38 randomized subjects were included in the Full Analysis Set (FAS).

Period 1

| | |
|------------------------------|--|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Subjects received 6 VX-509-matched placebo tablets orally once daily for 12 weeks.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

6 VX-509-matched placebo tablets orally once daily for 12 weeks.

| | |
|------------------|---------------|
| Arm title | VX-509 100 mg |
|------------------|---------------|

Arm description:

Subjects received 2 VX-509 50 milligram (mg) tablets and 4 VX-509-matched placebo tablets orally once daily for 12 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | VX-509 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 VX-509 50 mg tablets and 4 VX-509-matched placebo tablets orally once daily for 12 weeks.

| | |
|------------------|---------------|
| Arm title | VX-509 200 mg |
|------------------|---------------|

Arm description:

Subjects received 4 VX-509 50 mg tablets and 2 VX-509-matched placebo tablets orally once daily for 12 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | VX-509 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

4 VX-509 50 mg tablets and 2 VX-509-matched placebo tablets orally once daily for 12 weeks.

| | |
|--|---------------|
| Arm title | VX-509 300 mg |
| Arm description: Subjects received 6 VX-509 50 mg tablets orally once daily for 12 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | VX-509 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

6 VX-509 50 mg tablets orally once daily for 12 weeks.

| Number of subjects in period 1 | Placebo | VX-509 100 mg | VX-509 200 mg |
|---------------------------------------|---------|---------------|---------------|
| Started | 12 | 11 | 10 |
| Completed | 11 | 10 | 10 |
| Not completed | 1 | 1 | 0 |
| Consent withdrawn by subject | 1 | - | - |
| Lost to follow-up | - | 1 | - |

| Number of subjects in period 1 | VX-509 300 mg |
|---------------------------------------|---------------|
| Started | 10 |
| Completed | 10 |
| Not completed | 0 |
| Consent withdrawn by subject | - |
| Lost to follow-up | - |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Placebo |
| Reporting group description: Subjects received 6 VX-509-matched placebo tablets orally once daily for 12 weeks. | |
| Reporting group title | VX-509 100 mg |
| Reporting group description: Subjects received 2 VX-509 50 milligram (mg) tablets and 4 VX-509-matched placebo tablets orally once daily for 12 weeks. | |
| Reporting group title | VX-509 200 mg |
| Reporting group description: Subjects received 4 VX-509 50 mg tablets and 2 VX-509-matched placebo tablets orally once daily for 12 weeks. | |
| Reporting group title | VX-509 300 mg |
| Reporting group description: Subjects received 6 VX-509 50 mg tablets orally once daily for 12 weeks. | |

| Reporting group values | Placebo | VX-509 100 mg | VX-509 200 mg |
|------------------------------------|---------|---------------|---------------|
| Number of subjects | 12 | 11 | 10 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|----------------|----------------|
| Age continuous Units: years arithmetic mean standard deviation | 52.8 ± 12.25 | 56.7 ± 6.47 | 50.5 ± 11.9 |
| Gender categorical Units: Subjects | | | |
| Female | 10 | 8 | 5 |
| Male | 2 | 3 | 5 |

| Reporting group values | VX-509 300 mg | Total | |
|------------------------------------|---------------|-------|--|
| Number of subjects | 10 | 43 | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----------------|----|--|
| Age continuous Units: years arithmetic mean standard deviation | 54.9 ± 5.04 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 8 | 31 | |
| Male | 2 | 12 | |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Placebo |
| Reporting group description: Subjects received 6 VX-509-matched placebo tablets orally once daily for 12 weeks. | |
| Reporting group title | VX-509 100 mg |
| Reporting group description: Subjects received 2 VX-509 50 milligram (mg) tablets and 4 VX-509-matched placebo tablets orally once daily for 12 weeks. | |
| Reporting group title | VX-509 200 mg |
| Reporting group description: Subjects received 4 VX-509 50 mg tablets and 2 VX-509-matched placebo tablets orally once daily for 12 weeks. | |
| Reporting group title | VX-509 300 mg |
| Reporting group description: Subjects received 6 VX-509 50 mg tablets orally once daily for 12 weeks. | |

Primary: Percentage of Subjects Achieving American College of Rheumatology 20% (ACR20) C-Reactive Protein (ACR20-CRP) Response at Week 12

| | |
|--|--|
| End point title | Percentage of Subjects Achieving American College of Rheumatology 20% (ACR20) C-Reactive Protein (ACR20-CRP) Response at Week 12 |
| End point description: ACR20-CRP response: greater than equal (\geq) 20% improvement in tender joints count (TJC); \geq 20% improvement in swollen joints count (SJC); and \geq 20% improvement in at least 3 of 5 remaining ACR core measures: subject assessment of pain (assessed on 0-100 mm VAS, higher score = more pain); subject global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity); physician global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity); self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]); and CRP levels. Analysis was performed on FAS defined as all randomized subjects who received at least 1 dose of study drug. | |
| End point type | Primary |
| End point timeframe: Week 12 | |

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 5 | 10 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 25 | 63.6 | 80 | 60 |

Statistical analyses

| | |
|----------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | VX-509 100 mg v Placebo |

| | |
|---|---------------------------|
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0678 |
| Method | Miettinen-Nurminen method |
| Parameter estimate | Proportion difference |
| Point estimate | 38.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 68.8 |

| | |
|---|---------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | VX-509 200 mg v Placebo |
| Number of subjects included in analysis | 17 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0417 |
| Method | Miettinen-Nurminen method |
| Parameter estimate | Proportion difference |
| Point estimate | 55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.2 |
| upper limit | 82.8 |

| | |
|---|---------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | VX-509 300 mg v Placebo |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1043 |
| Method | Miettinen-Nurminen method |
| Parameter estimate | Proportion difference |
| Point estimate | 35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.2 |
| upper limit | 66.6 |

Primary: Change From Baseline in Disease Activity Score Using 28-Joint Count and

C-Reactive Protein (4 Variables) (DAS28-4 [CRP]) at Week 12

| | |
|--|---|
| End point title | Change From Baseline in Disease Activity Score Using 28-Joint Count and C-Reactive Protein (4 Variables) (DAS28-4 [CRP]) at Week 12 |
| End point description: DAS28-4 (CRP) was calculated from SJC and TJC using the 28 joints count, CRP [mg/L] and subject general health visual analogue scale score. A score of less than (<) 2.6 implied remission and ≤3.2 implied low disease activity. Analysis was performed on FAS. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 12 | |

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 5 | 10 |
| Units: units on scale | | | | |
| least squares mean (standard error) | -0.82 (± 0.419) | -1.41 (± 0.456) | -2.07 (± 0.541) | -2.25 (± 0.421) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: The mixed effect model for repeated measures was applied. The model includes the change from baseline of DAS28-4 (CRP) as the dependent variable, treatment group, visit, treatment by visit interaction as fixed effects, and subject as a random effect, with adjustment for the continuous baseline DAS28-4 (CRP), prior use of anti-TNF, and region. | |
| Comparison groups | VX-509 100 mg v Placebo |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2485 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.62 |
| upper limit | 0.42 |

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: Analysis was performed as described in Statistical Analysis 1. | |
| Comparison groups | VX-509 200 mg v Placebo |

| | |
|---|--------------------|
| Number of subjects included in analysis | 17 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0408 |
| Method | Mixed model effect |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.46 |
| upper limit | -0.05 |

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: Analysis was performed as described in Statistical Analysis 1. | |
| Comparison groups | VX-509 300 mg v Placebo |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0055 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.44 |
| upper limit | -0.43 |

Primary: Change from Baseline in Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Synovitis Score at Week 12

| | |
|--|---|
| End point title | Change from Baseline in Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Synovitis Score at Week 12 |
| End point description: Synovitis score: individual score 0-3, range 0-27 without interphalangeal (IP) joints. Wrist (4 joints) and metacarpophalangeal (MCP) joints (5 joints) were included in the calculation (IP joints were not included in the calculation). Minimum required number of evaluable joints were 3 for each segment (wrist and MCP joints). Segment scores are the sum of the joints within that segment. RAMRIS synovitis score is calculated as sum of the segment scores. Analysis was performed on FAS. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 12 | |

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 5 | 10 |
| Units: units on scale | | | | |
| least squares mean (standard error) | -0.44 (± 1.445) | -4.76 (± 1.467) | -5.76 (± 1.66) | -7.68 (± 1.528) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Statistical analysis description: | |
| The mixed effect model for repeated measures was applied. The model includes the change from baseline of each scale score of RAMRIS as the dependent variable, treatment group, visit, treatment by visit interaction as fixed effects and subject as a random effect, with adjustment for the continuous baseline, prior use of anti-TNF and region. | |
| Comparison groups | VX-509 100 mg v Placebo |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0095 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.5 |
| upper limit | -1.15 |

| Statistical analysis title | Statistical Analysis 2 |
|--|-------------------------|
| Statistical analysis description: | |
| Analysis was performed as described in Statistical Analysis 1. | |
| Comparison groups | VX-509 200 mg v Placebo |
| Number of subjects included in analysis | 17 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0088 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.32 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.18 |
| upper limit | -1.46 |

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: Analysis was performed as described in Statistical Analysis 1. | |
| Comparison groups | VX-509 300 mg v Placebo |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -7.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.66 |
| upper limit | -3.82 |

Primary: Change from Baseline in OMERACT RAMRIS Osteitis Score at Week 12

| | |
|--|--|
| End point title | Change from Baseline in OMERACT RAMRIS Osteitis Score at Week 12 |
| End point description: Osteitis (bone marrow edema) score: individual score 0-3, range 0-75 without IP joints. Wrist (15 joints) and MCP bones (10 joints) were included in the calculation (IP joints were not included in the calculation). Minimum required number of evaluable joints were 8 and 6 for wrist and MCP segment, respectively. Segment scores are the sum of the joints within that segment. RAMRIS synovitis score is calculated as sum of the segment scores. Analysis was performed on FAS. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 12 | |

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 5 | 10 |
| Units: units on scale | | | | |
| least squares mean (standard error) | -2.91 (± 1.478) | -4.71 (± 1.613) | -5.14 (± 1.765) | -7.41 (± 1.482) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| The mixed effect model for repeated measures was applied. The model includes the change from baseline of each scale score of RAMRIS as the dependent variable, treatment group, visit, treatment by visit interaction as fixed effects and subject as a random effect, with adjustment for the continuous baseline, prior use of anti-TNF and region. | |
| Comparison groups | VX-509 100 mg v Placebo |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2193 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.77 |
| upper limit | 1.16 |

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Analysis was performed as described in Statistical Analysis 1. | |
| Comparison groups | VX-509 200 mg v Placebo |
| Number of subjects included in analysis | 17 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.213 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.84 |
| upper limit | 1.38 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis was performed as described in Statistical Analysis 1.

| | |
|---|-------------------------|
| Comparison groups | VX-509 300 mg v Placebo |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0076 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.68 |
| upper limit | -1.33 |

Primary: Change from Baseline in OMERACT RAMRIS Erosion Score at Week 12

| | |
|---|---|
| End point title | Change from Baseline in OMERACT RAMRIS Erosion Score at Week 12 |
| End point description: | |
| Erosion score: individual score 0-10, range 0-250 without IP joints. Wrist (15 joints) and MCP bones (10 joints) were included in the calculation (IP joints were not included in the calculation). Minimum required number of evaluable joints were 8 and 6 for wrist and MCP segment, respectively. Segment scores are the sum of the joints within that segment. RAMRIS synovitis score is calculated as sum of the segment scores. Analysis was performed on FAS. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 5 | 10 |
| Units: units on scale | | | | |
| least squares mean (standard error) | 0.15 (± 0.177) | 0.45 (± 0.188) | 0.37 (± 0.212) | 0.35 (± 0.191) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| The mixed effect model for repeated measures was applied. The model includes the change from baseline of each scale score of RAMRIS as the dependent variable, treatment group, visit, treatment by visit interaction as fixed effects and subject as a random effect, with adjustment for the continuous baseline, prior use of anti-TNF and region. | |
| Comparison groups | Placebo v VX-509 100 mg |

| | |
|---|--------------------|
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1274 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.7 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis was performed as described in Statistical Analysis 1.

| | |
|---|-------------------------|
| Comparison groups | VX-509 200 mg v Placebo |
| Number of subjects included in analysis | 17 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3587 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | 0.71 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis was performed as described in Statistical Analysis 1.

| | |
|---|-------------------------|
| Comparison groups | VX-509 300 mg v Placebo |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3268 |
| Method | Mixed effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.22 |
| upper limit | 0.63 |

Secondary: Percentage of Subjects Achieving ACR50-CRP and ACR70-CRP Response at Week 12

| | |
|-----------------|--|
| End point title | Percentage of Subjects Achieving ACR50-CRP and ACR70-CRP Response at Week 12 |
|-----------------|--|

End point description:

ACR50-CRP/ACR70-CRP response: $\geq 50\%/70\%$ improvement in TJC; $\geq 50\%/70\%$ improvement in SJC; and $\geq 50\%/70\%$ improvement in at least 3 of 5 remaining ACR core measures: subject assessment of pain (assessed on 0-100 mm VAS, higher score = more pain); subject global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity); physician global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity); self-assessed disability (disability index of the HAQ); and CRP levels. Analysis was performed on safety set defined as all subjects who received at least 1 dose of study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 10 | 10 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| ACR50-CRP Response | 8.3 | 27.3 | 30 | 60 |
| ACR70-CRP Response | 8.3 | 18.2 | 10 | 20 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with DAS28-4 (CRP) Remission, DAS28-4 (ESR) Remission, and European League Against Rheumatism (EULAR) Moderate or Good Response at Week 12

| | |
|-----------------|---|
| End point title | Percentage of Subjects with DAS28-4 (CRP) Remission, DAS28-4 (ESR) Remission, and European League Against Rheumatism (EULAR) Moderate or Good Response at Week 12 |
|-----------------|---|

End point description:

DAS28-4 (CRP) is defined in second primary endpoint. DAS28-4 (CRP) and DAS28-4 (ESR) remission was defined as having a score <2.6 . EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline >1.2 with DAS28-4 (CRP) ≤ 3.2 ; moderate responders: change from baseline >1.2 with DAS28-4 (CRP) >3.2 or change from baseline >0.6 to ≤ 1.2 with DAS28-4 (CRP) ≤ 5.1 ; non-responders: change from baseline ≤ 0.6 or change from baseline >0.6 and ≤ 1.2 with DAS28-4 (CRP) >5.1 . DAS28-4 (CRP) remission was defined as having a score <2.6 .

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 10 | 10 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| DAS28-4 (CRP) Remission | 0 | 27.3 | 10 | 10 |
| DAS28-4 (ESR) Remission | 0 | 9.1 | 20 | 30 |
| EULAR Moderate/Good Response | 41.7 | 54.5 | 60 | 60 |

Statistical analyses

No statistical analyses for this end point

Secondary: ACR Hybrid Score at Week 12

| | |
|--|-----------------------------|
| End point title | ACR Hybrid Score at Week 12 |
| End point description: Evaluates the improvement in active RA by combining elements of the ACR20/50/70 with a continuous score of the mean change in core set measures. Analysis was performed on safety set. | |
| End point type | Secondary |
| End point timeframe: Week 12 | |

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------------|-----------------|------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 10 | 10 |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 10.83 (± 9.227) | 38.87 (± 10.007) | 38.81 (± 9.672) | 50.5 (± 9.236) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Health Assessment Questionnaire -Disability Index (HAQ-DI) at Week 12

| | |
|---|--|
| End point title | Change from baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI) at Week 12 |
| End point description: HAQ-DI is a self-completed subject questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily | |

activities. Each domain has at least 2 component questions. There are 4 possible responses for each component: 0=without any difficulty; 1=with some difficulty; 2=with much difficulty; 3=unable to do. Domain score = total score of individual questions divided by total number of questions. HAQ-DI total score = total of domain scores divided by number of domains, range: 0 (best) to 3 (worst). Analysis was performed on safety set.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 10 | 10 |
| Units: units on scale | | | | |
| least squares mean (standard error) | -0.12 (± 0.155) | -0.32 (± 0.168) | -0.47 (± 0.163) | -0.67 (± 0.156) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Physical Function Subscale and Physical and Mental Health Components of the SF-36 at Week 12

| | |
|-----------------|--|
| End point title | Change from Baseline in the Physical Function Subscale and Physical and Mental Health Components of the SF-36 at Week 12 |
|-----------------|--|

End point description:

The SF-36 is a general health status questionnaire that assesses 8 domains of functional health and well-being: Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, Social Functioning, Mental Health, Role Limitations due to Emotional Problems, Vitality, and General Health Perceptions. The score for a section is an average of the individual question scores, which are scaled 0-100 (100=highest level of functioning). Change from baseline for physical function subscale is reported. Analysis was performed on safety set.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|---|------------------|------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 10 | 8 | 9 |
| Units: units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 12 in Physical Functioning Score | 1.216 (± 5.3627) | 3.636 (± 6.0822) | 7.655 (± 8.9187) | 7.754 (± 6.6217) |
| Change at Week 12 in Mental Component Score | 5.111 (± 7.082) | 0.737 (± 7.03) | 1.645 (± 15.3951) | 1.772 (± 10.5995) |
| Change at Week 12 in Physical Component Score | 0.243 (± 6.3369) | 7.867 (± 8.2593) | 8.694 (± 8.9138) | 9.674 (± 7.8496) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in OMERACT RAMRIS Synovitis, Osteitis and Erosion Scores at Week 6

| | |
|-----------------|---|
| End point title | Change from Baseline in OMERACT RAMRIS Synovitis, Osteitis and Erosion Scores at Week 6 |
|-----------------|---|

End point description:

Different OMERACT RAMRIS scores are defined in Primary Endpoints. Analysis was performed on safety set.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 6

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 10 | 10 |
| Units: units on scale | | | | |
| least squares mean (standard error) | | | | |
| Change at Week 6 in Synovitis Score | -0.81 (\pm 1.301) | -3.23 (\pm 1.382) | -3.26 (\pm 1.3) | -5.56 (\pm 1.332) |
| Change at Week 6 in Osteitis Score | -3.8 (\pm 1.509) | -4.29 (\pm 1.655) | -5.17 (\pm 1.611) | -5.62 (\pm 1.441) |
| Change at Week 6 in Erosion Score | 0.21 (\pm 0.163) | 0.27 (\pm 0.177) | 0.43 (\pm 0.165) | 0.4 (\pm 0.17) |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters of VX -509 and its Metabolite in Plasma: Maximum Observed Concentration [Cmax] at Week 12

| | |
|-----------------|---|
| End point title | PK parameters of VX -509 and its Metabolite in Plasma: Maximum Observed Concentration [Cmax] at Week 12 |
|-----------------|---|

End point description:

As per Sponsor's decision to modify the drug development plan for VX-509, the PK and PK/PD analyses were not performed, hence no data could be reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 12

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | 0 ^[3] | 0 ^[4] |
| Units: ng/ml | | | | |
| number (not applicable) | | | | |

Notes:

[1] - Reason for no analysis is provided in endpoint description.

[2] - Reason for no analysis is provided in endpoint description.

[3] - Reason for no analysis is provided in endpoint description.

[4] - Reason for no analysis is provided in endpoint description.

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters of VX-509 and its Metabolite in Area Under The Concentration Versus Time Curve [AUC] at Week 12

| | |
|-----------------|---|
| End point title | PK parameters of VX-509 and its Metabolite in Area Under The Concentration Versus Time Curve [AUC] at Week 12 |
|-----------------|---|

End point description:

As per Sponsor's decision to modify the drug development plan for VX-509, the PK and PK/PD analyses were not performed, hence no data could be reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | 0 ^[7] | 0 ^[8] |
| Units: ng/mL | | | | |
| number (not applicable) | | | | |

Notes:

[5] - Reason for no analysis is provided in endpoint description.

[6] - Reason for no analysis is provided in endpoint description.

[7] - Reason for no analysis is provided in endpoint description.

[8] - Reason for no analysis is provided in endpoint description.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|--|

End point description:

AE: 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 is signed. AE included serious as well as non-serious AEs. SAE (subset of AE): medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, in-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. Analysis was performed on safety set included all subjects who received at least 1 dose of study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 16

| End point values | Placebo | VX-509 100 mg | VX-509 200 mg | VX-509 300 mg |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 11 | 10 | 10 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Subjects with AEs | 41.7 | 72.7 | 80 | 90 |
| Subjects with SAEs | 0 | 9.1 | 10 | 0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 16

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | VX-509 100 mg |
|-----------------------|---------------|

Reporting group description:

VX-509 100 mg tablet orally once daily for 12 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo matched to VX-509 tablet orally once daily for 12 weeks.

| | |
|-----------------------|---------------|
| Reporting group title | VX-509 300 mg |
|-----------------------|---------------|

Reporting group description:

VX-509 300 mg tablet orally once daily for 12 weeks.

| | |
|-----------------------|---------------|
| Reporting group title | VX-509 200 mg |
|-----------------------|---------------|

Reporting group description:

VX-509 200 mg tablet orally once daily for 12 weeks.

| Serious adverse events | VX-509 100 mg | Placebo | VX-509 300 mg |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | VX-509 200 mg | | |
|------------------------------------|---------------|--|--|
| Total subjects affected by serious | | | |

| | | | |
|---|-----------------|--|--|
| adverse events | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | VX-509 100 mg | Placebo | VX-509 300 mg |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 11 (63.64%) | 5 / 12 (41.67%) | 9 / 10 (90.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Genital rash | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pelvic pain | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Prostatomegaly subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Sinus congestion subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Cough subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 10 (20.00%) 2 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 10 (0.00%) 0 |
| Depression subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Investigations | | | |
| Blood erythropoietin increased subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|----------------------------------|----------------|-----------------|-----------------|
| complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 12 (16.67%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 2 / 10 (20.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry mouth | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Lip ulceration subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Stomatitis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 12 (8.33%) 1 | 1 / 10 (10.00%) 2 |
| Rash papular subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|------------------------------------|----------------|----------------|-----------------|
| Joint effusion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 12 (8.33%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 12 (8.33%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blister infected | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body tinea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 12 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|--|---------------------|---------------------|
| Hyperlipidaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Non-serious adverse events | VX-509 200 mg | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 8 / 10 (80.00%) | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| General disorders and administration site conditions Non-cardiac chest pain subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 | | |
| Reproductive system and breast disorders Genital rash subjects affected / exposed occurrences (all) Pelvic pain subjects affected / exposed occurrences (all) Prostatomegaly subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Sinus congestion subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Oropharyngeal pain | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Blood erythropoietin increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---|--|--|
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Eye disorders Vision blurred subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Lip ulceration subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|--|--|
| Rash | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash papular | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Swelling face | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Joint effusion | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sinusitis | | | |

| | | | |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Blister infected | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Body tinea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Herpes virus infection | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 05 September 2012 | Updated inclusion exclusion criteria. |
| 09 October 2012 | Added secondary endpoint: Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 12. Updated inclusion criteria. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported