Clinical trial results:
A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Dose Study of Two Doses of R935788 in Rheumatoid Arthritis Patients Failing to Respond to Methotrexate

Summary

EudraCT number	2008-000742-30
Trial protocol	HU BG PL
Global end of trial date	01 June 2009

Results information

Result version number	v1 (current)
This version publication date	01 September 2022
First version publication date	01 September 2022

Trial information

Trial identification

Sponsor protocol code	C-935788-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00665925
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigel Pharmaceuticals, Inc.
Sponsor organisation address	1180 Veterans Blvd, South San Francisco, CA, United States, 94080
Public contact	Lucy Yan, MD, Rigel Pharmaceuticals, Inc., +1 650-624-1313, lyan@rigel.com
Scientific contact	Lucy Yan, MD, Rigel Pharmaceuticals, Inc., +1 650-624-1313, lyan@rigel.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	16 December 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2009
Global end of trial reached?	Yes
Global end of trial date	01 June 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of this study is to confirm the efficacy of R788 100 mg PO bid as determined by ACR20 responder rates at 6 months.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki.

Background therapy:

-

Evidence for comparator:

Placebo tablets were provided to match the appearance of R788-containing 100 and 150 mg tablets. Placebo tablets were administered orally using the same treatment schedule as for R788-containing tablets.

Actual start date of recruitment	19 May 2008
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	Romania: 25
Country: Number of subjects enrolled	United States: 109
Country: Number of subjects enrolled	Mexico: 100
Country: Number of subjects enrolled	Colombia: 124
Country: Number of subjects enrolled	Poland: 80
Country: Number of subjects enrolled	Bulgaria: 19
Worldwide total number of subjects	457
EEA total number of subjects	124

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	376
From 65 to 84 years	80
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Cohort A: 152 subjects were enrolled and 131 completed the study.
Cohort B: 152 subjects were enrolled and 126 completed the study.
Cohort C: 76 subjects were enrolled and 59 completed the study.
Cohort D: 77 subjects were enrolled and 62 completed the study.

Subjects were recruited in US, Latin America and Europe

Pre-assignment

Screening details:

Male and female subjects who had active rheumatoid arthritis (RA) for a minimum of 6 months, and receiving a weekly methotrexate (MTX) dose for a minimum of 3 months were randomly assigned to receive R788 150 mg once daily or 100 mg twice daily, placebo once daily or placebo twice daily. It was planned to randomize approximately 420 subjects.

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, Monitor

Blinding implementation details:

In order to enhance the blinded scoring of subjective efficacy-related measurements, a trained and qualified IJA at each site was responsible for performing the tender and swollen joint counts and completing the global assessment of disease activity.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A R788 100 mg bid

Arm description:

R788 100 mg, oral tablets, twice daily, double-blind

Arm type	Experimental
Investigational medicinal product name	R935788
Investigational medicinal product code	R935788 sodium hexahydrate
Other name	R788 Sodium, R788 Na, R788
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

R788 100 mg, oral tablets, twice daily, double-blind

Arm title	Cohort B R788 150 mg qd

Arm description:

R788 150 mg, oral tablets, once daily, double-blind

Arm type	Experimental
Investigational medicinal product name	R935788
Investigational medicinal product code	R935788 sodium hexahydrate
Other name	R788 Sodium, R788 Na, R788
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

R788 150 mg, oral tablets, once daily, double-blind

Arm title	Cohort C Placebo 100 mg bid

Arm description:	
Placebo 100 mg, oral tablets, twice daily, double-blind	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo 100 mg, oral tablets, twice daily, double-blind	
Arm title	Cohort D Placebo 150 mg qd
Arm description:	
Placebo 150 mg, oral tablets, once daily, double-blind	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo 150 mg, oral tablets, once daily, double-blind	

Number of subjects in period 1	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid
Started	152	152	76
Completed	131	126	59
Not completed	21	26	17
Consent withdrawn by subject	2	3	2
Physician decision	2	1	-
Adverse event, non-fatal	5	10	5
Due to exclusion criteria	-	-	-
Enrolled by mistake	1	-	-
Lost to follow-up	2	2	2
Lack of efficacy	8	9	8
Protocol deviation	1	1	-

Number of subjects in period 1	Cohort D Placebo 150 mg qd
Started	77
Completed	62
Not completed	15
Consent withdrawn by subject	2
Physician decision	-
Adverse event, non-fatal	1
Due to exclusion criteria	1

Enrolled by mistake	-
Lost to follow-up	1
Lack of efficacy	10
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A R788 100 mg bid
Reporting group description:	
R788 100 mg, oral tablets, twice daily, double-blind	
Reporting group title	Cohort B R788 150 mg qd
Reporting group description:	
R788 150 mg, oral tablets, once daily, double-blind	
Reporting group title	Cohort C Placebo 100 mg bid
Reporting group description:	
Placebo 100 mg, oral tablets, twice daily, double-blind	
Reporting group title	Cohort D Placebo 150 mg qd
Reporting group description:	
Placebo 150 mg, oral tablets, once daily, double-blind	

Reporting group values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid
Number of subjects	152	152	76
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Please note, baseline data were only calculated for the placebo qd and placebo bid groups. Data from the placebo groups were only pooled for the efficacy analyses.			
Units: years			
arithmetic mean	52.5	52.6	53.4
standard deviation	± 12.97	± 12.31	± 12.66
Gender categorical			
Please note, baseline data were only calculated for the placebo qd and placebo bid groups. Data from the placebo groups were only pooled for the efficacy analyses.			
Units: Subjects			
Female	131	128	64
Male	21	24	12
Race			
Units: Subjects			
Asian	1	0	0
Black	4	2	3
Caucasian	58	75	32
Hispanic	88	74	41
Other	1	1	0

Height			
Units: cm			
arithmetic mean	160.13	161.35	161.08
standard deviation	± 8.156	± 9.618	± 9.913
Weight			
Units: kg			
arithmetic mean	70.67	72.25	70.95
standard deviation	± 15.673	± 16.213	± 19.475

Reporting group values	Cohort D Placebo 150 mg qd	Total	
Number of subjects	77	457	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Please note, baseline data were only calculated for the placebo qd and placebo bid groups. Data from the placebo groups were only pooled for the efficacy analyses.			
Units: years			
arithmetic mean	51.3		
standard deviation	± 13.68	-	
Gender categorical			
Please note, baseline data were only calculated for the placebo qd and placebo bid groups. Data from the placebo groups were only pooled for the efficacy analyses.			
Units: Subjects			
Female	67	390	
Male	10	67	
Race			
Units: Subjects			
Asian	0	1	
Black	4	13	
Caucasian	39	204	
Hispanic	34	237	
Other	0	2	
Height			
Units: cm			
arithmetic mean	160.93		
standard deviation	± 9.279	-	
Weight			
Units: kg			
arithmetic mean	69.60		
standard deviation	± 18.862	-	

End points

End points reporting groups

Reporting group title	Cohort A R788 100 mg bid
Reporting group description:	
R788 100 mg, oral tablets, twice daily, double-blind	
Reporting group title	Cohort B R788 150 mg qd
Reporting group description:	
R788 150 mg, oral tablets, once daily, double-blind	
Reporting group title	Cohort C Placebo 100 mg bid
Reporting group description:	
Placebo 100 mg, oral tablets, twice daily, double-blind	
Reporting group title	Cohort D Placebo 150 mg qd
Reporting group description:	
Placebo 150 mg, oral tablets, once daily, double-blind	
Subject analysis set title	Placebo Pooled
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
For analysis purposes, both Placebo groups (150 mg qd and 100 mg bid) have been pooled into one group.	

Primary: American College of Rheumatology 20 (ACR20) Response at 6 Months

End point title	American College of Rheumatology 20 (ACR20) Response at 6 Months[1][2]
End point description:	
The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)	
End point type	Primary
End point timeframe:	
after 6 months	

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 performed for primary endpoint. At Month 6, the ACR20 response was achieved by significantly more patients in both the R788 150 mg qd (57%) and 100 mg bid (67%) groups and in the combined R788 group (62%) versus the total placebo group (35%, p <0.001).
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	151	152	153	
Units: subjects				
Subjects achieving ACR20 criteria	101	87	53	

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 20 (ACR20) Response at 1 week

End point title	American College of Rheumatology 20 (ACR20) Response at 1 week[3]

End point description:

The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 1 week

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	146	151	153[4]	
Units: subjects				
Subjects achieving ACR20 criteria	53	34	21	

Notes:

[4] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 1 week

End point title	American College of Rheumatology 70 (ACR70) Response at 1 week[5]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

after 1 week

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	146	151	153[6]	
Units: subjects				
Subjects achieving ACR70 criteria	2	1	1	

Notes:

[6] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 1 week

End point title	American College of Rheumatology Index of Improvement (ACRn) at 1 week[7]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 1 week

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	145	151	153[8]	
Units: Score				
arithmetic mean (standard deviation)	16.22 (± 19.564)	10.75 (± 15.788)	7.07 (± 13.677)	

Notes:

[8] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 1 month

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 1 month[9]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 1 month

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	86	93	85[10]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	4	10	2	

Notes:

[10] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 1 month

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 1 month[11]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 1 month

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	86	93	85[12]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	15	15	6	

Notes:

[12] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 1 month

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 1 month[13]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

At 1 month

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	53	64[14]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	12	3	2	

Notes:

[14] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 1 month

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 1 month[15]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 1 month

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	53	64[16]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	18	6	3	

Notes:

[16] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at 6 months

End point title	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at 6 months[17]

End point description:

Change from baseline in FACIT-F, which is a subject-reported 13-item questionnaire that assesses fatigue, calculated as the score at 6 months minus the score at baseline. The FACIT-F runs from 0 to 52 with lower scores indicating higher fatigue. A positive change from baseline indicates an improvement in fatigue after treatment.

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	117	107	109[18]	
Units: Score				
arithmetic mean (standard deviation)				
After 6 months	7.4 (± 10.87)	5.7 (± 10.28)	4.5 (± 9.79)	

Notes:

[18] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Short Form Health Survey (SF-36) Physical Component Summary (PCS) at 6 Months

End point title	Short Form Health Survey (SF-36) Physical Component Summary (PCS) at 6 Months[19]

End point description:

Change from baseline in the PCS of the SF-36 (which assesses health and wellbeing), calculated as the score at 6 months minus the score at baseline. The PCS ranges from 0 to 100 with 100 indicating the highest level of functioning possible. A positive change indicates an improvement in PCS after treatment

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	129	124	118	
Units: Score				
arithmetic mean (standard deviation)				
After 6 months	8.524 (± 8.7068)	5.903 (± 8.9541)	4.902 (± 8.4808)	

Statistical analyses

No statistical analyses for this end point

Secondary: Short Form Health Survey (SF-36) Mental Component Summary (MCS) at 6 Months

End point title	Short Form Health Survey (SF-36) Mental Component Summary (MCS) at 6 Months[20]

End point description:

Change from baseline in the MCS of the SF-36 (which assesses health and wellbeing), calculated as the score at 6 months minus the score at baseline. The MCS ranges from 0 to 100 with 100 indicating the highest level of functioning possible. A positive change indicates an improvement in MCS after treatment

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	129	125	118[21]	
Units: Score				
arithmetic mean (standard deviation)				
After 6 months	3.990 (± 10.5129)	2.033 (± 10.7089)	3.711 (± 10.7098)	

Notes:

[21] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ALT values greater than 1.5 times the ULN

End point title	Number of subjects with ALT values greater than 1.5 times the ULN

End point description:

The number of intent-to-treat subjects with ALT (Alanine Aminotransferase) (a test of liver function) values greater than 1.5 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
Subjects	31	28	11	3

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with AST values greater than 1.5 times the ULN

End point title	The number of subjects with AST values greater than 1.5 times the ULN

End point description:

The number of participants with AST (Aspartate Aminotransferase) (a test of liver function) values greater than 1.5 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects	11	19	4	1

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with Alkaline Phosphatase >1.5 x Upper Limit of Normal (ULN) and >1.5 Times Baseline

End point title	The number of subjects with Alkaline Phosphatase >1.5 x Upper Limit of Normal (ULN) and >1.5 Times Baseline

End point description:

The number of intent-to-treat subjects with alkaline phosphatase (a test of liver function) values greater than 1.5 times the ULN and greater than 1.5 times baseline

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>1.5x ULN and baseline	6	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Bilirubin 1.5 times the Upper Limit of Normal (ULN)

End point title	Number of subjects with Bilirubin 1.5 times the Upper Limit of Normal (ULN)

End point description:

The number of intent-to-treat subjects with bilirubin (a test of liver function) values greater than 1.5 times the ULN

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>1.5 times	4	4	2	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Absolute Neutrophil Count (ANC) <1500/mm3

End point title	Number of subjects with Absolute Neutrophil Count (ANC) <1500/mm3

End point description:

The number of intent-to-treat subjecs with ANC values lower than 1500/mm3

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects	9	10	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 20 (ACR20) Response at 2 weeks

End point title	American College of Rheumatology 20 (ACR20) Response at 2 weeks[22]

End point description:

The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 2 weeks

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	148	152	153[23]	
Units: subjects				
Subjects achieving ACR20 criteria	67	47	29	

Notes:

[23] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 20 (ACR20) Response at 1 month

End point title	American College of Rheumatology 20 (ACR20) Response at 1 month[24]

End point description:

The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 1 month

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	151[25]	
Units: subjects				
Subjects achieving ACR20 criteria	89	72	48	

Notes:

[25] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 20 (ACR20) Response at 2 months

End point title	American College of Rheumatology 20 (ACR20) Response at 2 months[26]

End point description:

The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 2 months

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	149	151	151[27]	
Units: subjects				
Subjects achieving ACR20 criteria	95	81	58	

Notes:

[27] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 20 (ACR20) Response at 3 months

End point title	American College of Rheumatology 20 (ACR20) Response at 3 months[28]

End point description:

The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 3 months

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	152[29]	
Units: subjects				
Subjects achieving ACR20 criteria	97	79	64	

Notes:

[29] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 20 (ACR20) Response at 4 months

End point title	American College of Rheumatology 20 (ACR20) Response at 4 months[30]

End point description:

The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 4 months

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	147	151	152[31]	
Units: subjects				
Subjects achieving ACR20 criteria	100	71	57	

Notes:

[31] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 20 (ACR20) Response at 5 months

End point title	American College of Rheumatology 20 (ACR20) Response at 5 months[32]

End point description:

The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 5 months

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	151[33]	
Units: subjects				
Subjects achieving ACR20 criteria	97	84	61	

Notes:

[33] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 1 Week

End point title	American College of Rheumatology 50 (ACR50) Response at 1 Week[34]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 1 week

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	146	151	153[35]	
Units: subjects				
Subjects achieving ACR50 criteria	10	7	4	

Notes:

[35] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 2 weeks

End point title	American College of Rheumatology 50 (ACR50) Response at 2 weeks[36]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 2 weeks

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	148	152	153[37]	
Units: subjects				
Subjects achieving ACR50 criteria	21	15	7	

Notes:

[37] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 1 month

End point title	American College of Rheumatology 50 (ACR50) Response at 1 month[38]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 1 month

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	151[39]	
Units: subjects				
Subjects achieving ACR50 criteria	45	24	11	

Notes:

[39] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 6 weeks

End point title	American College of Rheumatology 50 (ACR50) Response at 6 weeks[40]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 6 weeks

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	151	148[41]	
Units: subjects				
Subjects achieving ACR50 criteria	43	30	19	

Notes:

[41] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 2 months

End point title	American College of Rheumatology 50 (ACR50) Response at 2 months[42]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 2 months

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	149	151	151[43]	
Units: subjects				
Subjects achieving ACR50 criteria	51	34	22	

Notes:

[43] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 3 months

End point title	American College of Rheumatology 50 (ACR50) Response at 3 months[44]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 3 months

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	152[45]	
Units: subjects				
Subjects achieving ACR50 criteria	58	43	23	

Notes:

[45] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 4 months

End point title	American College of Rheumatology 50 (ACR50) Response at 4 months[46]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 4 months

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	147	151	152[47]	
Units: subjects				
Subjects achieving ACR50 criteria	62	34	25	

Notes:

[47] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 5 months

End point title	American College of Rheumatology 50 (ACR50) Response at 5 months[48]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 5 months

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	151[49]	
Units: subjects				
Subjects achieving ACR50 criteria	62	41	25	

Notes:

[49] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 50 (ACR50) Response at 6 months

End point title	American College of Rheumatology 50 (ACR50) Response at 6 months[50]

End point description:

The number of intent-to-treat subjects with greater than or equal to 50% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	151	152	153[51]	
Units: subjects				
Subjects achieving ACR50 criteria	65	49	29	

Notes:

[51] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 2 weeks

End point title	American College of Rheumatology 70 (ACR70) Response at 2 weeks[52]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 2 weeks

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	148	152	153[53]	
Units: subjects				
Subjects achieving ACR70 criteria	7	5	1	

Notes:

[53] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 1 month

End point title	American College of Rheumatology 70 (ACR70) Response at 1 month[54]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 1 month

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	151[55]	
Units: subjects				
Subjects achieving ACR70 criteria	14	13	7	

Notes:

[55] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 6 weeks

End point title	American College of Rheumatology 70 (ACR70) Response at 6 weeks[56]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 6 weeks

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	151	148[57]	
Units: subjects				
Subjects achieving ACR70 criteria	16	13	5	

Notes:

[57] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 2 months

End point title	American College of Rheumatology 70 (ACR70) Response at 2 months[58]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 2 months

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	149	151	151[59]	
Units: subjects				
Subjects achieving ACR70 criteria	20	15	4	

Notes:

[59] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 3 months

End point title	American College of Rheumatology 70 (ACR70) Response at 3 months[60]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 3 months

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	152[61]	
Units: subjects				
Subjects achieving ACR70 criteria	30	19	10	

Notes:

[61] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 4 months

End point title	American College of Rheumatology 70 (ACR70) Response at 4 months[62]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 4 months

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	147	151	152[63]	
Units: subjects				
Subjects achieving ACR70 criteria	32	17	8	

Notes:

[63] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 5 months

End point title	American College of Rheumatology 70 (ACR70) Response at 5 months[64]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 5 months

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	152	151[65]	
Units: subjects				
Subjects achieving ACR70 criteria	33	20	8	

Notes:

[65] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 70 (ACR70) Response at 6 months

End point title	American College of Rheumatology 70 (ACR70) Response at 6 months[66]

End point description:

The number of intent-to-treat subjects with greater than or equal to 70% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	151	152	153[67]	
Units: subjects				
Subjects achieving ACR70 criteria	43	21	16	

Notes:

[67] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 2 weeks

End point title	American College of Rheumatology Index of Improvement (ACRn) at 2 weeks[68]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 2 weeks

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	145	150	151[69]	
Units: score				
arithmetic mean (standard deviation)				
Score	21.62 (± 23.491)	16.27 (± 20.899)	9.74 (± 16.987)	

Notes:

[69] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 1 month

End point title	American College of Rheumatology Index of Improvement (ACRn) at 1 month[70]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 1 month

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	146	148	149[71]	
Units: score				
arithmetic mean (standard deviation)				
Score	32.23 (± 26.304)	24.14 (± 25.428)	14.65 (± 20.537)	

Notes:

[71] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 6 weeks

End point title	American College of Rheumatology Index of Improvement (ACRn) at 6 weeks[72]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 6 weeks

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	146	146	145[73]	
Units: score				
arithmetic mean (standard deviation)				
Score	31.08 (± 27.789)	26.87 (± 26.893)	18.05 (± 22.904)	

Notes:

[73] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 2 months

End point title	American College of Rheumatology Index of Improvement (ACRn) at 2 months[74]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 2 months

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	143	145	148[75]	
Units: score				
arithmetic mean (standard deviation)				
Score	36.73 (± 28.254)	29.11 (± 26.827)	20.12 (± 23.179)	

Notes:

[75] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 3

months

End point title	American College of Rheumatology Index of Improvement (ACRn) at 3 months[76]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 3 months

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	142	141	147	
Units: score				
arithmetic mean (standard deviation)				
Score	39.04 (± 30.059)	31.79 (± 27.959)	22.11 (± 25.904)	

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 4 months

End point title	American College of Rheumatology Index of Improvement (ACRn) at 4 months[77]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 4 months

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	132	130	130[78]	
Units: score				
arithmetic mean (standard deviation)				
Score	44.70 (± 29.789)	30.24 (± 28.347)	22.61 (± 25.661)	

Notes:

[78] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 5 months

End point title	American College of Rheumatology Index of Improvement (ACRn) at 5 months[79]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 5 months

Notes:

[79] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	130	126	123[80]	
Units: score				
arithmetic mean (standard deviation)				
Score	44.76 (± 29.972)	35.35 (± 27.683)	25.66 (± 25.734)	

Notes:

[80] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology Index of Improvement (ACRn) at 6 months

End point title	American College of Rheumatology Index of Improvement (ACRn) at 6 months[81]

End point description:

The index of improvement in RA, where 0 indicates no improvement and 100 indicates a 100% improvement across all signs and symptoms of RA

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[81] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	130	126	121[82]	
Units: score				
arithmetic mean (standard deviation)				
Score	49.55 (± 30.189)	38.45 (± 29.108)	26.00 (± 29.402)	

Notes:

[82] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 2 months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 2 months[83]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 2 months

Notes:

[83] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	94	83[84]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	8	8	3	

Notes:

[84] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 3

months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 3 months[85]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 3 months

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	84	92	83[86]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	11	7	5	

Notes:

[86] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 4 months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 4 months[87]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 4 months

Notes:

[87] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	84	73[88]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	15	10	4	

Notes:

[88] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 5 months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 5 months[89]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 5 months

Notes:

[89] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	76	81	71[90]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	24	8	5	

Notes:

[90] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 6 months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <2.6 at 6 months[91]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[91] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	77	81	70[92]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	20	17	6	

Notes:

[92] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 2 months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 2 months[93]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 2 months

Notes:

[93] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	94	83[94]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	21	19	9	

Notes:

[94] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 3

months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 3 months[95]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 3 months

Notes:

[95] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	84	92	83[96]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	21	25	8	

Notes:

[96] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 4 months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 4 months[97]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 4 months

Notes:

[97] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	84	73[98]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	28	20	9	

Notes:

[98] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 5 months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 5 months[99]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 5 months

Notes:

[99] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	76	81	71[100]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	34	21	8	

Notes:

[100] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 6 months

End point title	Disease Activity Score-C-Reactive Protein (DAS28-CRP) <3.2 at 6 months[101]

End point description:

Number of intent-to-treat subjects with DAS28-CRP (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and CRP in patients with high CRP at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[101] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	77	81	70[102]	
Units: subjects				
Subjects achieving DAS28-CRP criteria	30	26	7	

Notes:

[102] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 2 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 2 months[103]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 2 months

Notes:

[103] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	60	50	64[104]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	13	4	4	

Notes:

[104] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.

6 at 3 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 3 months[105]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 3 months

Notes:

[105] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	49	64[106]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	19	3	4	

Notes:

[106] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 4 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 4 months[107]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 4 months

Notes:

[107] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	53	46	57[108]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	15	3	5	

Notes:

[108] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 5 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 5 months[109]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 5 months

Notes:

[109] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54	45	52[110]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	12	7	3	

Notes:

[110] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 6 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <2.6 at 6 months[111]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 2.6. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 2.6 indicates remission of RA symptoms

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[111] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54	44	51[112]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	21	9	3	

Notes:

[112] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 2 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 2 months[113]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 2 months

Notes:

[113] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	60	50	64[114]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	23	7	9	

Notes:

[114] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.

2 at 3 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 3 months[115]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 3 months

Notes:

[115] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	49	64[116]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	22	8	7	

Notes:

[116] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 4 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 4 months[117]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 4 months

Notes:

[117] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	53	46	57[118]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	23	6	8	

Notes:

[118] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 5 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 5 months[119]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 5 months

Notes:

[119] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54	45	52[120]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	24	8	7	

Notes:

[120] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 6 months

End point title	Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) <3.2 at 6 months[121]

End point description:

Number of intent-to-treat subjects with DAS28-ESR (measuring RA symptoms including: tender joint count, swollen joint count, patient's assessment of disease activity, and ESR in patients with high ESR at baseline), of less than 3.2. The DAS runs from 0 to 10 - higher scores indicate worse symptoms. A score of less than 3.2 indicates low disease activity

End point type	Secondary

End point timeframe:

After 6 months

Notes:

[121] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54	44	51[122]	
Units: subjects				
Subjects achieving DAS28-ESR criteria	29	11	8	

Notes:

[122] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ALT values greater than 1.5 to 2 times the ULN

End point title	Number of subjects with ALT values greater than 1.5 to 2 times the ULN

End point description:

The number of intent-to-treat subjects with ALT (Alanine Aminotransferase) (a test of liver function) values greater than 1.5 to 2 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>1.5 to 2 times	15	14	5	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ALT values greater than 2 to 3 times the ULN

End point title	Number of subjects with ALT values greater than 2 to 3 times the ULN

End point description:

The number of intent-to-treat subjects with ALT (Alanine Aminotransferase) (a test of liver function)

values greater than 2 to 3 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>2 to 3 times	10	8	4	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ALT values greater than 3 times the ULN

End point title	Number of subjects with ALT values greater than 3 times the ULN

End point description:

The number of intent-to-treat subjects with ALT (Alanine Aminotransferase) (a test of liver function) values greater than 3 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>3 times	6	6	2	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ALT values greater than 3 to 5 times the ULN

End point title	Number of subjects with ALT values greater than 3 to 5 times the ULN

End point description:

The number of intent-to-treat subjects with ALT (Alanine Aminotransferase) (a test of liver function) values greater than 3 to 5 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>3 to 5 times	3	3	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ALT values greater than 5 to 10 times the ULN

End point title	Number of subjects with ALT values greater than 5 to 10 times the ULN

End point description:

The number of intent-to-treat subjects with ALT (Alanine Aminotransferase) (a test of liver function) values greater than 5 to 10 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>5 to 10 times	3	3	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ALT values greater than 10 times the ULN

End point title	Number of subjects with ALT values greater than 10 times the

	ULN

End point description:

The number of intent-to-treat subjects with ALT (Alanine Aminotransferase) (a test of liver function) values greater than 10 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>10 times	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with AST values greater than 1.5 to 2 times the ULN

End point title	The number of subjects with AST values greater than 1.5 to 2 times the ULN

End point description:

The number of participants with AST (Aspartate Aminotransferase) (a test of liver function) values greater than 1.5 to 2 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects	5	13	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with AST values greater than 2 to 3 times the

ULN	
End point title	The number of subjects with AST values greater than 2 to 3 times the ULN

End point description:

The number of participants with AST (Aspartate Aminotransferase) (a test of liver function) values greater than 2 to 3 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>2 to 3 times	1	4	2	0

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with AST values greater than 3 times the ULN	
End point title	The number of subjects with AST values greater than 3 times the ULN

End point description:

The number of participants with AST (Aspartate Aminotransferase) (a test of liver function) values greater than 3 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>3 times	5	2	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with AST values greater than 3 to 5 times the ULN

End point title	The number of subjects with AST values greater than 3 to 5 times the ULN

End point description:

The number of participants with AST (Aspartate Aminotransferase) (a test of liver function) values greater than 3 to 5 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>3 to 5 times	5	2	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with AST values greater than 5 to 10 times the ULN

End point title	The number of subjects with AST values greater than 5 to 10 times the ULN

End point description:

The number of participants with AST (Aspartate Aminotransferase) (a test of liver function) values greater than 5 to 10 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>5 to 10 times	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with AST values greater than 10 times the ULN

End point title	The number of subjects with AST values greater than 10 times the ULN

End point description:

The number of participants with AST (Aspartate Aminotransferase) (a test of liver function) values greater than 10 times the ULN (Upper Limit of Normal)

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>10 times	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Bilirubin 2 times the Upper Limit of Normal (ULN)

End point title	Number of subjects with Bilirubin 2 times the Upper Limit of Normal (ULN)

End point description:

The number of intent-to-treat subjects with bilirubin (a test of liver function) values greater than 2 times the ULN

End point type	Secondary

End point timeframe:

Any time between baseline and 6 months

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid	Cohort D Placebo 150 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	152	76	77
Units: subjects				
>2 times	3	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheumatology 20 (ACR20) Response at 6 weeks

End point title	American College of Rheumatology 20 (ACR20) Response at 6 weeks[123]

End point description:

The number of intent-to-treat subjects with greater than or equal to 20% improvement in tender and swollen joint counts, AND in any 3 of the following: physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, HAQ-DI; and C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)

End point type	Secondary

End point timeframe:

After 6 weeks

Notes:

[123] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis.

End point values	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Placebo Pooled	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	151	148[124]	
Units: subjects				
Subjects achieving ACR20 criteria	84	75	55	

Notes:

[124] - Pooled placebo subjects from Cohorts C and D

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From ICF signature until visit 11 (Month 6) for AEs and until 30 days after the last dose of of study drug for SAEs.	
Adverse event reporting additional description:	
Please note, safety data were only calculated for the placebo qd and placebo bid groups. Data from the placebo groups were only pooled for the efficacy analyses	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	Cohort A R788 100 mg bid
Reporting group description:	
R788 100 mg, oral tablets, twice daily, double-blind	
Reporting group title	Cohort B R788 150 mg qd
Reporting group description:	
R788 150 mg, oral tablets, once daily, double-blind	
Reporting group title	Cohort C Placebo 100 mg bid
Reporting group description:	
Placebo 100 mg, oral tablets, twice daily, double-blind	
Reporting group title	Cohort D Placebo 150 mg qd
Reporting group description:	
Placebo 150 mg, oral tablets, once daily, double-blind	

Serious adverse events	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 152 (8.55%)	5 / 152 (3.29%)	4 / 76 (5.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma stage unspecified			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (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
Squamous cell carcinoma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (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

Carcinoma in situ of penis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (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
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Stillbirth			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (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
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 152 (0.00%)	0 / 152 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (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 haemorrhage			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (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
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 152 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder empyema			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (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
Herpes zoster ophthalmic			

subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 152 (0.66%)	0 / 152 (0.00%)	0 / 76 (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
Erysipelas			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 152 (0.66%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 152 (0.00%)	0 / 152 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 152 (0.00%)	0 / 152 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 152 (0.00%)	0 / 152 (0.00%)	0 / 76 (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	Cohort D Placebo 150 mg qd		

Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 77 (2.60%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma stage unspecified			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carcinoma in situ of penis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Stillbirth			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			

subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gallbladder empyema			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster ophthalmic			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthritis infective			

subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bursitis infective			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort A R788 100 mg bid	Cohort B R788 150 mg qd	Cohort C Placebo 100 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 152 (48.03%)	62 / 152 (40.79%)	20 / 76 (26.32%)
Investigations			
Transaminases increased	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	8 / 152 (5.26%)	7 / 152 (4.61%)	2 / 76 (2.63%)
occurrences (all)	9	7	2
Vascular disorders			
Hypertension	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	21 / 152 (13.82%)	18 / 152 (11.84%)	3 / 76 (3.95%)
occurrences (all)	21	18	3
Nervous system disorders			
Headache	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	9 / 152 (5.92%)	10 / 152 (6.58%)	6 / 76 (7.89%)
occurrences (all)	9	11	6
Gastrointestinal disorders			
Diarrhoea	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	29 / 152 (19.08%)	19 / 152 (12.50%)	1 / 76 (1.32%)
occurrences (all)	41	23	1
Nausea	Additional description: Data was entered only for affected subjects, not occurrences.		

subjects affected / exposed	7 / 152 (4.61%)	9 / 152 (5.92%)	6 / 76 (7.89%)
occurrences (all)	8	10	6
Skin and subcutaneous tissue disorders			
Rash	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	3 / 152 (1.97%)	2 / 152 (1.32%)	0 / 76 (0.00%)
occurrences (all)	3	3	0
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	1 / 152 (0.66%)	1 / 152 (0.66%)	1 / 76 (1.32%)
occurrences (all)	1	1	1
Infections and infestations			
Urinary tract infection	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	11 / 152 (7.24%)	6 / 152 (3.95%)	6 / 76 (7.89%)
occurrences (all)	12	7	6
Upper respiratory tract infection	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	10 / 152 (6.58%)	3 / 152 (1.97%)	2 / 76 (2.63%)
occurrences (all)	13	3	2
Influenza	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	5 / 152 (3.29%)	3 / 152 (1.97%)	4 / 76 (5.26%)
occurrences (all)	5	3	5
Metabolism and nutrition disorders			
Dyslipidaemia	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	5 / 152 (3.29%)	9 / 152 (5.92%)	2 / 76 (2.63%)
occurrences (all)	6	10	2

Non-serious adverse events	Cohort D Placebo 150 mg qd		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 77 (33.77%)		
Investigations			
Transaminases increased	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	3 / 77 (3.90%)		
occurrences (all)	3		
Vascular disorders			
Hypertension	Additional description: Data was entered only for affected subjects, not occurrences.		

subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Nervous system disorders			
Headache	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	3 / 77 (3.90%)		
occurrences (all)	4		
Gastrointestinal disorders			
Diarrhoea	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Nausea	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	1 / 77 (1.30%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	6		
Infections and infestations			
Urinary tract infection	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	2		
Upper respiratory tract infection	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	3 / 77 (3.90%)		
occurrences (all)	3		
Influenza	Additional description: Data was entered only for affected subjects, not occurrences.		
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Dyslipidaemia	Additional description: Data was entered only for affected subjects, not occurrences.		

subjects affected / exposed occurrences (all)	4 / 77 (5.19%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2008	Amendment 1 (Version 2), dated 19 March 2008, implemented prior to the first patient's first dose (19 May 2008). original protocol (Version 1), issued on 29 February 2008. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union. Changed the central laboratory, allowed sites to confirm ALT/ANC results that met dose adjustment/stopping guidelines using their local laboratory; and provided an updated version of the SF-36.
11 November 2008	Amendment 2 (Version 3), dated 19 March 2008, implemented after to the first patient's first dose (19 May 2008), original protocol (Version 1), issued on 29 February 2008, amendment 1 (version 2) issued on 19 March 2008 This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union. Clarified the inclusion criteria (ESR should be >ULN for the local laboratory rather than a set parameter given differences in local laboratory reference ranges), added serum pregnancy testing at Screening and Baseline in addition to a urine pregnancy test, specified that total and direct bilirubin should be reported, and clarified terms for non-SAEs, reporting requirements for hepatotoxicity, and that only SAEs identified within 30 days of the last dose of study drug administration were to be reported (not all AEs).

Notes:

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 2 placebo groups (bid and qd) were pooled for all efficacy data summaries and analysis since the observed ACR20 response rate difference between the placebo groups was <15 percentage points (prospectively defined in protocol).

Notes: