Clinical trial results:
A Phase 2/3 Open-label Extension Study to Evaluate Long-term Safety and Efficacy With VX-509 in a Treat to Target Setting in Subjects With Rheumatoid Arthritis on Disease-Modifying Antirheumatic Drugs

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2012-004342-14
Trial protocol	LT EE DK
Global end of trial date	29 July 2014

Results information

Result version number	v2 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015
Version creation reason	• Correction of full data set QC data set & address issues related to earlier EudraCT system bug

Trial information

Trial identification

Sponsor protocol code	VX12-509-104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01830985
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, 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 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of VX-509 treatment in subjects with rheumatoid arthritis (RA) on disease-modifying antirheumatic drug (DMARD) therapy.

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 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	38
EEA total number of subjects	2

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)	35
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who completed the assigned study drug treatment phase of a previously designated VX-509 study (VX12-509-103) were eligible for enrollment. A total of 38 subjects were enrolled and treated. Additionally, 1 subject was enrolled but did not receive study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	VX-509

Arm description:

Subjects received (2 VX-509 [100 milligram (mg)] or 3 VX-509 [150 mg] or 4 VX-509 [200 mg]) tablets orally once daily up to a maximum of 12.9 months.

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:

Study design allowed subjects to change their treatments. Subjects received 100, 150 and 200 mg VX-509 once daily. The planned duration of treatment was 104 weeks; however, the maximum actual duration of exposure was 12.9 months.

Number of subjects in period 1	VX-509
Started	38
Completed	33
Not completed	5
Consent withdrawn by subject	1
Death	1
Unspecified	1
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	VX-509
Reporting group description:	
Subjects received (2 VX-509 [100 milligram (mg)] or 3 VX-509 [150 mg] or 4 VX-509 [200 mg]) tablets orally once daily up to a maximum of 12.9 months.	

Reporting group values	VX-509	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	54.1		
standard deviation	± 9.42	-	
Gender categorical Units: Subjects			
Female	27	27	
Male	11	11	

End points

End points reporting groups

Reporting group title	VX-509
Reporting group description:	
Subjects received (2 VX-509 [100 milligram (mg)] or 3 VX-509 [150 mg] or 4 VX-509 [200 mg]) tablets orally once daily up to a maximum of 12.9 months.	
Subject analysis set title	VX-509 100 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 2 VX-509 (100 mg) tablets orally once daily up to a maximum of 12.9 months.	
Subject analysis set title	VX-509 150 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 2 VX-509 (150 mg) tablets orally once daily up to a maximum of 12.9 months.	
Subject analysis set title	VX-509 200 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 2 VX-509 (200 mg) tablets orally once daily up to a maximum of 12.9 months.	

Primary: Long Term Safety and Tolerability as Assessed by Adverse Events (AEs)

End point title	Long Term Safety and Tolerability as Assessed by Adverse Events (AEs)[1]
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. serious adverse-events (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. Percentage of subjects with AEs and SAEs are reported. Analysis was performed on Open Label Extension (OLE) set included all subjects who consented to participate in VX12-509-104 (2012-004342-14) and received at least 1 dose of study drug in VX12-509-104 (2012-004342-14).	
End point type	Primary
End point timeframe:	
From start of study up to safety follow-up (28 days after last dose [last dose = Week 56])	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned.

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38	32	18	
Units: percentage of subjects				
number (not applicable)				
Percentage of subjects with AEs	47.4	56.3	55.6	
Percentage of subjects with SAEs	2.6	9.4	5.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Clinical Disease Activity Index (CDAI) Low Disease Activity (LDA) (<=10) or CDAI Remission (<=2.8)

End point title	Percentage of Subjects Who Achieved Clinical Disease Activity Index (CDAI) Low Disease Activity (LDA) (<=10) or CDAI Remission (<=2.8)

End point description:

The CDAI is the numerical sum of 4 outcome parameters: tender joints count (TJC), swollen joints count (SJC), subject global assessment (assessed on 0-10 point scale, higher score = more disease activity), and physician global assessment of disease activity (assessed on 0-10 point scale, higher score = more disease activity). CDAI total score range: 0 – 76, CDAI less than equal to (<=) 2.8 indicates remission and CDAI <=10 indicates LDA. Analysis was performed on OLE set.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[2]	32[3]	18[4]	
Units: Percentage of subjects				
number (not applicable)				
Week 4: CDAI <= 10 (n= 38, 0, 0)	26.3	0	0	
Week 4: CDAI <= 2.8 (n= 38, 0, 0)	0	0	0	
Week 8: CDAI <= 10 (n= 38, 0, 0)	23.7	0	0	
Week 8: CDAI <= 2.8 (n= 38, 0, 0)	5.3	0	0	
Week 12: CDAI <= 10 (n= 13, 25, 0)	69.2	20	0	
Week 12: CDAI <= 2.8 (n= 13, 25, 0)	23.1	0	0	
Week 16: CDAI <= 10 (n= 13, 25, 0)	46.2	20	0	
Week 16: CDAI <= 2.8 (n= 13, 25, 0)	7.7	0	0	
Week 20: CDAI <= 10 (n= 9, 14, 15)	55.6	21.4	20	
Week 20: CDAI <= 2.8 (n= 9, 14, 15)	11.1	0	0	
Week 24: CDAI <= 10 (n= 9, 11, 15)	55.6	45.5	20	
Week 24: CDAI <= 2.8 (n= 9, 11, 15)	11.1	0	0	
Week 32: CDAI <= 10 (n= 6, 7, 15)	66.7	71.4	6.7	
Week 32: CDAI <= 2.8 (n= 6, 7, 15)	0	0	0	
Week 40: CDAI <= 10 (n= 4, 4, 8)	50	75	25	
Week 40: CDAI <= 2.8 (n= 4, 4, 8)	0	0	0	
Week 48: CDAI <= 10 (n= 2, 4, 6)	0	0	16.7	
Week 48: CDAI <= 2.8 (n= 2, 4, 6)	0	0	0	
Week 56: CDAI <= 10 (n= 1, 1, 4)	0	0	0	
Week 56: CDAI <= 2.8 (n= 1, 1, 4)	0	0	0	

Notes:

[2] - n = number of subjects at specified time-point

[3] - n = number of subjects at specified time-point

[4] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 20%, 50%, 70% (ACR20/50/70) C-Reactive Protein (ACR20/50/70-CRP) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 20%, 50%, 70% (ACR20/50/70) C-Reactive Protein (ACR20/50/70-CRP) Response

End point description:

ACR20/50/70-CRP response: greater than equal to (>=) 20/50/70% improvement in TJC; >= 20/50/70% improvement in SJC; and >= 20/50/70% improvement in at least 3 of 5 remaining ACR core measures: subject assessment of pain (assessed on 0-100 millimeter (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 OLE Set.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[5]	32[6]	18[7]	
Units: percentage of subjects				
number (not applicable)				
Week 4: ACR20-CRP Response (n= 38, 0, 0)	63.2	0	0	
Week 4: ACR50-CRP Response (n= 38, 0, 0)	36.8	0	0	
Week 4: ACR70-CRP Response (n= 38, 0, 0)	21.1	0	0	
Week 8: ACR20-CRP Response (n= 38, 0, 0)	68.4	0	0	
Week 8: ACR50-CRP Response (n= 38, 0, 0)	34.2	0	0	
Week 8: ACR70-CRP Response (n= 38, 0, 0)	15.8	0	0	
Week 12: ACR20-CRP Response (n= 13, 25, 0)	76.9	72	0	
Week 12: ACR50-CRP Response (n= 13, 25, 0)	69.2	44	0	
Week 12: ACR70-CRP Response (n= 13, 25, 0)	46.2	16	0	
Week 16: ACR20-CRP Response (n= 13, 25, 0)	69.2	72	0	
Week 16: ACR50-CRP Response (n= 13, 25, 0)	53.8	32	0	
Week 16: ACR70-CRP Response (n= 13, 25, 0)	30.8	8	0	
Week 20: ACR20-CRP Response (n= 9, 14, 15)	88.9	57.1	66.7	
Week 20: ACR50-CRP Response (n= 9, 14, 15)	55.6	57.1	33.3	
Week 20: ACR70-CRP Response (n= 9, 14, 15)	44.4	28.6	26.7	

Week 24: ACR20-CRP Response (n= 9, 11, 15)	88.9	54.5	60	
Week 24: ACR50-CRP Response (n= 9, 11, 15)	66.7	36.4	40	
Week 24: ACR70-CRP Response (n= 9, 11, 15)	33.3	9.1	26.7	
Week 32: ACR20-CRP Response (n= 6, 7, 15)	83.3	85.7	46.7	
Week 32: ACR50-CRP Response (n= 6, 7, 15)	83.3	42.9	40	
Week 32: ACR70-CRP Response (n= 6, 7, 15)	83.3	28.6	6.7	
Week 40: ACR20-CRP Response (n= 4, 4, 8)	50	75	37.5	
Week 40: ACR50-CRP Response (n= 4, 4, 8)	50	75	37.5	
Week 40: ACR70-CRP Response (n= 4, 4, 8)	50	50	25	
Week 48: ACR20-CRP Response (n= 2, 4, 6)	50	50	50	
Week 48: ACR50-CRP Response (n= 2, 4, 6)	50	25	33.3	
Week 48: ACR70-CRP Response (n= 2, 4, 6)	0	0	16.7	
Week 56: ACR20-CRP Response (n= 1, 1, 4)	0	0	50	
Week 56: ACR50-CRP Response (n= 1, 1, 4)	0	0	25	
Week 56: ACR70-CRP Response (n= 1, 1, 4)	0	0	0	

Notes:

[5] - n = number of subjects at specified time-point

[6] - n = number of subjects at specified time-point

[7] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Score Using 28-Joint Count and C-Reactive Protein (4 Variables) (DAS28-4 [CRP])

End point title	Change From Baseline in Disease Activity Score Using 28-Joint Count and C-Reactive Protein (4 Variables) (DAS28-4 [CRP])

End point description:

DAS28-4(CRP) was calculated from SJC and TJC using the 28 joints count, CRP milligram per liter [mg/L] and subject general health on visual analogue scale. A score of less than (<) 2.6 implied remission and <=3.2 implied low disease activity. Analysis was performed on OLE set. The number 99999 in data field signifies the data not available/applicable.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[8]	32[9]	18[10]	
Units: units on scale				
arithmetic mean (standard deviation)				
Week 4: (n= 38, 0, 0)	-1.888 (± 1.284)	0 (± 0)	0 (± 0)	
Week 8: (n= 37, 0, 0)	-2.183 (± 1.1887)	0 (± 0)	0 (± 0)	
Week 12: (n= 11, 23, 0)	-2.939 (± 1.2092)	-2.412 (± 1.1784)	0 (± 0)	
Week 16: (n= 12, 21, 0)	-2.047 (± 1.4031)	-2.372 (± 1.1644)	0 (± 0)	
Week 20: (n= 8, 10, 14)	-2.786 (± 0.9364)	-3.159 (± 1.3263)	-2.227 (± 1.3663)	
Week 24: (n= 8, 8, 13)	-2.581 (± 1.1552)	-2.858 (± 0.9788)	-2.282 (± 1.4409)	
Week 32: (n= 5, 6, 7)	-2.889 (± 0.5588)	-2.673 (± 0.6799)	-3.12 (± 0.9276)	
Week 40: (n= 3, 4, 3)	-2.368 (± 0.9968)	-3.152 (± 1.0118)	-3.734 (± 0.9939)	
Week 48: (n= 1, 3, 3)	-1.791 (± 99999)	-1.656 (± 0.9)	-2.961 (± 0.3821)	
Week 56: (n= 0, 1, 2)	0 (± 0)	-2.455 (± 99999)	-2.533 (± 1.1736)	

Notes:

[8] - n = number of subjects at specified time-point

[9] - n = number of subjects at specified time-point

[10] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With DAS28-4(CRP) <2.6 (DAS remission)

End point title	Percentage of Subjects With DAS28-4(CRP) <2.6 (DAS remission)

End point description:

DAS28-4(CRP) was calculated from SJC and TJC using the 28 joints count, CRP [mg/L] and subject general health on visual analogue scale. A score of less than (<) 2.6 implied remission and <=3.2 implied low disease activity. Analysis was performed on OLE set.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[11]	32[12]	18[13]	
Units: percentage of subjects				
number (not applicable)				
Week 4: (n= 38, 0, 0)	18.4	0	0	
Week 8: (n= 38, 0, 0)	23.7	0	0	

Week 12: (n= 13, 25, 0)	53.8	16	0	
Week 16: (n= 13, 25, 0)	23.1	16	0	
Week 20: (n= 9, 14, 15)	66.7	21.4	0	
Week 24: (n= 9, 11, 15)	33.3	27.3	13.3	
Week 32: (n= 6, 7, 15)	50	42.9	6.7	
Week 40: (n= 4, 4, 8)	50	75	25	
Week 48: (n= 2, 4, 6)	0	25	0	
Week 56: (n= 1, 1, 4)	0	100	0	

Notes:

[11] - n = number of subjects at specified time-point

[12] - n = number of subjects at specified time-point

[13] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With European League Against Rheumatism (EULAR) Good or Moderate Response

End point title	Percentage of Subjects With European League Against Rheumatism (EULAR) Good or Moderate Response

End point description:

DAS28-4 (CRP) EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline (BL) 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 greater than (>) 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 CPR >5.1. Analysis was performed on OLE set.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[14]	32[15]	18[16]	
Units: percentage of subjects				
number (not applicable)				
Week 4: (n= 38, 0, 0)	71.1	0	0	
Week 8: (n= 38, 0, 0)	81.6	0	0	
Week 12: (n= 13, 25, 0)	84.6	84	0	
Week 16: (n= 13, 25, 0)	76.9	72	0	
Week 20: (n= 9, 14, 15)	88.9	71.4	73.3	
Week 24: (n= 9, 11, 15)	88.9	72.7	66.7	
Week 32: (n= 6, 7, 15)	83.3	85.7	46.7	
Week 40: (n= 4, 4, 8)	75	100	37.5	
Week 48: (n= 2, 4, 6)	50	75	50	
Week 56: (n= 1, 1, 4)	0	100	50	

Notes:

[14] - n = number of subjects at specified time-point

[15] - n = number of subjects at specified time-point

[16] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift from Baseline in Dose of Disease-Modifying Anti-rheumatic Drug (DMARD) And Corticosteroid

End point title	Number of Subjects With Shift from Baseline in Dose of Disease-Modifying Anti-rheumatic Drug (DMARD) And Corticosteroid

End point description:

DMARDs dose was classified as Standard-dose (SD) DMARD, Low-dose (LD) DMARD, and No DMARD. Corticosteroid (Cort) dose was classified as Full-dose (FD) Corticosteroids, Low-dose (LD) Corticosteroids, and No Corticosteroids. Shift from baseline (BL) is reported. Analysis was performed on OLE set.

End point type	Secondary

End point timeframe:

Week (Wk) 8, 16, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[17]	32[18]	18[19]	
Units: subjects				
number (not applicable)				
BL SD DMARDs, Wk 8 SD DMARDs (n=38,0,0)	35	0	0	
BL LD DMARDs, Wk 8 LD DMARDs (n=38,0,0)	3	0	0	
BL SD DMARDs, Wk 16 SD DMARDs (n=12,23,0)	10	20	0	
BL SD DMARDs, Wk 16 LD DMARDs (n=12,23,0)	0	2	0	
BL LD DMARDs, Wk 16 LD DMARDs (n=12,23,0)	2	1	0	
BL SD DMARDs, Wk 24 SD DMARDs (n=8,8,14)	4	7	12	
BL SD DMARDs, Wk 24 LD DMARDs (n=8,8,14)	2	1	1	
BL LD DMARDs, Wk 24 LD DMARDs (n=8,8,14)	2	0	1	
BL SD DMARDs, Wk 32 SD DMARDs (n=5,6,11)	2	5	9	
BL SD DMARDs, Wk 32 LD DMARDs (n=5,6,11)	2	1	1	
BL LD DMARDs, Wk 32 LD DMARDs (n=5,6,11)	1	0	1	
BL SD DMARDs, Wk 40 SD DMARDs (n=3,4,3)	2	3	2	

BL SD DMARDs, Wk 40 LD DMARDs (n=3,4,3)	1	1	1	
BL SD DMARDs, Wk 48 SD DMARDs (n=1,4,3)	0	3	2	
BL SD DMARDs, Wk 48 LD DMARDs (n=1,4,3)	1	1	1	
BL SD DMARDs, Wk 56 SD DMARDs (n=0,1,2)	0	1	2	
BL FD Cort, WK 8 FD Cort (n=38,0,0)	6	0	0	
BL LD Cort, WK 8 LD Cort (n=38,0,0)	9	0	0	
BL no Cort, WK 8 no Cort (n=38,0,0)	23	0	0	
BL FD Cort, WK 16 FD Cort (n=12,23,0)	0	4	0	
BL LD Cort, WK 16 LD Cort (n=12,23,0)	4	4	0	
BL no Cort, WK 16 no Cort (n=12,23,0)	8	15	0	
BL FD Cort, WK 24 FD Cort (n=8,8,14)	0	0	3	
BL FD Cort, WK 24 LD Cort (n=8,8,14)	0	1	0	
BL LD Cort, WK 24 LD Cort (n=8,8,14)	1	2	2	
BL no Cort, WK 24 no Cort (n=8,8,14)	7	5	9	
BL FD Cort, WK 32 FD Cort (n=5,6,11)	0	0	2	
BL FD Cort, WK 32 LD Cort (n=5,6,11)	0	0	1	
BL LD Cort, WK 32 LD Cort (n=5,6,11)	1	1	0	
BL no Cort, WK 32 no Cort (n=5,6,11)	4	5	8	
BL FD Cort, WK 40 FD Cort (n=3,4,3)	0	0	1	
BL FD Cort, WK 40 LD Cort (n=3,4,3)	0	0	1	
BL LD Cort, WK 40 LD Cort (n=3,4,3)	0	1	0	
BL no Cort, WK 40 no Cort (n=3,4,3)	3	3	1	
BL FD Cort, WK 48 FD Cort (n=1,4,3)	0	0	1	
BL FD Cort, WK 48 LD Cort (n=1,4,3)	0	0	1	
BL LD Cort, WK 48 LD Cort (n=1,4,3)	0	1	0	
BL no Cort, WK 48 no Cort (n=1,4,3)	1	3	1	
BL FD Cort, WK 56 FD Cort (n=0,1,2)	0	0	1	
BL LD Cort, WK 56 LD Cort (n=0,1,2)	0	1	0	
BL no Cort, WK 56 no Cort (n=0,1,2)	0	0	1	

Notes:

[17] - n = number of subjects at specified time-point

[18] - n = number of subjects at specified time-point

[19] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: ACR Hybrid Score

End point title	ACR Hybrid Score

End point description:

ACR hybrid score 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 OLE set. The number 99999 in data field signifies data not available/applicable.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[20]	32[21]	18[22]	
Units: units on scale				
arithmetic mean (standard deviation)				
Week 4: (n= 37, 0, 0)	43.688 (± 25.8279)	0 (± 0)	0 (± 0)	
Week 8: (n= 38, 0, 0)	45.033 (± 25.1458)	0 (± 0)	0 (± 0)	
Week 12: (n= 12, 24, 0)	64.419 (± 26.1777)	49.437 (± 23.2752)	0 (± 0)	
Week 16: (n= 12, 23, 0)	46.936 (± 38.995)	49.012 (± 20.2113)	0 (± 0)	
Week 20: (n= 8, 10, 14)	62.974 (± 20.9817)	61.483 (± 25.6113)	49.939 (± 23.2619)	
Week 24: (n= 8, 8, 14)	67.045 (± 15.9479)	52.163 (± 22.4091)	47.198 (± 27.8454)	
Week 32: (n= 5, 6, 7)	78.725 (± 8.6201)	64.12 (± 16.2678)	66.442 (± 8.6957)	
Week 40: (n= 3, 4, 3)	59.129 (± 34.994)	64.301 (± 30.5619)	76.041 (± 11.9408)	
Week 48: (n= 1, 3, 3)	61.861 (± 99999)	38.481 (± 20.9365)	58.64 (± 10.2764)	
Week 56: (n= 0, 1, 2)	0 (± 0)	19.99 (± 99999)	52.159 (± 19.5505)	

Notes:

[20] - n = number of subjects at specified time-point

[21] - n = number of subjects at specified time-point

[22] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With DAS28 4(ESR) Remission and Low Disease Activity

End point title	Percentage of Subjects With DAS28 4(ESR) Remission and Low Disease Activity

End point description:

DAS28-4 erythrocyte sedimentation rate (ESR) was calculated from SJC and TJC using the 28 joints count, ESR millimeter per hour (mm/hour) and subject general health on visual analogue scale. A score of <2.6 implied remission and <=3.2 implied low disease activity. Analysis was performed on OLE Set.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[23]	32[24]	18[25]	
Units: percentage of subjects				
number (not applicable)				
Week 4: DAS28-4(ESR) (<2.6) (n= 38, 0, 0)	10.5	0	0	
Week 4: DAS28-4(ESR) (<=3.2) (n= 38, 0, 0)	21.1	0	0	
Week 8: DAS28-4(ESR) (<2.6) (n= 38, 0, 0)	18.4	0	0	
Week 8: DAS28-4(ESR) (<=3.2) (n= 38, 0, 0)	21.1	0	0	
Week 12: DAS28-4(ESR) (<2.6) (n= 13, 25, 0)	30.8	12	0	
Week 12: DAS28-4(ESR) (<=3.2) (n= 13, 25, 0)	61.5	16	0	
Week 16: DAS28-4(ESR) (<2.6) (n= 13, 25, 0)	15.4	0	0	
Week 16: DAS28-4(ESR) (<=3.2) (n= 13, 25, 0)	30.8	8	0	
Week 20: DAS28-4(ESR) (<2.6) (n= 9, 14, 15)	22.2	14.3	0	
Week 20: DAS28-4(ESR) (<=3.2) (n= 9, 14, 15)	44.4	35.7	6.7	
Week 24: DAS28-4(ESR) (<2.6) (n= 9, 11, 15)	22.2	27.3	0	
Week 24: DAS28-4(ESR) (<=3.2) (n= 9, 11, 15)	33.3	36.4	13.3	
Week 32: DAS28-4(ESR) (<2.6) (n= 6, 7, 15)	0	28.6	13.3	
Week 32: DAS28-4(ESR) (<=3.2) (n= 6, 7, 15)	50	42.9	13.3	
Week 40: DAS28-4(ESR) (<2.6) (n= 4, 4, 8)	0	50	25	
Week 40: DAS28-4(ESR) (<=3.2) (n= 4, 4, 8)	25	100	25	
Week 48: DAS28-4(ESR) (<2.6) (n= 2, 4, 6)	0	0	16.7	
Week 48: DAS28-4(ESR) (<=3.2) (n= 2, 4, 6)	0	25	16.7	
Week 56: DAS28-4(ESR) (<2.6) (n= 1, 1, 4)	0	0	0	
Week 56: DAS28-4(ESR) (<=3.2) (n= 1, 1, 4)	0	100	25	

Notes:

[23] - n = number of subjects at specified time-point

[24] - n = number of subjects at specified time-point

[25] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Health Assessment Questionnaire -Disability Index (HAQ-DI)

End point title	Change from Baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI)

End point description:

The 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; 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 OLE set.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[26]	32[27]	18[28]	
Units: units on scale				
arithmetic mean (standard deviation)				
Week 4: (n= 38, 0, 0)	-0.4704 (± 0.54944)	0 (± 0)	0 (± 0)	
Week 8: (n= 38, 0, 0)	-0.4309 (± 0.52769)	0 (± 0)	0 (± 0)	
Week 12: (n= 12, 24, 0)	-0.7396 (± 0.45992)	-0.4479 (± 0.42336)	0 (± 0)	
Week 16: (n= 12, 23, 0)	-0.7604 (± 0.47511)	-0.4022 (± 0.33277)	0 (± 0)	
Week 20: (n= 8, 10, 14)	-0.75 (± 0.47716)	-0.475 (± 0.40311)	-0.5 (± 0.3766)	
Week 24: (n= 8, 8, 14)	-0.7188 (± 0.46651)	-0.4688 (± 0.32562)	-0.5089 (± 0.39365)	
Week 32: (n= 5, 6, 7)	-1.25 (± 0.08839)	-0.4167 (± 0.3594)	-0.6786 (± 0.40734)	
Week 40: (n= 3, 4, 3)	-0.9167 (± 0.68845)	-0.5938 (± 0.27717)	-0.625 (± 0.5)	
Week 48: (n= 1, 3, 3)	-0.625 (± 99999)	-0.7083 (± 0.52042)	-0.5833 (± 0.43899)	
Week 56: (n= 0, 1, 2)	0 (± 0)	-0.875 (± 99999)	-0.5625 (± 0.08839)	

Notes:

[26] - n = number of subjects at specified time-point

[27] - n = number of subjects at specified time-point

[28] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With DAS28-4(CRP) <3.2 (DAS LDA)

End point title	Percentage of Subjects With DAS28-4(CRP) <3.2 (DAS LDA)

End point description:

DAS28-4 (ESR) was calculated from SJC and TJC using the 28 joints count, ESR (mm/hour) and subject general health on visual analogue scale. A score of <2.6 implied remission and <=3.2 implied low disease activity. Analysis was performed on OLE Set.

End point type	Secondary

End point timeframe:
Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and 56

End point values	VX-509 100 mg	VX-509 150 mg	VX-509 200 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38[29]	32[30]	18[31]	
Units: percentage of subjects				
number (not applicable)				
Week 4: DAS28-4(CRP) (<=3.2) (n= 38, 0, 0)	42.1	0	0	
Week 8: DAS28-4(CRP) (<=3.2) (n= 38, 0, 0)	39.5	0	0	
Week 12: DAS28-4(CRP) (<=3.2) (n= 13, 25, 0)	69.2	28	0	
Week 16: DAS28-4(CRP) (<=3.2) (n= 13, 25, 0)	61.5	24	0	
Week 20: DAS28-4(CRP) (<=3.2) (n= 9, 14, 15)	66.7	57.1	33.3	
Week 24: DAS28-4(CRP) (<=3.2) (n= 9, 11, 15)	66.7	54.5	26.7	
Week 32: DAS28-4(CRP) (<=3.2) (n= 6, 7, 15)	83.3	71.4	26.7	
Week 40: DAS28-4(CRP) (<=3.2) (n= 4, 4, 8)	50	100	25	
Week 48: DAS28-4(CRP) (<=3.2) (n= 2, 4, 6)	0	25	33.3	
Week 56: DAS28-4(CRP) (<=3.2) (n= 1, 1, 4)	0	100	25	

Notes:

[29] - n = number of subjects at specified time-point

[30] - n = number of subjects at specified time-point

[31] - n = number of subjects at specified time-point

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study up to safety follow-up (28 days after last dose [last dose = Week 56])	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1
Reporting groups	
Reporting group title	VX-509
Reporting group description:	
Subjects received (2 VX-509 [100 mg] or 3 VX-509 [150 mg] or 4 VX-509 [200 mg]) tablets orally once daily up to a maximum of 12.9 months.	

Serious adverse events	VX-509		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis chronic			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	VX-509		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 38 (76.32%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

Sinus congestion subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3		
Pleurisy subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Pneumonitis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Cough subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Anxiety subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Blood magnesium decreased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Blood cholesterol increased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Transaminases increased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Blood triglycerides increased			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Post herpetic neuralgia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Eye disorders			
Cataract nuclear			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

Gingival ulceration subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Oral pain subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Skin and subcutaneous tissue disorders			
Actinic keratosis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 3		
Dermatitis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Ecchymosis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Livedo reticularis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Rosacea subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Petechiae subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Skin ulcer subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Rheumatoid nodule			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tendon pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gastroenteritis viral			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Subcutaneous abscess			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		

Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early on 01-May-2014 by the sponsor due to a decision to modify the drug development plan. The planned treatment duration was 104 weeks; however subjects received treatment up to Week 56.

Notes: